# Clinical trial results:
# Effect of MD1003 in spinal progressive multiple sclerosis: a pivotal randomized double blind placebo controlled study

## Summary

| | |
|---|---|
| EudraCT number | 2013-002113-35 |
| Trial protocol | FR |
| Global end of trial date | 04 June 2020 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 19 November 2020 |
| First version publication date | 19 November 2020 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | MD1003CT2013-02MS-SPI |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Medday Pharmaceuticals S.A. |
| Sponsor organisation address | 24-26 rue de la Pépinière, Paris, France, |
| Public contact | Clinical Trials Information Desk, Medday Pharmaceuticals S.A., +33 0180401465, |
| Scientific contact | Clinical Trials Information Desk, Medday Pharmaceuticals S.A., +33 0180401465, |

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 | 04 June 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 24 February 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 June 2020 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate the superiority of MD1003 300 mg/day over placebo in clinical improvement of patients with spinal progressive 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 | 02 September 2013 |
| 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 | France: 154 |
| Worldwide total number of subjects | 154 |
| EEA total number of subjects | 154 |

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) | 152 |
| From 65 to 84 years | 2 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details: -

### Pre-assignment period milestones

| | |
|---|---|
| Number of subjects started | 166[1] |
| Number of subjects completed | 154 |

### Pre-assignment subject non-completion reasons

| | |
|---|---|
| Reason: Number of subjects | inclusion/exclusion criteria: 12 |

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 phase |
| 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** | MD1003 |

Arm description: -

| | |
|---|---|
| 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:

100 mg 3 times/day (1 capsule in the morning, 1 at noon, 1 in the evening)

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

Arm description: -

| | |
|---|---|
| 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:

One placebo capsule 3 times/day

| Number of subjects in period 1 | MD1003 | Placebo |
|---|---|---|
| Started | 103 | 51 |
| Completed | 91 | 42 |
| Not completed | 12 | 9 |
| Consent withdrawn by subject | 5 | 4 |
| Physician decision | 3 | 2 |
| Adverse event, non-fatal | 3 | 3 |
| Protocol deviation | 1 | - |

**Period 2**

| | |
|---|---|
| Period 2 title | Open-label extension phase M12-M78 |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

**Arms**

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | MD1003-MD1003 |

Arm description:

MD1003 300 mg/day for 12 months in the double-blind phase and MD1003 300 mg/day for 66 additional months in the open-label extension phase.

| | |
|---|---|
| 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:

100 mg 3 times/day (1 capsule in the morning, 1 at noon, 1 in the evening)

| | |
|---|---|
| **Arm title** | Placebo-MD1003 |

Arm description:

Placebo for 12 months in the double-blind phase, then switch to MD1003 300 mg/day for 66 additional months in the open-label extension phase.

| | |
|---|---|
| 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:

100 mg 3 times/day (1 capsule in the morning, 1 at noon, 1 in the evening)

| **Number of subjects in period 2** | MD1003-MD1003 | Placebo-MD1003 |
|---|---|---|
| Started | 91 | 42 |
| Completed | 36 | 19 |
| Not completed | 55 | 23 |
| Consent withdrawn by subject | 13 | 8 |
| Adverse event, non-fatal | 7 | 3 |
| Other | 9 | 3 |
| Lack of efficacy | 26 | 9 |

## Baseline characteristics

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

| Reporting group values | MD1003 | Placebo | Total |
|---|---|---|---|
| Number of subjects | 103 | 51 | 154 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 101 | 0 | 101 |
| From 65-84 years | 2 | 51 | 53 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 51.8 | 50.7 | |
| standard deviation | ± 9.1 | ± 8.4 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 53 | 30 | 83 |
| Male | 50 | 21 | 71 |
| Demographic characteristics at baseline by baseline EDSS<br>Units: Subjects | | | |
| EDSS 4.5 to 5.5 | 28 | 7 | 35 |
| EDSS 6 to 7 | 75 | 44 | 119 |

| Subject analysis sets | |
|---|---|
| Subject analysis set title | ITT population |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

All randomized patients who received at least one dose of study medication and with at least one baseline EDSS and one baseline TW25 assessment will be included. All analyses will be performed according to the intent-to-treat principle, i.e. patients will be analyzed according to the treatment arm they were assigned to.

| | |
|---|---|
| Subject analysis set title | Safety set |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

All patients who received at least one dose of study medication will be included in the Safety population. Patients were analyzed according to the treatment they actually received.

| **Reporting group values** | ITT population | Safety set | |
|---|---|---|---|
| Number of subjects | 154 | 154 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 152 | 152 | |
| From 65-84 years | 2 | 2 | |
| 85 years and over | 0 | 0 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 51.4 | 51.4 | |
| standard deviation | ± 8.9 | ± 8.9 | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 83 | 83 | |
| Male | 71 | 71 | |
| Demographic characteristics at baseline by baseline EDSS<br>Units: Subjects | | | |
| EDSS 4.5 to 5.5 | 35 | 35 | |
| EDSS 6 to 7 | 119 | 119 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | MD1003 |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |
| Reporting group title | MD1003-MD1003 |
| Reporting group description: | |
| MD1003 300 mg/day for 12 months in the double-blind phase and MD1003 300 mg/day for 66 additional months in the open-label extension phase. | |
| Reporting group title | Placebo-MD1003 |
| Reporting group description: | |
| Placebo for 12 months in the double-blind phase, then switch to MD1003 300 mg/day for 66 additional months in the open-label extension phase. | |
| Subject analysis set title | ITT population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| All randomized patients who received at least one dose of study medication and with at least one baseline EDSS and one baseline TW25 assessment will be included. All analyses will be performed according to the intent-to-treat principle, i.e. patients will be analyzed according to the treatment arm they were assigned to. | |
| Subject analysis set title | Safety set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| All patients who received at least one dose of study medication will be included in the Safety population. Patients were analyzed according to the treatment they actually received. | |

### Primary: Proportion of patients with improvement of either the EDSS or the TW25 at M9 confirmed at M12

| | |
|---|---|
| End point title | Proportion of patients with improvement of either the EDSS or the TW25 at M9 confirmed at M12 |

End point description:

• Improvement of Expanded Disability Status Scale (EDSS) at M9 confirmed at M12 is defined as:
  - A decrease of at least ≥ 0.5 point if baseline EDSS within [6; 7]
  - A decrease of at least ≥ 1 point if baseline EDSS within [4.5; 5.5]
• Improvement of Time to Walk 25 Feet (TW25) is defined as a decrease of at least ≥ 20% at M9 confirmed at M12 compared to baseline TW25.

| | |
|---|---|
| End point type | Primary |
| End point timeframe: | |
| M0-M12 | |

| End point values | MD1003 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 103 | 51 | | |
| Units: Number of patients | 13 | 0 | | |

**Statistical analyses**

| **Statistical analysis title** | Fisher's exact test |
|---|---|
| Comparison groups | MD1003 v Placebo |
| Number of subjects included in analysis | 154 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0051 |
| Method | Fisher exact |

## Secondary: CGI score at M12

| End point title | CGI score at M12 |
|---|---|

End point description:

The Clinical Global Impression - Improvement scale (CGI-I) is a 7 point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention. The 7-point scale goes from: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse.

| End point type | Secondary |
|---|---|

End point timeframe:

M0-M12

| **End point values** | MD1003 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 | 45 | | |
| Units: CGI score | | | | |
| arithmetic mean (standard deviation) | 4.05 (± 0.81) | 4.62 (± 0.75) | | |

**Statistical analyses**

| **Statistical analysis title** | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003 v Placebo |
| Number of subjects included in analysis | 139 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Proportions of patients with improvement of both EDSS and TW25 at M9 and confirmed at M12

| End point title | Proportions of patients with improvement of both EDSS and TW25 at M9 and confirmed at M12 |
|---|---|

End point description:

Improvement of both EDSS and TW25 is defined as follows:
- decreased EDSS (at least 0.5 point if baseline EDSS from 6 to 7 and at least 1 point if baseline EDSS from 4.5 to 5.5) and
- decreased TW25 (at least 20%) at M9 confimred at M12.

| End point type | Secondary |
|---|---|

End point timeframe:

M0-M12

| **End point values** | MD1003 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 103 | 51 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 2 | 0 | | |

**Statistical analyses**

| **Statistical analysis title** | Fisher's exact test |
|---|---|
| Comparison groups | MD1003 v Placebo |
| Number of subjects included in analysis | 154 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 1 |
| Method | Fisher exact |

**Secondary: Proportion of patients with increased EDSS score at M9 and confirmed at M12**

| End point title | Proportion of patients with increased EDSS score at M9 and confirmed at M12 |
|---|---|

End point description:

Increased EDSS score is defined as:
- An increase of at least ≥ 0.5 point if baseline EDSS within the [6; 7] range;
- An increase of at least ≥ 1 point if baseline EDSS within the [4.5; 5.5] range.

| End point type | Secondary |
|---|---|

End point timeframe:

M0-M12

| End point values | MD1003 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 95 | 44 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 4 | 6 | | |

**Statistical analyses**

| Statistical analysis title | Fisher's exact test |
|---|---|
| Comparison groups | MD1003 v Placebo |
| Number of subjects included in analysis | 139 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0727 |
| Method | Fisher exact |

**Secondary: Proportion of patients with stable EDSS score at M9 and confirmed at M12**

| End point title | Proportion of patients with stable EDSS score at M9 and confirmed at M12 |
|---|---|

End point description:

The definition of stable EDSS is by default: it corresponds to all patients excluding those with decreased and those with increased EDSS score.

| End point type | Secondary |
|---|---|

End point timeframe:

M0-M12

| End point values | MD1003 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 103 | 51 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 81 | 38 | | |

**Statistical analyses**

| Statistical analysis title | Fisher's exact test |
|---|---|
| Comparison groups | MD1003 v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 154 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.6832 |
| Method | Fisher exact |

## Secondary: Mean change in General Health Sub-score of the SF36 questionnaire between M0 and M12

| | |
|---|---|
| End point title | Mean change in General Health Sub-score of the SF36 questionnaire between M0 and M12 |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

M0-M12

| End point values | MD1003 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 103 | 51 | | |
| Units: SF36 score | | | | |
| arithmetic mean (standard deviation) | -4.43 (± 16.75) | 2.25 (± 16.23) | | |

### Statistical analyses

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003 v Placebo |
| Number of subjects included in analysis | 154 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0349 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in the fatigue impact scale (M-FIS) between M0 and M12

| | |
|---|---|
| End point title | Mean change in the fatigue impact scale (M-FIS) between M0 and M12 |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

M0-M12

| End point values | MD1003 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 96 | 47 | | |
| Units: Fatigue impact scale | | | | |
| arithmetic mean (standard deviation) | 1.38 (± 16.04) | 1.30 (± 15.69) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003 v Placebo |
| Number of subjects included in analysis | 143 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.8466 |
| Method | Wilcoxon (Mann-Whitney) |

**Secondary: Mean change of the Nine Hole Peg Test (9HPT) between M0 and M12 (Best hand)**

| End point title | Mean change of the Nine Hole Peg Test (9HPT) between M0 and M12 (Best hand) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

M0-M12

| End point values | MD1003 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 95 | 47 | | |
| Units: 9HPT score | | | | |
| arithmetic mean (standard deviation) | 2.06 (± 5.21) | 1.40 (± 7.06) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003 v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 142 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.9757 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M12 (visual)

| | |
|---|---|
| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M12 (visual) |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

M0-M12

| **End point values** | MD1003 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 103 | 51 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.05 (± 0.81) | -0.10 (± 0.5) | | |

### Statistical analyses

| **Statistical analysis title** | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003 v Placebo |
| Number of subjects included in analysis | 154 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.183 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in EDSS between M0 and M18

| | |
|---|---|
| End point title | Mean change in EDSS between M0 and M18 |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

M0-M18

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 87 | 41 | | |
| Units: EDSS score | | | | |
| arithmetic mean (standard deviation) | -0.02 (± 0.61) | 0.13 (± 0.45) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | Placebo-MD1003 v MD1003-MD1003 |
| Number of subjects included in analysis | 128 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0273 |
| Method | Wilcoxon (Mann-Whitney) |

**Secondary: Mean change in EDSS between M0 and M24**

| End point title | Mean change in EDSS between M0 and M24 |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

M0-M24

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 82 | 41 | | |
| Units: EDSS score | | | | |
| arithmetic mean (standard deviation) | 0.04 (± 0.62) | 0.15 (± 0.37) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |

| | |
|---|---|
| Number of subjects included in analysis | 123 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.1283 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in EDSS between M0 and M30

| | |
|---|---|
| End point title | Mean change in EDSS between M0 and M30 |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

M0-M30

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 70 | 37 | | |
| Units: EDSS score | | | | |
| arithmetic mean (standard deviation) | 0.1 (± 0.68) | 0.23 (± 0.3) | | |

### Statistical analyses

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 107 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.041 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in EDSS between M0 and M36

| | |
|---|---|
| End point title | Mean change in EDSS between M0 and M36 |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

M0-M36

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 64 | 33 | | |
| Units: EDSS score | | | | |
| arithmetic mean (standard deviation) | 0.11 (± 0.69) | 0.18 (± 0.33) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.4285 |
| Method | Wilcoxon (Mann-Whitney) |

**Secondary: Mean change in EDSS between M0 and M42**

| End point title | Mean change in EDSS between M0 and M42 |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

M0-M42

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 55 | 29 | | |
| Units: EDSS score | | | | |
| arithmetic mean (standard deviation) | 0.17 (± 0.73) | 0.28 (± 0.56) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |

| | |
|---|---|
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.3653 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in EDSS between M0 and M48

| | |
|---|---|
| End point title | Mean change in EDSS between M0 and M48 |
| End point description: | |

| | |
|---|---|
| End point type | Secondary |
| End point timeframe: | |
| M0-M48 | |

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 52 | 26 | | |
| Units: EDSS score | | | | |
| arithmetic mean (standard deviation) | 0.16 (± 0.77) | 0.4 (± 0.49) | | |

### Statistical analyses

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | Placebo-MD1003 v MD1003-MD1003 |
| Number of subjects included in analysis | 78 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.1742 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in EDSS between M0 and M54

| | |
|---|---|
| End point title | Mean change in EDSS between M0 and M54 |
| End point description: | |

| | |
|---|---|
| End point type | Secondary |
| End point timeframe: | |
| M0-M54 | |

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 23 | | |
| Units: EDSS score | | | | |
| arithmetic mean (standard deviation) | 0.17 (± 0.75) | 0.43 (± 0.51) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 65 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.135 |
| Method | Wilcoxon (Mann-Whitney) |

**Secondary: Mean change in EDSS between M0 and M60**

| End point title | Mean change in EDSS between M0 and M60 |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

M0-M60

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 40 | 22 | | |
| Units: EDSS score | | | | |
| arithmetic mean (standard deviation) | 0.21 (± 0.75) | 0.39 (± 0.43) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |

| | |
|---|---|
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.25 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in the MS walking scale (MSWS) between M0 and M24

| | |
|---|---|
| End point title | Mean change in the MS walking scale (MSWS) between M0 and M24 |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

M0-M24

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 85 | 38 | | |
| Units: MSWS | | | | |
| arithmetic mean (standard deviation) | 2.06 (± 17.22) | 5.05 (± 27.07) | | |

### Statistical analyses

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 123 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.6415 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in the MS walking scale (MSWS) between M0 and M12

| | |
|---|---|
| End point title | Mean change in the MS walking scale (MSWS) between M0 and M12 |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

M0-M12

| End point values | MD1003 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 95 | 46 | | |
| Units: MSWS | | | | |
| arithmetic mean (standard deviation) | 0.79 (± 17.12) | 5.26 (± 22.51) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003 v Placebo |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.8118 |
| Method | Wilcoxon (Mann-Whitney) |

**Secondary: CGI score at M24**

| End point title | CGI score at M24 |
|---|---|

End point description:

The Clinical Global Impression - Improvement scale (CGI-I) is a 7 point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention. The 7-point scale goes from: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse.

| End point type | Secondary |
|---|---|

End point timeframe:

M24

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 90 | 42 | | |
| Units: CGI score | | | | |
| arithmetic mean (standard deviation) | 4.17 (± 0.97) | 4.24 (± 0.73) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | Placebo-MD1003 v MD1003-MD1003 |

| | |
|---|---|
| Number of subjects included in analysis | 132 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.8173 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: CGI score at M36

| | |
|---|---|
| End point title | CGI score at M36 |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

M36

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 90 | 42 | | |
| Units: CGI score | | | | |
| arithmetic mean (standard deviation) | 4.28 (± 0.97) | 4.29 (± 0.81) | | |

### Statistical analyses

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 132 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.9648 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean percent change in TW25 between M0 and M12

| | |
|---|---|
| End point title | Mean percent change in TW25 between M0 and M12 |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

M0-M12

| End point values | MD1003 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 | 42 | | |
| Units: TW25 | | | | |
| arithmetic mean (standard deviation) | 67.71 (± 203.27) | 98.18 (± 253.73) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | Placebo v MD1003 |
| Number of subjects included in analysis | 136 |
| Analysis specification | Post-hoc |
| Analysis type | other |
| P-value | = 0.6393 |
| Method | Wilcoxon (Mann-Whitney) |

**Secondary: Mean percent change in TW25 between M0 and M24**

| End point title | Mean percent change in TW25 between M0 and M24 |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

M0-M24

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 80 | 39 | | |
| Units: TW25 | | | | |
| arithmetic mean (standard deviation) | 95.77 (± 221.26) | 121.51 (± 256.29) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |

| | |
|---|---|
| Number of subjects included in analysis | 119 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.823 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean percent change in TW25 between M0 and M36

| | |
|---|---|
| End point title | Mean percent change in TW25 between M0 and M36 |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

M0-M36

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 30 | | |
| Units: TW25 | | | | |
| arithmetic mean (standard deviation) | 125.28 (± 387.7) | 165.11 (± 297.1) | | |

### Statistical analyses

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.4669 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Proportions of patients with improvement of both EDSS and TW25 at M18 and confirmed at M24

| | |
|---|---|
| End point title | Proportions of patients with improvement of both EDSS and TW25 at M18 and confirmed at M24 |

End point description:

Improvement of both EDSS and TW25 is defined as follows:
- decreased EDSS (at least 0.5 point if baseline EDSS from 6 to 7 and at least 1 point if baseline EDSS from 4.5 to 5.5) and
- decreased TW25 (at least 20%) at the corresponding visit confirmed at the next visit compared to the baseline value.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:
M18-M24

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 2 | 0 | | |

**Statistical analyses**

| Statistical analysis title | Fisher's exact test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 1 |
| Method | Fisher exact |

**Secondary: Proportions of patients with improvement of both EDSS and TW25 at M24 and confirmed at M30**

| End point title | Proportions of patients with improvement of both EDSS and TW25 at M24 and confirmed at M30 |
|---|---|

End point description:

Improvement of both EDSS and TW25 is defined as follows:
- decreased EDSS (at least 0.5 point if baseline EDSS from 6 to 7 and at least 1 point if baseline EDSS from 4.5 to 5.5) and
- decreased TW25 (at least 20%) at the corresponding visit confirmed at the next visit compared to the baseline value.

| End point type | Secondary |
|---|---|

End point timeframe:
M24-M30

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 1 | 0 | | |

### Statistical analyses

| Statistical analysis title | Fisher's exact test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 1 |
| Method | Fisher exact |

## Secondary: Proportions of patients with improvement of both EDSS and TW25 at M36 and confirmed at M42

| End point title | Proportions of patients with improvement of both EDSS and TW25 at M36 and confirmed at M42 |
|---|---|

End point description:

Improvement of both EDSS and TW25 is defined as follows:
- decreased EDSS (at least 0.5 point if baseline EDSS from 6 to 7 and at least 1 point if baseline EDSS from 4.5 to 5.5) and
- decreased TW25 (at least 20%) at the corresponding visit confirmed at the next visit compared to the baseline value.

| End point type | Secondary |
|---|---|

End point timeframe:

M36-M42

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 0 | 0 | | |

### Statistical analyses

| Statistical analysis title | Fisher's exact test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |

| | |
|---|---|
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0 [1] |
| Method | Fisher exact |

Notes:

[1] - No p-value had been calculated

## Secondary: Proportions of patients with improvement of both EDSS and TW25 at M30 and confirmed at M36

| | |
|---|---|
| End point title | Proportions of patients with improvement of both EDSS and TW25 at M30 and confirmed at M36 |

End point description:

Improvement of both EDSS and TW25 is defined as follows:
- decreased EDSS (at least 0.5 point if baseline EDSS from 6 to 7 and at least 1 point if baseline EDSS from 4.5 to 5.5) and
- decreased TW25 (at least 20%) at the corresponding visit confirmed at the next visit compared to the baseline value.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

M30-M36

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 0 | 0 | | |

### Statistical analyses

| Statistical analysis title | Fisher's exact test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0 [2] |
| Method | Fisher exact |

Notes:

[2] - No p-value had been calculated

## Secondary: Proportions of patients with improvement of both EDSS and TW25 at M42 and confirmed at M48

| | |
|---|---|
| End point title | Proportions of patients with improvement of both EDSS and TW25 at M42 and confirmed at M48 |

End point description:

Improvement of both EDSS and TW25 is defined as follows:

- decreased EDSS (at least 0.5 point if baseline EDSS from 6 to 7 and at least 1 point if baseline EDSS from 4.5 to 5.5) and
- decreased TW25 (at least 20%) at the corresponding visit confirmed at the next visit compared to the baseline value.

| End point type | Secondary |
|---|---|

End point timeframe:

M42-M48

| **End point values** | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 0 | 0 | | |

**Statistical analyses**

| **Statistical analysis title** | Fisher's exact test |
|---|---|
| Comparison groups | Placebo-MD1003 v MD1003-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0 [3] |
| Method | Fisher exact |

Notes:

[3] - No p-value had been calculated

**Secondary: Proportions of patients with improvement of both EDSS and TW25 at M48 and confirmed at M54**

| End point title | Proportions of patients with improvement of both EDSS and TW25 at M48 and confirmed at M54 |
|---|---|

End point description:

Improvement of both EDSS and TW25 is defined as follows:
- decreased EDSS (at least 0.5 point if baseline EDSS from 6 to 7 and at least 1 point if baseline EDSS from 4.5 to 5.5) and
- decreased TW25 (at least 20%) at the corresponding visit confirmed at the next visit compared to the baseline value.

| End point type | Secondary |
|---|---|

End point timeframe:

M48-M54

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 0 | 0 | | |

**Statistical analyses**

| Statistical analysis title | Fisher's exact test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0 [4] |
| Method | Fisher exact |

Notes:

[4] - No p-value had been calculated

**Secondary: Proportion of patients with increased EDSS score at M18 confirmed at M24**

| End point title | Proportion of patients with increased EDSS score at M18 confirmed at M24 |
|---|---|

End point description:

Increased EDSS score is defined as:
- An increase of at least ≥ 0.5 point if baseline EDSS within the [6; 7] range;
- An increase of at least ≥ 1 point if baseline EDSS within the [4.5; 5.5] range.

| End point type | Secondary |
|---|---|

End point timeframe:

M18-M24

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 41 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 8 | 13 | | |

**Statistical analyses**

| Statistical analysis title | Fisher's exact test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |

| | |
|---|---|
| Number of subjects included in analysis | 122 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0045 |
| Method | Fisher exact |

## Secondary: Proportion of patients with increased EDSS score at M12 and confirmed at M18

| | |
|---|---|
| End point title | Proportion of patients with increased EDSS score at M12 and confirmed at M18 |

End point description:

Increased EDSS score is defined as:
- An increase of at least ≥ 0.5 point if baseline EDSS within the [6; 7] range;
- An increase of at least ≥ 1 point if baseline EDSS within the [4.5; 5.5] range.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

M12-M18

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 87 | 40 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 7 | 7 | | |

### Statistical analyses

| Statistical analysis title | Fisher's exact test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.1332 |
| Method | Fisher exact |

## Secondary: Proportion of patients with increased EDSS score at M24 and confirmed at M30

| | |
|---|---|
| End point title | Proportion of patients with increased EDSS score at M24 and confirmed at M30 |

End point description:

Increased EDSS score is defined as:
- An increase of at least ≥ 0.5 point if baseline EDSS within the [6; 7] range;
- An increase of at least ≥ 1 point if baseline EDSS within the [4.5; 5.5] range.

| | |
|---|---|
| End point type | Secondary |

| End point timeframe:<br>M24-M30 |
|---|

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 69 | 36 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 10 | 10 | | |

**Statistical analyses**

| Statistical analysis title | Fisher's exact test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 105 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.1199 |
| Method | Fisher exact |

**Secondary: Proportion of patients with increased EDSS score at M30 and confirmed at M36**

| End point title | Proportion of patients with increased EDSS score at M30 and confirmed at M36 |
|---|---|

End point description:

Increased EDSS score is defined as:
- An increase of at least ≥ 0.5 point if baseline EDSS within the [6; 7] range;
- An increase of at least ≥ 1 point if baseline EDSS within the [4.5; 5.5] range.

| End point type | Secondary |
|---|---|

End point timeframe:

M30-M36

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 64 | 33 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 12 | 9 | | |

**Statistical analyses**

| Statistical analysis title | Fisher's exact test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.4357 |
| Method | Fisher exact |

## Secondary: Proportion of patients with increased EDSS score at M36 and confirmed at M42

| End point title | Proportion of patients with increased EDSS score at M36 and confirmed at M42 |
|---|---|

End point description:

Increased EDSS score is defined as:
- An increase of at least ≥ 0.5 point if baseline EDSS within the [6; 7] range;
- An increase of at least ≥ 1 point if baseline EDSS within the [4.5; 5.5] range.

| End point type | Secondary |
|---|---|

End point timeframe:

M36-M42

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 55 | 29 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 14 | 8 | | |

### Statistical analyses

| Statistical analysis title | Fisher's exact test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 1 |
| Method | Fisher exact |

## Secondary: Proportion of patients with increased EDSS score at M42 and confirmed at M48

| End point title | Proportion of patients with increased EDSS score at M42 and confirmed at M48 |
|---|---|

End point description:

Increased EDSS score is defined as:

- An increase of at least ≥ 0.5 point if baseline EDSS within the [6; 7] range;
- An increase of at least ≥ 1 point if baseline EDSS within the [4.5; 5.5] range.

| End point type | Secondary |
|---|---|

End point timeframe:

M42-M48

| **End point values** | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 51 | 26 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 12 | 8 | | |

**Statistical analyses**

| **Statistical analysis title** | Fisher's exact test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 77 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.5851 |
| Method | Fisher exact |

**Secondary: Proportion of patients with increased EDSS score at M48 and confirmed at M54**

| End point title | Proportion of patients with increased EDSS score at M48 and confirmed at M54 |
|---|---|

End point description:

Increased EDSS score is defined as:
- An increase of at least ≥ 0.5 point if baseline EDSS within the [6; 7] range;
- An increase of at least ≥ 1 point if baseline EDSS within the [4.5; 5.5] range.

| End point type | Secondary |
|---|---|

End point timeframe:

M48-M54

| **End point values** | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 23 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 12 | 8 | | |

**Statistical analyses**

| **Statistical analysis title** | Fisher's exact test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 65 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.7792 |
| Method | Fisher exact |

**Secondary: Proportion of patients with increased EDSS score at M54 and confirmed at M60**

| End point title | Proportion of patients with increased EDSS score at M54 and confirmed at M60 |
|---|---|

End point description:

Increased EDSS score is defined as:
- An increase of at least ≥ 0.5 point if baseline EDSS within the [6; 7] range;
- An increase of at least ≥ 1 point if baseline EDSS within the [4.5; 5.5] range.

| End point type | Secondary |
|---|---|

End point timeframe:

M54-M60

| **End point values** | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 40 | 22 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 14 | 8 | | |

**Statistical analyses**

| **Statistical analysis title** | Fisher's exact test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |

| | |
|---|---|
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 1 |
| Method | Fisher exact |

## Secondary: Proportion of patients with stable EDSS score at M12 and confirmed at M18

| | |
|---|---|
| End point title | Proportion of patients with stable EDSS score at M12 and confirmed at M18 |

End point description:

The definition of stable EDSS is by default: it corresponds to all patients excluding those with decreased and those with increased EDSS score.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

M12-M18

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 72 | 32 | | |

### Statistical analyses

| Statistical analysis title | Fisher's exact test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.8216 |
| Method | Fisher exact |

## Secondary: Proportion of patients with stable EDSS score at M24 and confirmed at M30

| | |
|---|---|
| End point title | Proportion of patients with stable EDSS score at M24 and confirmed at M30 |

End point description:

The definition of stable EDSS is by default: it corresponds to all patients excluding those with decreased and those with increased EDSS score.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

M24-M30

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 53 | 26 | | |

**Statistical analyses**

| Statistical analysis title | Fisher's exact test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.7089 |
| Method | Fisher exact |

**Secondary: Proportion of patients with stable EDSS score at M36 and confirmed at M42**

| End point title | Proportion of patients with stable EDSS score at M36 and confirmed at M42 |
|---|---|

End point description:

The definition of stable EDSS is by default: it corresponds to all patients excluding those with decreased and those with increased EDSS score.

| End point type | Secondary |
|---|---|

End point timeframe:

M36-M42

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 33 | 21 | | |

**Statistical analyses**

| Statistical analysis title | Fisher's exact test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.1833 |
| Method | Fisher exact |

## Secondary: Proportion of patients with stable EDSS score at M48 and confirmed at M54

| End point title | Proportion of patients with stable EDSS score at M48 and confirmed at M54 |
|---|---|

End point description:

The definition of stable EDSS is by default: it corresponds to all patients excluding those with decreased and those with increased EDSS score.

| End point type | Secondary |
|---|---|

End point timeframe:

M48-M54

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Number of patients | | | | |
| number (not applicable) | 24 | 15 | | |

### Statistical analyses

| Statistical analysis title | Fisher's exact test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.3083 |
| Method | Fisher exact |

## Secondary: Mean change of the General Health Sub-score of the SF36 questionnaire between M0 and M24

| End point title | Mean change of the General Health Sub-score of the SF36 questionnaire between M0 and M24 |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M24

| **End point values** | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: SF36 score | | | | |
| arithmetic mean (standard deviation) | -3.95 (± 15.68) | 1.37 (± 19.26) | | |

**Statistical analyses**

| **Statistical analysis title** | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other[5] |
| P-value | = 0.1722 |
| Method | Wilcoxon (Mann-Whitney) |

Notes:
[5] - The LOCF method was used.

**Secondary: Mean change in the fatigue impact scale (M-FIS) between M0 and M24**

| End point title | Mean change in the fatigue impact scale (M-FIS) between M0 and M24 |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M24

| **End point values** | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 85 | 38 | | |
| Units: FIS | | | | |
| arithmetic mean (standard deviation) | -0.40 (± 13.49) | 0.79 (± 13.88) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 123 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.9716 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change of the Nine Hole Peg Test (9HPT) between M0 and M24 (best hand)

| End point title | Mean change of the Nine Hole Peg Test (9HPT) between M0 and M24 (best hand) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

M0-M24

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 88 | 38 | | |
| Units: 9HPT score | | | | |
| arithmetic mean (standard deviation) | 3.43 (± 8.44) | 2.76 (± 9.20) | | |

### Statistical analyses

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 126 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.7713 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change of the Nine Hole Peg Test (9HPT) between M0 and M24 (worst hand)

| End point title | Mean change of the Nine Hole Peg Test (9HPT) between M0 and M24 (worst hand) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M24

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 90 | 40 | | |
| Units: 9HPT score | | | | |
| arithmetic mean (standard deviation) | 8.87 (± 33.86) | 7.70 (± 32.17) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.7694 |
| Method | Wilcoxon (Mann-Whitney) |

**Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M12 (brain stem)**

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M12 (brain stem) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M12

| End point values | MD1003 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 103 | 51 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.10 (± 0.69) | -0.08 (± 0.82) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003 v Placebo |
| Number of subjects included in analysis | 154 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.1912 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M12 (pyramidal)

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M12 (pyramidal) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

M0-M12

| End point values | MD1003 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 103 | 51 | | |
| Units: Kurztke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | -0.03 (± 0.55) | 0.04 (± 0.53) | | |

### Statistical analyses

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003 v Placebo |
| Number of subjects included in analysis | 154 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.5404 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M12 (cerebellar)

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M12 (cerebellar) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M12

| End point values | MD1003 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 101 | 49 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.19 (± 0.86) | 0.14 (± 1.12) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003 v Placebo |
| Number of subjects included in analysis | 150 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.5376 |
| Method | Wilcoxon (Mann-Whitney) |

**Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M12 (sensory)**

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M12 (sensory) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M12

| End point values | MD1003 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 103 | 51 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | -0.25 (± 0.93) | 0.06 (± 0.88) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003 v Placebo |
| Number of subjects included in analysis | 154 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0896 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M12 (bowel and bladder)

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M12 (bowel and bladder) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

M0-M12

| End point values | MD1003 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 103 | 51 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.14 (± 0.83) | 0.20 (± 0.98) | | |

### Statistical analyses

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | Placebo v MD1003 |
| Number of subjects included in analysis | 154 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.6801 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M12 (cerebral)

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M12 (cerebral) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M12

| End point values | MD1003 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 103 | 51 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | -0.08 (± 0.76) | 0.08 (± 0.91) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003 v Placebo |
| Number of subjects included in analysis | 154 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.2619 |
| Method | Wilcoxon (Mann-Whitney) |

**Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M24 (visual)**

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M24 (visual) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M24

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.04 (± 1) | 0.17 (± 1.19) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.7312 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M24 (brain stem)

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M24 (brain stem) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

M0-M24

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.09 (± 0.89) | 0.14 (± 0.84) | | |

### Statistical analyses

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.5761 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M24 (pyramidal)

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M24 (pyramidal) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M24

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.12 (± 0.61) | 0.12 (± 0.59) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.878 |
| Method | Wilcoxon (Mann-Whitney) |

**Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M24 (cerebellar)**

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M24 (cerebellar) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M24

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 89 | 41 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.09 (± 0.91) | 0.05 (± 1.53) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.8181 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M24 (sensory)

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M24 (sensory) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

M0-M24

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | -0.08 (± 0.96) | -0.17 (± 0.99) | | |

### Statistical analyses

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.6394 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M24 (bowel and bladder)

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M24 (bowel and bladder) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M24

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.12 (± 0.89) | 0.02 (± 0.92) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.8062 |
| Method | Wilcoxon (Mann-Whitney) |

**Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M24 (cerebral)**

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M24 (cerebral) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M24

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | -0.01 (± 0.89) | 0 (± 0.96) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.7453 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M36 (visual)

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M36 (visual) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

M0-M36

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.03 (± 1.08) | 0.12 (± 1.15) | | |

### Statistical analyses

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | Placebo-MD1003 v MD1003-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.921 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M36 (brain stem)

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M36 (brain stem) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

| End point timeframe:<br>M0-M36 |
|---|

| **End point values** | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.08 (± 0.91) | 0 (± 0.83) | | |

**Statistical analyses**

| **Statistical analysis title** | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.8211 |
| Method | Wilcoxon (Mann-Whitney) |

**Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M36 (pyramidal)**

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M36 (pyramidal) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M36

| **End point values** | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.16 (± 0.75) | 0.19 (± 0.74) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.7737 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M36 (cerebellar)

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M36 (cerebellar) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

M0-M36

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 89 | 41 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.13 (± 1.04) | 0.22 (± 1.37) | | |

### Statistical analyses

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.8437 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M36 (sensory)

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M36 (sensory) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M36

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | -0.16 (± 0.93) | -0.02 (± 1) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | Placebo-MD1003 v MD1003-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.4809 |
| Method | Wilcoxon (Mann-Whitney) |

**Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M36 (bowel and bladder)**

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M36 (bowel and bladder) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M36

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.13 (± 0.96) | 0.19 (± 0.97) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.5514 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M36 (cerebral)

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M36 (cerebral) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

M0-M36

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | -0.03 (± 0.87) | 0.07 (± 0.92) | | |

### Statistical analyses

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.5806 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M48 (visual)

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M48 (visual) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M48

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.03 (± 1.06) | -0.1 (± 0.73) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.4782 |
| Method | Wilcoxon (Mann-Whitney) |

**Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M48 (brain stem)**

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M48 (brain stem) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M48

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.14 (± 0.88) | 0.05 (± 0.85) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.8818 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M48 (pyramidal)

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M48 (pyramidal) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

M0-M48

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.21 (± 0.77) | 0.26 (± 0.83) | | |

### Statistical analyses

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.7643 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M48 (cerebellar)

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M48 (cerebellar) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M48

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 89 | 41 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.18 (± 1.05) | 0.12 (± 1.5) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.8652 |
| Method | Wilcoxon (Mann-Whitney) |

**Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M48 (sensory)**

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M48 (sensory) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M48

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | -0.11 (± 1) | 0.12 (± 0.97) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.2847 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M48 (bowel and bladder)

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M48 (bowel and bladder) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

M0-M48

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.1 (± 0.98) | 0.26 (± 0.94) | | |

### Statistical analyses

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.2531 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M48 (cerebral)

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M48 (cerebral) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M48

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.02 (± 1.05) | 0.1 (± 0.93) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.4569 |
| Method | Wilcoxon (Mann-Whitney) |

**Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M60 (visual)**

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M60 (visual) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M60

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.05 (± 1.07) | -0.07 (± 0.81) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.4438 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M60 (brain stem)

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M60 (brain stem) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

M0-M60

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.12 (± 0.88) | 0.05 (± 0.88) | | |

### Statistical analyses

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.8021 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M60 (pyramidal)

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M60 (pyramidal) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

| End point timeframe:<br>M0-M60 |
|---|

| **End point values** | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.22 (± 0.73) | 0.26 (± 0.8) | | |

**Statistical analyses**

| **Statistical analysis title** | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.664 |
| Method | Wilcoxon (Mann-Whitney) |

**Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M60 (cerebellar)**

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M60 (cerebellar) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M60

| **End point values** | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 89 | 41 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.16 (± 1.09) | 0.12 (± 1.5) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | Placebo-MD1003 v MD1003-MD1003 |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.7363 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M60 (sensory)

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M60 (sensory) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

M0-M60

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | -0.09 (± 1.03) | 0.12 (± 0.99) | | |

### Statistical analyses

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.2937 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M60 (bowel and bladder)

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M60 (bowel and bladder) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M60

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | 0.25 (± 1.08) | 0.24 (± 0.93) | | |

**Statistical analyses**

| Statistical analysis title | Mann-Whitney's U test |
|---|---|
| Comparison groups | MD1003-MD1003 v Placebo-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.8206 |
| Method | Wilcoxon (Mann-Whitney) |

**Secondary: Mean change in sub-score of the Kurtzke functional score between M0 and M60 (cerebral)**

| End point title | Mean change in sub-score of the Kurtzke functional score between M0 and M60 (cerebral) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
M0-M60

| End point values | MD1003-MD1003 | Placebo-MD1003 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 42 | | |
| Units: Kurtzke fonctionnal score | | | | |
| arithmetic mean (standard deviation) | -0.01 (± 0.9) | -0.02 (± 0.95) | | |

**Statistical analyses**

| **Statistical analysis title** | Mann-Whitney's U test |
|---|---|
| Comparison groups | Placebo-MD1003 v MD1003-MD1003 |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.9151 |
| Method | Wilcoxon (Mann-Whitney) |

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: From ICF signature to M84 | |
| Assessment type | Systematic |
| **Dictionary used** | |
| Dictionary name | MedDRA |
| Dictionary version | 16 |
| **Reporting groups** | |
| Reporting group title | MD1003 |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |
| Reporting group title | MD1003-MD1003 extension phase |
| Reporting group description: - | |
| Reporting group title | Placebo-MD1003 extension phase |
| Reporting group description: - | |

| Serious adverse events | MD1003 | Placebo | MD1003-MD1003 extension phase |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 21 / 103 (20.39%) | 12 / 51 (23.53%) | 32 / 91 (35.16%) |
| number of deaths (all causes) | 1 | 0 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal cancer | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Phlebitis | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 0 / 91 (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 |
| **Surgical and medical procedures** | | | |
| Cholecystectomy | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 51 (1.96%) | 0 / 91 (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 |
| Gamma radiation therapy to brain | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 51 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hospitalisation | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 51 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac ablation | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip arthroplasty | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 0 / 91 (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 |
| Intrathecal pump insertion | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 0 / 91 (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 |
| Rehabilitation therapy | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary cystectomy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urostomy | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| 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 disorders and administration site conditions | | | |
| Condition aggravated | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| 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 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| 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 | | | |
| Breast mass | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostatitis | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 0 / 91 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthmatic crisis | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung disorder | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Completed suicide | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 51 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Mental disorder | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 51 (1.96%) | 0 / 91 (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 |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Inflammatory marker increased | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laboratory test interference | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 0 / 91 (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 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural | | | |

| | | | |
|---|---|---|---|
| complications | | | |
| Fibula fracture | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 51 (1.96%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Overdose | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 51 (1.96%) | 0 / 91 (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 |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 51 (1.96%) | 0 / 91 (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 |
| Wrist fracture | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 0 / 91 (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 |
| Fractured sacrum | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 0 / 91 (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 |
| Hip fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 0 / 91 (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 |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic fracture | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 0 / 91 (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 |
| Radiation necrosis | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal fracture | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 0 / 91 (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 |
| Cardiac disorders | | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 0 / 91 (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 |
| Nervous system disorders | | | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 51 (1.96%) | 0 / 91 (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 |
| Multiple sclerosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 103 (0.97%) | 1 / 51 (1.96%) | 4 / 91 (4.40%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 6 / 103 (5.83%) | 4 / 51 (7.84%) | 11 / 91 (12.09%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 4 | 5 / 16 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscle spasticity | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 51 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| 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 disorder | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Trigeminal neuralgia | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uhthoff's phenomenon | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| 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 thrombocytopenia | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 0 / 91 (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 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 51 (1.96%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 51 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenitis | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 51 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 51 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|---|---|---|
| Mucocutaneous rash | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 51 (0.00%) | 0 / 91 (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 |
| Renal and urinary disorders | | | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 51 (1.96%) | 0 / 91 (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 tract disorder | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| 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 | | | |
| Goitre | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 51 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Myopathy | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 0 / 91 (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 |
| Infections and infestations | | | |
| Enterocolitis infectious | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 51 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 51 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bursitis infective staphylococcal | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 0 / 91 (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 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Placebo-MD1003 extension phase | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 16 / 42 (38.10%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rectal cancer | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Vascular disorders | | | | |
| Deep vein thrombosis | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Phlebitis | | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Surgical and medical procedures | | | | |
| Cholecystectomy | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gamma radiation therapy to brain | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hospitalisation | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac ablation | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hip arthroplasty | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intrathecal pump insertion | | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rehabilitation therapy | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary cystectomy | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urostomy | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| General disorders and administration site conditions | | | | |
| Condition aggravated | | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| General physical health deterioration | | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Reproductive system and breast disorders | | | | |
| Breast mass | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

| | | | | |
|---|---|---|---|---|
| Prostatitis | | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory, thoracic and mediastinal disorders | | | | |
| Asthmatic crisis | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung disorder | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pulmonary embolism | | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Psychiatric disorders | | | | |
| Completed suicide | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Mental disorder | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Suicide attempt | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Investigations | | | | |
| Inflammatory marker increased | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Laboratory test interference | | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Weight decreased | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Injury, poisoning and procedural complications | | | | |
| Fibula fracture | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Humerus fracture | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Overdose | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tibia fracture | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Wrist fracture | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Clavicle fracture | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Femoral neck fracture | | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fractured sacrum | | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hip fracture | | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lower limb fracture | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pelvic fracture | | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Radiation necrosis | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal fracture | | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac disorders | | | | |
| Supraventricular tachycardia | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myocardial infarction | | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nervous system disorders | | | | |
| Haemorrhage intracranial | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Multiple sclerosis | | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Multiple sclerosis relapse | | | | |
| subjects affected / exposed | 5 / 42 (11.90%) | | | |
| occurrences causally related to treatment / all | 1 / 7 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Muscle spasticity | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cerebrovascular accident | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Epilepsy | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nervous system disorder | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Trigeminal neuralgia | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Uhthoff's phenomenon | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Blood and lymphatic system disorders | | | | |
| Anaemia | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Immune thrombocytopenia | | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal disorders | | | | |
| Abdominal pain | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diarrhoea | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Duodenitis | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Inguinal hernia | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 42 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Mucocutaneous rash | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract disorder | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Myopathy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Enterocolitis infectious | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bursitis infective staphylococcal | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Viral infection | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 42 (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 | Placebo | MD1003-MD1003 extension phase |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 21 / 103 (20.39%) | 13 / 51 (25.49%) | 78 / 91 (85.71%) |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 5 / 91 (5.49%) |
| occurrences (all) | 0 | 0 | 5 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 2 / 91 (2.20%) |
| occurrences (all) | 0 | 0 | 2 |
| Cardiac disorders | | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 8 / 91 (8.79%) |
| occurrences (all) | 0 | 0 | 9 |
| Nervous system disorders | | | |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 6 / 103 (5.83%) | 4 / 51 (7.84%) | 14 / 91 (15.38%) |
| occurrences (all) | 8 | 4 | 21 |
| Headache | | | |
| subjects affected / exposed | 4 / 103 (3.88%) | 3 / 51 (5.88%) | 0 / 91 (0.00%) |
| occurrences (all) | 5 | 7 | 0 |
| General disorders and administration site conditions | | | |
| Back pain | | | |
| subjects affected / exposed | 4 / 103 (3.88%) | 3 / 51 (5.88%) | 6 / 91 (6.59%) |
| occurrences (all) | 4 | 3 | 6 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 4 / 51 (7.84%) | 0 / 91 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |
| Asthenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 5 / 91 (5.49%) |
| occurrences (all) | 0 | 0 | 6 |
| Immune system disorders | | | |
| Multiple sclerosis | | | |
| subjects affected / exposed | 12 / 103 (11.65%) | 7 / 51 (13.73%) | 9 / 91 (9.89%) |
| occurrences (all) | 13 | 9 | 10 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 1 / 91 (1.10%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle spasticity | | | |
| subjects affected / exposed | 4 / 103 (3.88%) | 6 / 51 (11.76%) | 3 / 91 (3.30%) |
| occurrences (all) | 4 | 7 | 3 |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 7 / 91 (7.69%) |
| occurrences (all) | 0 | 0 | 7 |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 5 / 91 (5.49%) |
| occurrences (all) | 0 | 0 | 5 |
| Osteoporosis | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 4 / 91 (4.40%) |
| occurrences (all) | 0 | 0 | 4 |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 11 / 103 (10.68%) | 6 / 51 (11.76%) | 18 / 91 (19.78%) |
| occurrences (all) | 13 | 9 | 33 |
| Bronchitis | | | |
| subjects affected / exposed | 5 / 103 (4.85%) | 6 / 51 (11.76%) | 6 / 91 (6.59%) |
| occurrences (all) | 5 | 6 | 7 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 5 / 103 (4.85%) | 3 / 51 (5.88%) | 5 / 91 (5.49%) |
| occurrences (all) | 5 | 4 | 8 |
| Influenza | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 5 / 91 (5.49%) |
| occurrences (all) | 0 | 0 | 5 |

| | | | |
|---|---|---|---|
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 51 (0.00%) | 3 / 91 (3.30%) |
| occurrences (all) | 0 | 0 | 4 |

| **Non-serious adverse events** | Placebo-MD1003 extension phase | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 38 / 42 (90.48%) | | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | | |
| occurrences (all) | 2 | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | |
| occurrences (all) | 3 | | |
| Cardiac disorders | | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nervous system disorders | | | |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 6 / 42 (14.29%) | | |
| occurrences (all) | 9 | | |
| Headache | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | |
| occurrences (all) | 0 | | |
| General disorders and administration site conditions | | | |
| Back pain | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | |
| occurrences (all) | 3 | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | |
| occurrences (all) | 0 | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | | |
| occurrences (all) | 2 | | |
| Immune system disorders | | | |

| | | | |
|---|---|---|---|
| Multiple sclerosis | | | |
| subjects affected / exposed | 5 / 42 (11.90%) | | |
| occurrences (all) | 7 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | |
| occurrences (all) | 4 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle spasticity | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | |
| occurrences (all) | 3 | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | | |
| occurrences (all) | 2 | | |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | |
| occurrences (all) | 0 | | |
| Osteoporosis | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | |
| occurrences (all) | 3 | | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 11 / 42 (26.19%) | | |
| occurrences (all) | 24 | | |
| Bronchitis | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | | |
| occurrences (all) | 4 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Influenza | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | |
| occurrences (all) | 3 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 24 September 2013 | I) Modification of the study design<br>II) Addition of the ancillary study<br>III) Modification of one of the non-inclusion criteria<br>IV) Addition of a non inclusion criteria |
| 22 January 2014 | I) Modification of the primary endpoint<br>II) Modification of the secondary endpoints<br>III) Modification of the age inclusion crietria<br>IV) Modification of a non inclusion criteria<br>V) Deletion of the exclusion criteria<br>VI) Creation of a Data and Safety Monitoring Board (DSMB)<br>VII) Modification of the number of patients included in the study |
| 02 May 2014 | I) Clarification of the primary endpoint<br>II) Addition of a secondary endpoint<br>III) Addition of a homostasis assessment during and at the end of the study |
| 06 June 2014 | Clarification on the primary endpoint without any change on patients' safety |
| 22 July 2014 | Addition of a secondary endpoint |
| 22 January 2015 | I) Update of the investigator's brochure with new non clinical data having an impact on patients' safety and the trial protocol<br>II) Update of the number of included patients<br>III) Modification of the protocol according to new clinical and non clinical events<br>IV) Modification of the protocol with addition of a brain MRI at M24<br>V) Clarification on the MRI follow up protocol and addition of new MRI analyses<br>VI) Clarification on protocol for the interim analysis of the results related to the double blind 12-month period.<br>VII) Modification of the patient information sheet following new clinical and non clinical events and clarification on the MRI follow up protocol with addition of new analyses of MRI data |
| 07 September 2015 | Extension of the follow-up period for the patients' cohort up to 3 year follow-up |
| 15 June 2016 | To increase the follow-up period of the patients' cohort, it is proposed to continue the study up to 4 year follow-up (until M48) + update of sponsor's contact details + update of investigators' list. |
| 08 June 2017 | In order to increase the duration of cohorts follow-up, it is proposed to continue the study until Marketing Authorisation is obtained, with visits every 6 months. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported