



Clinical trial results:

A phase II, multicentre study to evaluate the long-term safety and efficacy of MT-1303 in subjects with relapsing-remitting multiple sclerosis who have completed the MT-1303-E04 study

Summary

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2012-002639-27 |
| Trial protocol | GB HU ES FI BE LT CZ PL BG IT |
| Global end of trial date | 15 March 2016 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 16 March 2017 |
| First version publication date | 16 March 2017 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | MT-1303-E05 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|---------------------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01890655 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | MOMENTUM extention study: MT-1303-E05 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Mitsubishi Tanabe Pharma Corporation |
| Sponsor organisation address | 17-10, Nihonbashi-Koamicho, Chuo-ku, Tokyo, Japan, 103-8405 |
| Public contact | General Information , Mitsubishi Tanabe Pharma Europe Ltd. , regulatory@mt-pharma-eu.com |
| Scientific contact | General Information , Mitsubishi Tanabe Pharma Europe Ltd. , regulatory@mt-pharma-eu.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 02 August 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 March 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 March 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to evaluate the long-term safety and tolerability of MT-1303 in subjects with relapsing-remitting multiple sclerosis (RRMS).

Protection of trial subjects:

Subjects will be permanently withdrawn from study medication in the following circumstances:

- Confirmed absolute lymphocyte count values $<200/\mu\text{L}$, on 2 consecutive occasions
- Documented relapse of MS symptoms; or new or exacerbation of pre-existing conditions requiring treatment with one or more prohibited medications
- Development of any clinically significant abnormalities on ECG, including but not limited to: Symptomatic bradycardia; New onset 2nd degree AV block, Mobitz Type II; New onset 3rd degree AV block; Confirmed QTcF interval prolongation $>500\text{msec}$ and/or QTcF interval increase from baseline $>60\text{msec}$
- Development of any clinically significant liver dysfunction as follows:
 - ALT or AST $>8 \times \text{ULN}$, or
 - ALT or AST $>5 \times \text{ULN}$ and persists for more than 2 consecutive visits, or
 - ALT or AST $>3 \times \text{ULN}$ in conjunction with elevated total bilirubin $>2 \times \text{ULN}$ or
 - ALT or AST $>3 \times \text{ULN}$ with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia ($>5\%$)
- Development of macular oedema during the study
- Recurrence of the abnormality at re-challenge

In addition, a subject may voluntarily withdraw or be permanently withdrawn from the study at any time for reasons including, but not limited to, the following:

- The subject wishes to withdraw from further participation
- The subject is non-compliant with the protocol
- The treatment blind is broken for the subject for the reasons other than regulatory reporting (during Part 1 only)
- Continuation in the study would be detrimental to the subject's safety in the opinion of the Investigator
- Pregnancy
- The Investigator or the Sponsor, for any reason, stops the study

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

| | |
|---|------------------|
| Actual start date of recruitment | 31 January 2013 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 21 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Poland: 78 |
| Country: Number of subjects enrolled | Spain: 19 |
| Country: Number of subjects enrolled | United Kingdom: 15 |
| Country: Number of subjects enrolled | Belgium: 9 |
| Country: Number of subjects enrolled | Bulgaria: 54 |
| Country: Number of subjects enrolled | Czech Republic: 54 |
| Country: Number of subjects enrolled | Finland: 6 |
| Country: Number of subjects enrolled | Germany: 3 |
| Country: Number of subjects enrolled | Hungary: 22 |
| Country: Number of subjects enrolled | Italy: 9 |
| Country: Number of subjects enrolled | Lithuania: 2 |
| Country: Number of subjects enrolled | Canada: 4 |
| Country: Number of subjects enrolled | Croatia: 3 |
| Country: Number of subjects enrolled | Russian Federation: 22 |
| Country: Number of subjects enrolled | Serbia: 25 |
| Country: Number of subjects enrolled | Turkey: 17 |
| Country: Number of subjects enrolled | Ukraine: 25 |
| Worldwide total number of subjects | 367 |
| EEA total number of subjects | 274 |

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) | 367 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Part 1-Double Blind: subjects were randomised to receive 0.1mg, 0.2mg or 0.4mg of MT-1303. Part 2-Open Label: subjects with a minimum of 12 weeks left in the DB Period received OL treatment with the effective dose(s) for the remainder of the 18-month treatment period. Safety Follow Up: subjects then entered a 12-week Safety Follow Up Period

Pre-assignment

Screening details:

After providing the informed consent former MT-1303-E04 subjects could enter the MT-1303-E05 Double Blind period once all eligibility criteria were validated. There was no screening period.

Period 1

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

Blinding implementation details:

During the double-blind part (part 1/2) of the E05 study lymphocyte counts, subsets and WBC were not provided to any site/study personnel to maintain the study medication blind. Also all subjects underwent recommended monitoring of cardiovascular safety within the clinic for at least 6 h following the first dose of study medication at E05 Visit 1. All 3 doses of MT-1303 capsules were identical in appearance, taste and smell and the same number of capsules were given.

Arms

| | |
|------------------------------|------------------------------------|
| Are arms mutually exclusive? | No |
| Arm title | MT-1303 0.1 mg (Safety Population) |

Arm description:

MT-1303 0.1 mg (oral capsules) taken from Wk 0 up to Wk 24 in MT-1303-E04 and during double-blind period of MT-1303-E05 or taken only from Wk 0 in MT-1303-E05 after switching from placebo and during the double-blind period of MT-1303-E05. (Overall Summary all Treatments)

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | MT-1303 |
| Investigational medicinal product code | MT-1303 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

1 capsule, containing MT-1303 0.1mg, taken orally daily for 18 months.

| | |
|------------------|------------------------------------|
| Arm title | MT-1303 0.2 mg (Safety Population) |
|------------------|------------------------------------|

Arm description:

MT-1303 0.2 mg (oral capsules) taken from Wk 0 up to Wk 24 in MT-1303-E04 and during both double-blind and open-label periods of MT-1303-E05 or taken only from Wk 0 in MT-1303-E05 after switching from placebo then throughout the MT-1303-E05 treatment periods. (Overall Summary all Treatments)

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|----------|
| Investigational medicinal product name | MT-1303 |
| Investigational medicinal product code | MT-1303 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

1 capsule, containing MT-1303 0.2mg, taken orally daily for 18 months.

| | |
|------------------|------------------------------------|
| Arm title | MT-1303 0.4 mg (Safety Population) |
|------------------|------------------------------------|

Arm description:

MT-1303 0.4 mg (oral capsules) taken from Wk 0 up to Wk 24 in MT-1303-E04 and during both double-blind and open-label periods of MT-1303-E05 or taken only from Wk 0 in MT-1303-E05 after switching from placebo then throughout the MT-1303-E05 treatment periods. (Overall Summary all Treatments)

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | MT-1303 |
| Investigational medicinal product code | MT-1303 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

1 capsule, containing MT-1303 0.4mg, taken orally daily for 18 months.

| Number of subjects in period 1 | MT-1303 0.1 mg (Safety Population) | MT-1303 0.2 mg (Safety Population) | MT-1303 0.4 mg (Safety Population) |
|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|
| Started | 123 | 123 | 121 |
| Completed | 108 | 115 | 107 |
| Not completed | 15 | 8 | 14 |
| Protocol Specific | 2 | - | 3 |
| Consent withdrawn by subject | 6 | 1 | 1 |
| Protocol-specific reason | - | 2 | - |
| Adverse event, non-fatal | 1 | - | 1 |
| Other | - | 2 | 5 |
| Completed during E05 DB period | 6 | 3 | 4 |

Period 2

| | |
|------------------------------|-----------------------------|
| Period 2 title | Open-Label Treatment Period |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|----|
| Are arms mutually exclusive? | No |
|------------------------------|----|

| | |
|---|------------------------------------|
| Arm title | MT-1303 0.2 mg (Safety Population) |
| Arm description: MT-1303 0.2 mg (oral capsules) taken from Wk 0 up to Wk 24 in MT-1303-E04 and during both double-blind and open-label periods of MT-1303-E05 or taken only from Wk 0 in MT-1303-E05 after switching from placebo then throughout the MT-1303-E05 treatment periods or taken only from start of open-label period in MT-1303-E05 after switching from MT-1303 0.1 mg then throughout the MT-1303-E05 open label treatment period. (Overall Summary all Treatments) | |
| Arm type | Experimental |
| Investigational medicinal product name | MT-1303 |
| Investigational medicinal product code | MT-1303 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

1 capsule, containing MT-1303 0.2mg, taken orally daily for 18 months.

| | |
|---|------------------------------------|
| Arm title | MT-1303 0.4 mg (Safety Population) |
| Arm description: MT-1303 0.4 mg (oral capsules) taken from Wk 0 up to Wk 24 in MT-1303-E04 and during both double-blind and open-label periods of MT-1303-E05 or taken only from Wk 0 in MT-1303-E05 after switching from placebo then throughout the MT-1303-E05 treatment periods or taken only from start of open-label period in MT-1303-E05 after switching from MT-1303 0.1 mg then throughout the MT-1303-E05 open label treatment period. (Overall Summary all Treatments) | |
| Arm type | Experimental |
| Investigational medicinal product name | MT-1303 |
| Investigational medicinal product code | MT-1303 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

1 capsule, containing MT-1303 0.4mg, taken orally daily for 18 months.

| Number of subjects in period 2 | MT-1303 0.2 mg (Safety Population) | MT-1303 0.4 mg (Safety Population) |
|---------------------------------------|---|---|
| Started | 169 | 161 |
| Completed | 157 | 152 |
| Not completed | 12 | 9 |
| Protocol Specific | 2 | 1 |
| Adverse event, serious fatal | - | 1 |
| Consent withdrawn by subject | 4 | 2 |
| Adverse event, non-fatal | 3 | 4 |
| Other | 2 | 1 |
| Pregnancy | 1 | - |

| | |
|--|------------------------------------|
| Period 3 | |
| Period 3 title | Safety Follow-up Period |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |
| Arms | |
| Are arms mutually exclusive? | No |
| Arm title | MT-1303 0.1 mg (Safety Population) |
| Arm description: MT-1303 0.1 mg (oral capsules) taken from Wk 0 up to Wk 24 in MT-1303-E04 and during double-blind period of MT-1303-E05 or taken only from Wk 0 in MT-1303-E05 after switching from placebo and during the double-blind period of MT-1303-E05. (Overall Summary all Treatments) | |
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| Arm title | MT-1303 0.2 mg (Safety Population) |
| Arm description: MT-1303 0.2 mg (oral capsules) taken from Wk 0 up to Wk 24 in MT-1303-E04 and during both double-blind and open-label periods of MT-1303-E05 or taken only from Wk 0 in MT-1303-E05 after switching from placebo then throughout the MT-1303-E05 treatment periods. (Overall Summary all Treatments) | |
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| Arm title | MT-1303 0.4 mg (Safety Population) |
| Arm description: MT-1303 0.4 mg (oral capsules) taken from Wk 0 up to Wk 24 in MT-1303-E04 and during both double-blind and open-label periods of MT-1303-E05 or taken only from Wk 0 in MT-1303-E05 after switching from placebo then throughout the MT-1303-E05 treatment periods. (Overall Summary all Treatments) | |
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 3 | MT-1303 0.1 mg (Safety Population) | MT-1303 0.2 mg (Safety Population) | MT-1303 0.4 mg (Safety Population) |
|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|
| Started | 121 | 119 | 117 |
| Completed | 116 | 116 | 114 |
| Not completed | 5 | 3 | 3 |
| Consent withdrawn by subject | 2 | 1 | 1 |
| Other | 2 | 2 | 2 |
| Lost to follow-up | 1 | - | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------------------------|
| Reporting group title | MT-1303 0.1 mg (Safety Population) |
|-----------------------|------------------------------------|

Reporting group description:

MT-1303 0.1 mg (oral capsules) taken from Wk 0 up to Wk 24 in MT-1303-E04 and during double-blind period of MT-1303-E05 or taken only from Wk 0 in MT-1303-E05 after switching from placebo and during the double-blind period of MT-1303-E05. (Overall Summary all Treatments)

| | |
|-----------------------|------------------------------------|
| Reporting group title | MT-1303 0.2 mg (Safety Population) |
|-----------------------|------------------------------------|

Reporting group description:

MT-1303 0.2 mg (oral capsules) taken from Wk 0 up to Wk 24 in MT-1303-E04 and during both double-blind and open-label periods of MT-1303-E05 or taken only from Wk 0 in MT-1303-E05 after switching from placebo then throughout the MT-1303-E05 treatment periods. (Overall Summary all Treatments)

| | |
|-----------------------|------------------------------------|
| Reporting group title | MT-1303 0.4 mg (Safety Population) |
|-----------------------|------------------------------------|

Reporting group description:

MT-1303 0.4 mg (oral capsules) taken from Wk 0 up to Wk 24 in MT-1303-E04 and during both double-blind and open-label periods of MT-1303-E05 or taken only from Wk 0 in MT-1303-E05 after switching from placebo then throughout the MT-1303-E05 treatment periods. (Overall Summary all Treatments)

| Reporting group values | MT-1303 0.1 mg (Safety Population) | MT-1303 0.2 mg (Safety Population) | MT-1303 0.4 mg (Safety Population) |
|--|---------------------------------------|---------------------------------------|---------------------------------------|
| Number of subjects | 123 | 123 | 121 |
| Age categorical | | | |
| 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) | 123 | 123 | 121 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 37 | 38.1 | 37.5 |
| standard deviation | ± 9.27 | ± 9.56 | ± 8.53 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 83 | 87 | 82 |
| Male | 40 | 36 | 39 |
| Baseline EDSS Score | | | |
| Expanded Disability Status Scale (EDSS) score taken during enrollment into the MT-1303-E05 study | | | |
| Units: No units | | | |
| arithmetic mean | 2.8 | 2.7 | 2.5 |
| standard deviation | ± 1.3 | ± 1.3 | ± 1.3 |

| | | | |
|--|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 367 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 367 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 252 | | |
| Male | 115 | | |
| Baseline EDSS Score | | | |
| Expanded Disability Status Scale (EDSS) score taken during enrollment into the MT-1303-E05 study | | | |
| Units: No units | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

End points

End points reporting groups

| | |
|---|------------------------------------|
| Reporting group title | MT-1303 0.1 mg (Safety Population) |
| Reporting group description: MT-1303 0.1 mg (oral capsules) taken from Wk 0 up to Wk 24 in MT-1303-E04 and during double-blind period of MT-1303-E05 or taken only from Wk 0 in MT-1303-E05 after switching from placebo and during the double-blind period of MT-1303-E05. (Overall Summary all Treatments) | |
| Reporting group title | MT-1303 0.2 mg (Safety Population) |
| Reporting group description: MT-1303 0.2 mg (oral capsules) taken from Wk 0 up to Wk 24 in MT-1303-E04 and during both double-blind and open-label periods of MT-1303-E05 or taken only from Wk 0 in MT-1303-E05 after switching from placebo then throughout the MT-1303-E05 treatment periods. (Overall Summary all Treatments) | |
| Reporting group title | MT-1303 0.4 mg (Safety Population) |
| Reporting group description: MT-1303 0.4 mg (oral capsules) taken from Wk 0 up to Wk 24 in MT-1303-E04 and during both double-blind and open-label periods of MT-1303-E05 or taken only from Wk 0 in MT-1303-E05 after switching from placebo then throughout the MT-1303-E05 treatment periods. (Overall Summary all Treatments) | |
| Reporting group title | MT-1303 0.2 mg (Safety Population) |
| Reporting group description: MT-1303 0.2 mg (oral capsules) taken from Wk 0 up to Wk 24 in MT-1303-E04 and during both double-blind and open-label periods of MT-1303-E05 or taken only from Wk 0 in MT-1303-E05 after switching from placebo then throughout the MT-1303-E05 treatment periods or taken only from start of open-label period in MT-1303-E05 after switching from MT-1303 0.1 mg then throughout the MT-1303-E05 open label treatment period. (Overall Summary all Treatments) | |
| Reporting group title | MT-1303 0.4 mg (Safety Population) |
| Reporting group description: MT-1303 0.4 mg (oral capsules) taken from Wk 0 up to Wk 24 in MT-1303-E04 and during both double-blind and open-label periods of MT-1303-E05 or taken only from Wk 0 in MT-1303-E05 after switching from placebo then throughout the MT-1303-E05 treatment periods or taken only from start of open-label period in MT-1303-E05 after switching from MT-1303 0.1 mg then throughout the MT-1303-E05 open label treatment period. (Overall Summary all Treatments) | |
| Reporting group title | MT-1303 0.1 mg (Safety Population) |
| Reporting group description: MT-1303 0.1 mg (oral capsules) taken from Wk 0 up to Wk 24 in MT-1303-E04 and during double-blind period of MT-1303-E05 or taken only from Wk 0 in MT-1303-E05 after switching from placebo and during the double-blind period of MT-1303-E05. (Overall Summary all Treatments) | |
| Reporting group title | MT-1303 0.2 mg (Safety Population) |
| Reporting group description: MT-1303 0.2 mg (oral capsules) taken from Wk 0 up to Wk 24 in MT-1303-E04 and during both double-blind and open-label periods of MT-1303-E05 or taken only from Wk 0 in MT-1303-E05 after switching from placebo then throughout the MT-1303-E05 treatment periods. (Overall Summary all Treatments) | |
| Reporting group title | MT-1303 0.4 mg (Safety Population) |
| Reporting group description: MT-1303 0.4 mg (oral capsules) taken from Wk 0 up to Wk 24 in MT-1303-E04 and during both double-blind and open-label periods of MT-1303-E05 or taken only from Wk 0 in MT-1303-E05 after switching from placebo then throughout the MT-1303-E05 treatment periods. (Overall Summary all Treatments) | |

Primary: Not Applicable - none reported as safety is primary endpoint

| | |
|-----------------|---|
| End point title | Not Applicable - none reported as safety is primary endpoint ^[1] |
|-----------------|---|

End point description:

No primary endpoints were defined for efficacy or PD variables. Safety was the only primary endpoint.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Not applicable

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There was no formal statistical analysis performed as safety was the primary endpoint

| End point values | MT-1303 0.1 mg (Safety Population) | MT-1303 0.2 mg (Safety Population) | MT-1303 0.4 mg (Safety Population) | MT-1303 0.2 mg (Safety Population) |
|-----------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[2] | 0 ^[3] | 0 ^[4] | 0 ^[5] |
| Units: n/a | | | | |

Notes:

[2] - There are no pre-defined study endpoints. Safety was the only parameter measured

[3] - There are no pre-defined study endpoints. Safety was the only parameter measured

[4] - There are no pre-defined study endpoints. Safety was the only parameter measured

[5] - There are no pre-defined study endpoints. Safety was the only parameter measured

| End point values | MT-1303 0.4 mg (Safety Population) | | | |
|-----------------------------|------------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[6] | | | |
| Units: n/a | | | | |

Notes:

[6] - There are no pre-defined study endpoints. Safety was the only parameter measured

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were considered to be treatment-emergent if they started or worsened on or after the first dose of MT-1303-E04 or MT-1303-E05 study medication.

Adverse event reporting additional description:

For summaries by treatment period (E04 study period, E05 study periods, overall), data for AEs were assigned to the treatment period (and therefore study treatment) they started in each period. Subjects were carefully monitored by the Investigator for AEs, including regular questioning of the subject, although no leading questions were asked.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 17 |

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | MT-1303 0.2 mg only (Selected Treatment Sequences) |
|-----------------------|--|

Reporting group description:

MT-1303 0.2 mg (oral capsules) taken from Wk 0 in MT-1303-E04 study and throughout both treatment periods of MT-1303-E05 (Overall for Selected Treatment Sequences)

| | |
|-----------------------|--|
| Reporting group title | MT-1303 0.4 mg only (Selected Treatment Sequences) |
|-----------------------|--|

Reporting group description:

MT-1303 0.4 mg (oral capsules) taken from Wk 0 in MT-1303-E04 study and throughout both treatment periods of MT-1303-E05 (Overall for Selected Treatment Sequences)

| | |
|-----------------------|--|
| Reporting group title | Placebo to MT-1303 0.2 mg (Selected Treatment Sequences) |
|-----------------------|--|

Reporting group description:

MT-1303 0.2 mg (oral capsules) taken throughout both treatment periods in MT-1303-E05 after switching from Placebo administered during the complete treatment period of MT-1303-E04 (Overall for Selected Treatment Sequences)

| | |
|-----------------------|--|
| Reporting group title | Placebo to MT-1303 0.4 mg (Selected Treatment Sequences) |
|-----------------------|--|

Reporting group description:

MT-1303 0.4 mg (oral capsules) taken throughout both treatment periods in MT-1303-E05 after switching from Placebo administered during the complete treatment period of MT-1303-E04 (Overall for Selected Treatment Sequences)

| Serious adverse events | MT-1303 0.2 mg only (Selected Treatment Sequences) | MT-1303 0.4 mg only (Selected Treatment Sequences) | Placebo to MT-1303 0.2 mg (Selected Treatment Sequences) |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 21 / 90 (23.33%) | 11 / 92 (11.96%) | 9 / 33 (27.27%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Uterine leiomyoma | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 90 (0.00%) | 1 / 92 (1.09%) | 0 / 33 (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 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 90 (3.33%) | 0 / 92 (0.00%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 90 (2.22%) | 0 / 92 (0.00%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 1 / 90 (1.11%) | 0 / 92 (0.00%) | 0 / 33 (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 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 1 / 92 (1.09%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Exposure via father | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 92 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fibula fracture | | | |
| subjects affected / exposed | 1 / 90 (1.11%) | 0 / 92 (0.00%) | 0 / 33 (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 |
| Joint injury | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 1 / 92 (1.09%) | 0 / 33 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 92 (0.00%) | 0 / 33 (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 |
| Upper limb fracture | | | |
| subjects affected / exposed | 1 / 90 (1.11%) | 0 / 92 (0.00%) | 0 / 33 (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 |
| Wrist fracture | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 1 / 92 (1.09%) | 0 / 33 (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 |
| Surgical and medical procedures | | | |
| Finger amputation | | | |
| subjects affected / exposed | 1 / 90 (1.11%) | 0 / 92 (0.00%) | 0 / 33 (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 |
| Hysterectomy | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 1 / 92 (1.09%) | 0 / 33 (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 |
| Mammoplasty | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 92 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Grand mal convulsion | | | |
| subjects affected / exposed | 1 / 90 (1.11%) | 0 / 92 (0.00%) | 0 / 33 (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 |
| Lumbar radiculopathy | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 1 / 92 (1.09%) | 0 / 33 (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 relapse | | | |
| subjects affected / exposed | 11 / 90 (12.22%) | 3 / 92 (3.26%) | 6 / 33 (18.18%) |
| occurrences causally related to treatment / all | 0 / 15 | 0 / 3 | 0 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radiculitis lumbosacral | | | |
| subjects affected / exposed | 1 / 90 (1.11%) | 0 / 92 (0.00%) | 0 / 33 (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 |
| Gastrointestinal disorders | | | |
| Enteritis | | | |
| subjects affected / exposed | 1 / 90 (1.11%) | 0 / 92 (0.00%) | 0 / 33 (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 |
| Reproductive system and breast disorders | | | |
| Cervical dysplasia | | | |
| subjects affected / exposed | 1 / 90 (1.11%) | 0 / 92 (0.00%) | 0 / 33 (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 |
| Ovarian cyst | | | |
| subjects affected / exposed | 1 / 90 (1.11%) | 1 / 92 (1.09%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine enlargement | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 1 / 92 (1.09%) | 0 / 33 (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 |
| Psychiatric disorders | | | |
| Alcohol abuse | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 92 (0.00%) | 0 / 33 (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 |
| Confusional state | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 92 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mood disorder due to a general medical condition | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 92 (0.00%) | 0 / 33 (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 |
| Renal and urinary disorders | | | |
| Calculus ureteric | | | |
| subjects affected / exposed | 2 / 90 (2.22%) | 0 / 92 (0.00%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 92 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 92 (0.00%) | 1 / 33 (3.03%) |
| 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 osteoarthritis | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 92 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Campylobacter gastroenteritis | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 1 / 92 (1.09%) | 0 / 33 (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 infection | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 90 (0.00%) | 1 / 92 (1.09%) | 0 / 33 (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 |

| | | | |
|---|---|--|--|
| Serious adverse events | Placebo to MT-1303 0.4 mg (Selected Treatment Sequences) | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 28 (25.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|----------------|--|--|
| Exposure via father | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fibula fracture | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Joint injury | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Meniscus injury | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wrist fracture | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Finger amputation | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hysterectomy | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mammoplasty | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Grand mal convulsion | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lumbar radiculopathy | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 5 / 28 (17.86%) | | |
| occurrences causally related to treatment / all | 0 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Radiculitis lumbosacral | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Enteritis | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Cervical dysplasia | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|----------------|--|--|
| Uterine enlargement | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Alcohol abuse | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mood disorder due to a general medical condition | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Calculus ureteric | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal osteoarthritis | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Campylobacter gastroenteritis | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | MT-1303 0.2 mg only (Selected Treatment Sequences) | MT-1303 0.4 mg only (Selected Treatment Sequences) | Placebo to MT-1303 0.2 mg (Selected Treatment Sequences) |
|--|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 71 / 90 (78.89%) | 75 / 92 (81.52%) | 30 / 33 (90.91%) |
| Investigations | | | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 15 / 90 (16.67%) | 24 / 92 (26.09%) | 6 / 33 (18.18%) |
| occurrences (all) | 16 | 26 | 7 |
| Gamma glutamyltransferase increased | | | |
| subjects affected / exposed | 8 / 90 (8.89%) | 6 / 92 (6.52%) | 2 / 33 (6.06%) |
| occurrences (all) | 9 | 6 | 2 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 4 / 90 (4.44%) | 6 / 92 (6.52%) | 2 / 33 (6.06%) |
| occurrences (all) | 4 | 6 | 2 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 90 (2.22%) | 3 / 92 (3.26%) | 2 / 33 (6.06%) |
| occurrences (all) | 2 | 3 | 2 |
| Blood creatine phosphokinase increased | | | |

| | | | |
|--|------------------------|------------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 1 / 90 (1.11%) 1 | 1 / 92 (1.09%) 3 | 0 / 33 (0.00%) 0 |
| Blood triglycerides increased subjects affected / exposed occurrences (all) | 3 / 90 (3.33%) 3 | 1 / 92 (1.09%) 1 | 1 / 33 (3.03%) 1 |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 4 / 90 (4.44%) 4 | 2 / 92 (2.17%) 3 | 1 / 33 (3.03%) 1 |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 1 / 90 (1.11%) 1 | 4 / 92 (4.35%) 5 | 3 / 33 (9.09%) 5 |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 5 / 90 (5.56%) 5 | 2 / 92 (2.17%) 2 | 1 / 33 (3.03%) 1 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 18 / 90 (20.00%) 40 | 15 / 92 (16.30%) 91 | 5 / 33 (15.15%) 12 |
| Multiple sclerosis relapse subjects affected / exposed occurrences (all) | 4 / 90 (4.44%) 6 | 3 / 92 (3.26%) 3 | 2 / 33 (6.06%) 2 |
| Dizziness subjects affected / exposed occurrences (all) | 4 / 90 (4.44%) 10 | 6 / 92 (6.52%) 7 | 4 / 33 (12.12%) 4 |
| Paraesthesia subjects affected / exposed occurrences (all) | 2 / 90 (2.22%) 2 | 7 / 92 (7.61%) 7 | 2 / 33 (6.06%) 2 |
| Sciatica subjects affected / exposed occurrences (all) | 0 / 90 (0.00%) 0 | 2 / 92 (2.17%) 2 | 2 / 33 (6.06%) 2 |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) | 4 / 90 (4.44%) 6 | 2 / 92 (2.17%) 2 | 1 / 33 (3.03%) 1 |
| Pain | | | |

| | | | |
|---|---------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 90 (1.11%) 1 | 1 / 92 (1.09%) 2 | 2 / 33 (6.06%) 2 |
| Pyrexia subjects affected / exposed occurrences (all) | 2 / 90 (2.22%) 2 | 5 / 92 (5.43%) 6 | 0 / 33 (0.00%) 0 |
| Blood and lymphatic system disorders Iron deficiency anaemia subjects affected / exposed occurrences (all) | 1 / 90 (1.11%) 1 | 0 / 92 (0.00%) 0 | 2 / 33 (6.06%) 2 |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 4 / 90 (4.44%) 5 | 7 / 92 (7.61%) 11 | 1 / 33 (3.03%) 1 |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 90 (0.00%) 0 | 5 / 92 (5.43%) 6 | 3 / 33 (9.09%) 5 |
| Nausea subjects affected / exposed occurrences (all) | 5 / 90 (5.56%) 5 | 3 / 92 (3.26%) 3 | 1 / 33 (3.03%) 3 |
| Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all) | 4 / 90 (4.44%) 6 | 9 / 92 (9.78%) 15 | 1 / 33 (3.03%) 1 |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 8 / 90 (8.89%) 8 | 1 / 92 (1.09%) 1 | 2 / 33 (6.06%) 3 |
| Arthralgia subjects affected / exposed occurrences (all) | 4 / 90 (4.44%) 4 | 5 / 92 (5.43%) 9 | 3 / 33 (9.09%) 3 |
| Intervertebral disc protrusion subjects affected / exposed occurrences (all) | 0 / 90 (0.00%) 0 | 0 / 92 (0.00%) 0 | 2 / 33 (6.06%) 4 |
| Neck pain subjects affected / exposed occurrences (all) | 2 / 90 (2.22%) 2 | 0 / 92 (0.00%) 0 | 0 / 33 (0.00%) 0 |

| | | | |
|---|------------------------|------------------------|-----------------------|
| Pain in extremity subjects affected / exposed occurrences (all) | 5 / 90 (5.56%) 6 | 1 / 92 (1.09%) 4 | 0 / 33 (0.00%) 0 |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 14 / 90 (15.56%) 18 | 13 / 92 (14.13%) 16 | 5 / 33 (15.15%) 10 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 8 / 90 (8.89%) 14 | 9 / 92 (9.78%) 13 | 6 / 33 (18.18%) 8 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 4 / 90 (4.44%) 8 | 5 / 92 (5.43%) 6 | 4 / 33 (12.12%) 9 |
| Influenza subjects affected / exposed occurrences (all) | 6 / 90 (6.67%) 12 | 10 / 92 (10.87%) 12 | 1 / 33 (3.03%) 1 |
| Bronchitis subjects affected / exposed occurrences (all) | 4 / 90 (4.44%) 4 | 1 / 92 (1.09%) 1 | 2 / 33 (6.06%) 2 |
| Cystitis subjects affected / exposed occurrences (all) | 5 / 90 (5.56%) 8 | 2 / 92 (2.17%) 3 | 2 / 33 (6.06%) 2 |
| Gastroenteritis subjects affected / exposed occurrences (all) | 6 / 90 (6.67%) 6 | 2 / 92 (2.17%) 2 | 2 / 33 (6.06%) 2 |
| Oral herpes subjects affected / exposed occurrences (all) | 2 / 90 (2.22%) 5 | 5 / 92 (5.43%) 10 | 0 / 33 (0.00%) 0 |
| Sinusitis subjects affected / exposed occurrences (all) | 1 / 90 (1.11%) 1 | 5 / 92 (5.43%) 8 | 0 / 33 (0.00%) 0 |
| Tonsillitis subjects affected / exposed occurrences (all) | 1 / 90 (1.11%) 1 | 2 / 92 (2.17%) 3 | 2 / 33 (6.06%) 2 |
| Viral upper respiratory tract infection | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 90 (0.00%) | 6 / 92 (6.52%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 7 | 1 |

| | | | |
|--|---|--|--|
| Non-serious adverse events | Placebo to MT-1303 0.4 mg (Selected Treatment Sequences) | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 22 / 28 (78.57%) | | |
| Investigations | | | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences (all) | 1 | | |
| Gamma glutamyltransferase increased | | | |
| subjects affected / exposed | 2 / 28 (7.14%) | | |
| occurrences (all) | 3 | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 28 (10.71%) | | |
| occurrences (all) | 4 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 3 / 28 (10.71%) | | |
| occurrences (all) | 4 | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 2 / 28 (7.14%) | | |
| occurrences (all) | 2 | | |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 2 / 28 (7.14%) | | |
| occurrences (all) | 2 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 2 / 28 (7.14%) | | |
| occurrences (all) | 2 | | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vascular disorders | | | |
| Hypertension | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 2 / 28 (7.14%) | | |
| occurrences (all) | 2 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 3 / 28 (10.71%) | | |
| occurrences (all) | 4 | | |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences (all) | 2 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences (all) | 1 | | |
| Sciatica | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 28 (7.14%) | | |
| occurrences (all) | 3 | | |
| Pain | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences (all) | 1 | | |
| Blood and lymphatic system disorders | | | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences (all) | 1 | | |

| | | | |
|---|---------------------|--|--|
| Vomiting subjects affected / exposed occurrences (all) | 0 / 28 (0.00%) 0 | | |
| Nausea subjects affected / exposed occurrences (all) | 1 / 28 (3.57%) 1 | | |
| Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all) | 0 / 28 (0.00%) 0 | | |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 1 / 28 (3.57%) 2 | | |
| Arthralgia subjects affected / exposed occurrences (all) | 1 / 28 (3.57%) 1 | | |
| Intervertebral disc protrusion subjects affected / exposed occurrences (all) | 0 / 28 (0.00%) 0 | | |
| Neck pain subjects affected / exposed occurrences (all) | 2 / 28 (7.14%) 2 | | |
| Pain in extremity subjects affected / exposed occurrences (all) | 2 / 28 (7.14%) 3 | | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 28 (7.14%) 2 | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 2 / 28 (7.14%) 3 | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 28 (7.14%) 3 | | |

| | | | |
|---|----------------|--|--|
| Influenza | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences (all) | 2 | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cystitis | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences (all) | 1 | | |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | | |
| occurrences (all) | 2 | | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences (all) | 0 | | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | | |
| occurrences (all) | 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|---|
| 12 August 2013 | Inclusion of two additional safety monitoring visits, between Visit 1 (Week 0) and Visit 2 (Week 12) to ensure consistent review of safety parameters for all patients in transit from the MT-1303-E04 study to the MT-1303-E05 study. Visit 1a and 1b at Week 4 and Week 8 respectively. |
| 24 March 2015 | In light of the increasing evidence from recent research for other disease-modifying therapies (DMTs) in MS, an amendment was made to allow patients to receive DMT during the Safety Follow-up Period if this was considered appropriate. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported