Clinical trial results:
A phase II, multicentre, randomised, double-blind, parallel group, placebo-controlled, dose-finding study to evaluate the safety and efficacy of three different oral doses of MT-1303 administered for a period of 24 weeks in subjects with relapsing remitting multiple sclerosis

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2012-002470-31
Trial protocol	GB LT CZ HU FI BE IT PL BG ES
Global end of trial date	23 October 2014

Results information

Result version number	v1 (current)
This version publication date	27 July 2016
First version publication date	27 July 2016

Trial information

Trial identification

Sponsor protocol code	MT-1303-E04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01742052
WHO universal trial number (UTN)	-
Other trial identifiers	Momentum Study: MT-1303-E04

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	17 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2014
Global end of trial reached?	Yes
Global end of trial date	23 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial is to evaluate the effects of three oral doses of MT-1303 compared to placebo given for a period of 24 weeks in subjects with relapsing-remitting multiple sclerosis (RRMS) on MRI parameters. It is also to evaluate the safety and tolerability of three oral doses of MT-1303 compared to placebo given for a period of 24 weeks in subjects with RRMS.

Protection of trial subjects:

Subjects will be permanently withdrawn from study medication in the following circumstances:
• Confirmed absolute lymphocyte count values <200/µL, 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 >500msec and/or QTcF interval increase from baseline >60msec
• Development of any clinically significant liver dysfunction as follows:
  o ALT or AST > 8 × ULN, or
  o ALT or AST >5 × ULN and persists for more than 2 consecutive visits, or
  o ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or
  o ALT or AST >3 × 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
• Interruption to study medication lasting more than 14 days.

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
• 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: -

Evidence for comparator: -

Actual start date of recruitment	31 January 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	Poland: 84
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Bulgaria: 64
Country: Number of subjects enrolled	Czech Republic: 59
Country: Number of subjects enrolled	Finland: 7
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Hungary: 22
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Lithuania: 4
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Croatia: 3
Country: Number of subjects enrolled	Russian Federation: 25
Country: Number of subjects enrolled	Serbia: 30
Country: Number of subjects enrolled	Turkey: 21
Country: Number of subjects enrolled	Ukraine: 30
Worldwide total number of subjects	415
EEA total number of subjects	304

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)	415
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

415 subjects randomised across 84 sites in 17 countries (BEL, BUL, CAN, HRZ, CZE, FIN, GER, HUN, ITA, LIT, POL, RUS, SER, ESP, TUR, UKR, GBR). FSFV (screen) 31 Jan 13, LSI (screen) 24 Dec 13. FSFV (randomised) 01 Mar 13. LSI (randomised) 15 Feb 14. Conducted in university/public/private hospitals and specialised multiple sclerosis care practices.

Pre-assignment

Screening details:

Up to 6 week screening period

Period 1

Period 1 title	Overall trial (overall 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:

Lymphotcyte count and WBC differential were not provided to any site/study personel except the Unblinded Independent Monitor to maintain the study medication blind. PK results were not provided by the PK lab until after database lock.
MT-1303/placebo capsules appeared the same and same number of capsules were given.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Once daily oral placebo capsules taken from Baseline Week 0 to End of Treatment

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:

1 capsule, containing placebo taken orally daily for 24 weeks.

Arm title	MT-1303 0.1 mg

Arm description:

Once daily oral MT-1303 0.1mg capsules taken from Baseline Week 0 to End of Treatment

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 24 weeks.

Arm title	MT-1303 0.2mg

Arm description:

Once daily oral MT-1303 0.2mg capsules taken from Baseline Week 0 to End of Treatment

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 24 weeks.

Arm title	MT-1303 0.4mg

Arm description:

Once daily oral MT-1303 0.4mg capsules taken from Baseline Week 0 to End of Treatment

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 24 weeks.

Number of subjects in period 1	Placebo	MT-1303 0.1 mg	MT-1303 0.2mg
Started	103	105	103
Completed	96	96	95
Not completed	7	9	8
Consent withdrawn by subject	1	4	4
Adverse event, non-fatal	2	2	1
Other	1	1	1
Protocol Specified	3	2	2

Number of subjects in period 1	MT-1303 0.4mg
Started	104
Completed	94
Not completed	10
Consent withdrawn by subject	2
Adverse event, non-fatal	4
Other	1
Protocol Specified	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Once daily oral placebo capsules taken from Baseline Week 0 to End of Treatment	
Reporting group title	MT-1303 0.1 mg
Reporting group description:	
Once daily oral MT-1303 0.1mg capsules taken from Baseline Week 0 to End of Treatment	
Reporting group title	MT-1303 0.2mg
Reporting group description:	
Once daily oral MT-1303 0.2mg capsules taken from Baseline Week 0 to End of Treatment	
Reporting group title	MT-1303 0.4mg
Reporting group description:	
Once daily oral MT-1303 0.4mg capsules taken from Baseline Week 0 to End of Treatment	

Reporting group values	Placebo	MT-1303 0.1 mg	MT-1303 0.2mg
Number of subjects	103	105	103
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)	103	105	103
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	37.2	37.2	38
standard deviation	± 8.54	± 9.42	± 9.61
Gender categorical Units: Subjects			
Female	67	69	73
Male	36	36	30
Baseline EDSS Score			
Expanded Disability Status Scale (EDSS) score taken during screening			
Units: No Unit			
arithmetic mean	2.7	2.88	2.77
standard deviation	± 1.309	± 1.296	± 1.272

Reporting group values	MT-1303 0.4mg	Total	
Number of subjects	104	415	

Age categorical 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)	104	415	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	37.6		
standard deviation	± 8.66	-	
Gender categorical Units: Subjects			
Female	72	281	
Male	32	134	
Baseline EDSS Score			
Expanded Disability Status Scale (EDSS) score taken during screening			
Units: No Unit			
arithmetic mean	2.61		
standard deviation	± 1.338	-	

Subject analysis sets

Subject analysis set title	Evaluable Population-placebo
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects that received at least one dose of study medication (Placebo) who do not have any major protocol deviations, do not discontinue study medication prematurely and have at least 3 valid post-dose MRI scans

Subject analysis set title	Evaluable Population-0.1 mg
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects that received at least one dose of study medication (MT-1303 0.1mg) who do not have any major protocol deviations, do not discontinue study medication prematurely and have at least 3 valid post-dose MRI scans

Subject analysis set title	Evaluable Population-0.2 mg
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects that received at least one dose of study medication (MT-1303 0.2mg) who do not have any major protocol deviations, do not discontinue study medication prematurely and have at least 3 valid post-dose MRI scans

Subject analysis set title	Evaluable Population-0.4 mg
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects that received at least one dose of study medication (MT-1303 0.4mg) who do not have any major protocol deviations, do not discontinue study medication prematurely and have at least 3 valid post-dose MRI scans

Subject analysis set title	ITT-placebo

Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised subjects who
received at least one dose of study medication (placebo) and have at least one post-dose efficacy assessment. Subjects will be analyzed according to treatment assignment regardless of whether the subject receives any study treatment or the wrong treatment.

Subject analysis set title	ITT-0.1 mg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised subjects who received at least one dose of study medication (MT-1303 0.1mg) and have at least one post-dose efficacy assessment. Subjects will be analyzed according to treatment assignment regardless of whether the subject receives any study treatment or the wrong treatment.

Subject analysis set title	ITT-0.2 mg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised subjects who received at least one dose of study medication (MT-1303 0.2mg) and have at least one post-dose efficacy assessment. Subjects will be analyzed according to treatment assignment regardless of whether the subject receives any study treatment or the wrong treatment.

Subject analysis set title	ITT-0.4 mg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised subjects who received at least one dose of study medication (MT-1303 0.4mg) and have at least one post-dose efficacy assessment. Subjects will be analyzed according to treatment assignment regardless of whether the subject receives any study treatment or the wrong treatment.

Reporting group values	Evaluable Population-placebo	Evaluable Population-0.1 mg	Evaluable Population-0.2 mg
Number of subjects	94	95	94
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)	94	95	94
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	37.6	37.3	38.2
standard deviation	± 8.52	± 9.66	± 9.81
Gender categorical Units: Subjects			
Female	62	67	65
Male	32	28	29
Baseline EDSS Score			
Expanded Disability Status Scale (EDSS) score taken during screening			
Units: No Unit			
arithmetic mean	2.68	2.85	2.74
standard deviation	± 1.287	± 1.303	± 1.315

Reporting group values	Evaluable Population-0.4 mg	ITT-placebo	ITT-0.1 mg
Number of subjects	94	103	105
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)	94	103	105
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	37.3	37.2	37.2
standard deviation	± 8.53	± 8.54	± 9.42
Gender categorical			
Units: Subjects			
Female	64	67	69
Male	30	36	36
Baseline EDSS Score			
Expanded Disability Status Scale (EDSS) score taken during screening			
Units: No Unit			
arithmetic mean	2.52	2.7	2.88
standard deviation	± 1.29	± 1.309	± 1.296

Reporting group values	ITT-0.2 mg	ITT-0.4 mg	
Number of subjects	103	104	
Age categorical			
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)	103	104	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	38	37.6	
standard deviation	± 9.61	± 8.66	
Gender categorical			
Units: Subjects			
Female	73	72	
Male	30	32	

Baseline EDSS Score			
Expanded Disability Status Scale (EDSS) score taken during screening			
Units: No Unit			
arithmetic mean	2.77	2.61	
standard deviation	± 1.272	± 1.338	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Once daily oral placebo capsules taken from Baseline Week 0 to End of Treatment	
Reporting group title	MT-1303 0.1 mg
Reporting group description:	
Once daily oral MT-1303 0.1mg capsules taken from Baseline Week 0 to End of Treatment	
Reporting group title	MT-1303 0.2mg
Reporting group description:	
Once daily oral MT-1303 0.2mg capsules taken from Baseline Week 0 to End of Treatment	
Reporting group title	MT-1303 0.4mg
Reporting group description:	
Once daily oral MT-1303 0.4mg capsules taken from Baseline Week 0 to End of Treatment	
Subject analysis set title	Evaluable Population-placebo
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects that received at least one dose of study medication (Placebo) who do not have any major protocol deviations, do not discontinue study medication prematurely and have at least 3 valid post-dose MRI scans	
Subject analysis set title	Evaluable Population-0.1 mg
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects that received at least one dose of study medication (MT-1303 0.1mg) who do not have any major protocol deviations, do not discontinue study medication prematurely and have at least 3 valid post-dose MRI scans	
Subject analysis set title	Evaluable Population-0.2 mg
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects that received at least one dose of study medication (MT-1303 0.2mg) who do not have any major protocol deviations, do not discontinue study medication prematurely and have at least 3 valid post-dose MRI scans	
Subject analysis set title	Evaluable Population-0.4 mg
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects that received at least one dose of study medication (MT-1303 0.4mg) who do not have any major protocol deviations, do not discontinue study medication prematurely and have at least 3 valid post-dose MRI scans	
Subject analysis set title	ITT-placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomised subjects who received at least one dose of study medication (placebo) and have at least one post-dose efficacy assessment. Subjects will be analyzed according to treatment assignment regardless of whether the subject receives any study treatment or the wrong treatment.	
Subject analysis set title	ITT-0.1 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomised subjects who received at least one dose of study medication (MT-1303 0.1mg) and have at least one post-dose efficacy assessment. Subjects will be analyzed according to treatment assignment regardless of whether the subject receives any study treatment or the wrong treatment.	
Subject analysis set title	ITT-0.2 mg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised subjects who received at least one dose of study medication (MT-1303 0.2mg) and have at least one post-dose efficacy assessment. Subjects will be analyzed according to treatment assignment regardless of whether the subject receives any study treatment or the wrong treatment.

Subject analysis set title	ITT-0.4 mg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised subjects who received at least one dose of study medication (MT-1303 0.4mg) and have at least one post-dose efficacy assessment. Subjects will be analyzed according to treatment assignment regardless of whether the subject receives any study treatment or the wrong treatment.

Primary: Total Number of Gd-Enhanced T1-weighted Lesions across Weeks 8-24

End point title	Total Number of Gd-Enhanced T1-weighted Lesions across Weeks 8-24

End point description:

This endpoint is regarded as a countable end point however in order to present the summary statistics in the database it has been entered as a measurable endpoint. The measure type should be Incidence Rate and the point estimate parameter type should be Incidence Rate Ratio however the database does not allow these options.

End point type	Primary

End point timeframe:

Week 8 - Week 24

End point values	Evaluable Population-placebo	Evaluable Population-0.1 mg	Evaluable Population-0.2 mg	Evaluable Population-0.4 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	94	95	94	94
Units: number of lesions				
least squares mean (confidence interval 95%)	5.04 (3.6 to 7)	2.69 (1.9 to 3.7)	1.97 (1.4 to 2.8)	1.16 (0.8 to 1.7)

Statistical analyses

Statistical analysis title	No. T1-weighted lesions 8-24 wks 0.1mg vs placebo

Statistical analysis description:

"P-values based on Negative Binomial model using log link with total (cumulative) Gd-enhanced T1-weighted lesions over Wks 8 -24 as the response variable. The independent variables are baseline number of Gd-enhanced T1-weighted lesions, treatment and pooled centre.

Comparison groups	Evaluable Population-placebo v Evaluable Population-0.1 mg
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Negative Binomial Regression
Parameter estimate	Incidence rate ratio
Point estimate	0.53

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.8

Statistical analysis title	No. T1-weighted lesions 8-24 wks 0.2mg vs placebo

Statistical analysis description:

"P-values based on Negative Binomial model using log link with total (cumulative) Gd-enhanced T1-weighted lesions over Wks 8 -24 as the response variable. The independent variables are baseline number of Gd-enhanced T1-weighted lesions, treatment and pooled centre.

Comparison groups	Evaluable Population-placebo v Evaluable Population-0.2 mg
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Negative Binomial Regression
Parameter estimate	Incidence rate ratio
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.6

Statistical analysis title	No. T1-weighted lesions 8-24 wks 0.4mg vs placebo

Statistical analysis description:

"P-values based on Negative Binomial model using log link with total (cumulative) Gd-enhanced T1-weighted lesions over Wks 8 -24 as the response variable. The independent variables are baseline number of Gd-enhanced T1-weighted lesions, treatment and pooled centre.

Comparison groups	Evaluable Population-placebo v Evaluable Population-0.4 mg
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Negative Binomial Regression
Parameter estimate	Incidence rate ratio
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.4

Secondary: Total Numbers of Gd-Enhanced T1-weighted Lesions across Weeks 4-24

End point title	Total Numbers of Gd-Enhanced T1-weighted Lesions across Weeks 4-24

End point description:

This endpoint is regarded as a countable end point however in order to present the summary statistics in the database it has been entered as a measurable endpoint. The measure type should be Incidence Rate and the point estimate parameter type should be Incidence Rate Ratio however the database does not allow these options.

End point type	Secondary

End point timeframe:

Weeks 4 - 24

End point values	Evaluable Population-placebo	Evaluable Population-0.1 mg	Evaluable Population-0.2 mg	Evaluable Population-0.4 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	94	95	94	94
Units: number of lesions				
least squares mean (confidence interval 95%)	5.8 (4.2 to 8)	3.54 (2.6 to 4.9)	3.28 (2.4 to 4.6)	1.93 (1.4 to 2.7)

Statistical analyses

Statistical analysis title	No. T1-weighted lesions 4-24 wks 0.1mg vs placebo

Statistical analysis description:

"P-values are based on a Negative Binomial model using log link with total (cumulative) Gd-enhanced T1-weighted lesions over weeks 4, 8, 12, 16, 20, and 24 as the response variable. The independent variables are baseline number of Gd-enhanced T1-weighted lesions, treatment and pooled centre

Comparison groups	Evaluable Population-placebo v Evaluable Population-0.1 mg
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	Negative Binomial Regression
Parameter estimate	Incidence rate ratio
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1

Statistical analysis title	No. T1-weighted lesions 4-24 wks 0.2mg vs placebo

Statistical analysis description:

"P-values are based on a Negative Binomial model using log link with total (cumulative) Gd-enhanced T1-weighted lesions over weeks 4, 8, 12, 16, 20, and 24 as the response variable. The independent variables are baseline number of Gd-enhanced T1-weighted lesions, treatment and pooled centre

Comparison groups	Evaluable Population-placebo v Evaluable Population-0.2 mg

Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018
Method	Negative Binomial Regression
Parameter estimate	Incidence rate ratio
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.9

Statistical analysis title	No. T1-weighted lesions 4-24 wks 0.4mg vs placebo

Statistical analysis description:

"P-values are based on a Negative Binomial model using log link with total (cumulative) Gd-enhanced T1-weighted lesions over weeks 4, 8, 12, 16, 20, and 24 as the response variable. The independent variables are baseline number of Gd-enhanced T1-weighted lesions, treatment and pooled centre

Comparison groups	Evaluable Population-placebo v Evaluable Population-0.4 mg
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Negative Binomial Regression
Parameter estimate	Incidence rate ratio
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.5

Secondary: Total Number of New or Enlarged T2-weighted Lesions across Weeks 4-24

End point title	Total Number of New or Enlarged T2-weighted Lesions across Weeks 4-24

End point description:

This endpoint is regarded as a countable end point however in order to present the summary statistics in the database it has been entered as a measurable endpoint. The measure type should be Incidence Rate and the point estimate parameter type should be Incidence Rate Ratio however the database does not allow these options.

End point type	Secondary

End point timeframe:

Weeks 4 -24

End point values	Evaluable Population-placebo	Evaluable Population-0.1 mg	Evaluable Population-0.2 mg	Evaluable Population-0.4 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	94	95	94	94
Units: number of lesions				
least squares mean (confidence interval 95%)	10.08 (7.1 to 14.3)	7.62 (5.3 to 10.9)	4.57 (3.2 to 6.5)	3.13 (2.2 to 4.5)

Statistical analyses

Statistical analysis title	No. T2-weighted lesions 4-24 wks 0.1mg vs placebo

Statistical analysis description:

"Total number of new or enlarged T2 weighted lesions across weeks 4-24 versus placebo. P-values are based on a Negative Binomial model using log link with total (cumulative) number of new or enlarged T2-weighted lesions over weeks 4, 8, 12, 16, 20, and 24 as the response variable. The independent variables are treatment and pooled centre.

Comparison groups	Evaluable Population-placebo v Evaluable Population-0.1 mg
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.272
Method	Negative Binomial Regression
Parameter estimate	Incidence rate ratio
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.2

Statistical analysis title	No. T2-weighted lesions 4-24 wks 0.2mg vs placebo

Statistical analysis description:

"Total number of new or enlarged T2 weighted lesions across weeks 4-24 versus placebo. P-values are based on a Negative Binomial model using log link with total (cumulative) number of new or enlarged T2-weighted lesions over weeks 4, 8, 12, 16, 20, and 24 as the response variable. The independent variables are treatment and pooled centre.

Comparison groups	Evaluable Population-placebo v Evaluable Population-0.2 mg
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Negative Binomial Regression
Parameter estimate	Incidence rate ratio
Point estimate	0.45

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.7

Statistical analysis title	No. T2-weighted lesions 4-24 wks 0.4mg vs placebo

Statistical analysis description:

"Total number of new or enlarged T2 weighted lesions across weeks 4-24 versus placebo. P-values are based on a Negative Binomial model using log link with total (cumulative) number of new or enlarged T2-weighted lesions over weeks 4, 8, 12, 16, 20, and 24 as the response variable. The independent variables are treatment and pooled centre.

Comparison groups	Evaluable Population-placebo v Evaluable Population-0.4 mg
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Negative Binomial Regression
Parameter estimate	Incidence rate ratio
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.5

Secondary: Annualised Relapse Rate (ARR) at Week 24

End point title	Annualised Relapse Rate (ARR) at Week 24

End point description:

This endpoint is regarded as a countable end point however in order to present the summary statistics in the database it has been entered as a measurable endpoint. The measure type should be Incidence Rate and the point estimate parameter type should be Incidence Rate Ratio however the database does not allow these options.

End point type	Secondary

End point timeframe:

Week 0 - 24

End point values	ITT-placebo	ITT-0.1 mg	ITT-0.2 mg	ITT-0.4 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	103	105	103	104
Units: Relapses/year				
least squares mean (confidence interval 95%)	0.42979 (0.2104 to 0.8778)	0.35467 (0.1732 to 0.7263)	0.42316 (0.1977 to 0.9059)	0.07834 (0.0311 to 0.1975)

Statistical analyses

Statistical analysis title	Annualised Relapse Rate MT-1303 0.1mg vs placebo

Statistical analysis description:

"P-values are based on a Negative Binomial model using log link with individual annualised relapse rate as the response variable. The independent variables are number of relapses in the 12 months prior to the study, treatment and pooled centre.

Comparison groups	ITT-placebo v ITT-0.1 mg
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.706
Method	Negative Binomial Regression
Parameter estimate	Incidence rate ratio
Point estimate	0.82521
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3044
upper limit	2.2368

Statistical analysis title	Annualised Relapse Rate MT-1303 0.2mg vs placebo

Statistical analysis description:

"P-values are based on a Negative Binomial model using log link with individual annualised relapse rate as the response variable. The independent variables are number of relapses in the 12 months prior to the study, treatment and pooled centre.

Comparison groups	ITT-placebo v ITT-0.2 mg
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.977
Method	Negative Binomial Regression
Parameter estimate	Incidence rate ratio
Point estimate	0.98457
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3382
upper limit	2.866

Statistical analysis title	Annualised Relapse Rate MT-1303 0.4mg vs placebo

Statistical analysis description:

"P-values are based on a Negative Binomial model using log link with individual annualised relapse rate as the response variable. The independent variables are number of relapses in the 12 months prior to the study, treatment and pooled centre.

Comparison groups	ITT-placebo v ITT-0.4 mg
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Negative Binomial Regression
Parameter estimate	Incidence rate ratio
Point estimate	0.18227
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.0559
upper limit	0.5938

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Start of double-blind treatment to end of 12 week follow-up period. Treatment-Emergent AEs were defined as those which started or worsened in severity after the first dose of double-blind study medication.

Adverse event reporting additional description:

During the study visits regular questioning of each subject by study staff. No leading questions were asked. Data recorded under "Non-Serious Adverse Events" also includes serious adverse events as that is how data was reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Placebo

Reporting group description:

Once daily oral placebo capsules taken from Baseline Week 0 to end of treatment

Reporting group title	MT-1303 0.1mg

Reporting group description:

Once daily oral MT-1303 0.1mg capsules taken from Baseline Week 0 to end of treatment

Reporting group title	MT-1303 0.2mg

Reporting group description:

Once daily oral MT-1303 0.2mg capsules taken from Baseline Week 0 to end of treatment

Reporting group title	MT-1303 0.4mg

Reporting group description:

Once daily oral MT-1303 0.4mg capsules taken from Baseline Week 0 to end of treatment

Serious adverse events	Placebo	MT-1303 0.1mg	MT-1303 0.2mg
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 103 (9.71%)	8 / 105 (7.62%)	7 / 103 (6.80%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 103 (0.00%)	0 / 105 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			

subjects affected / exposed	0 / 103 (0.00%)	0 / 105 (0.00%)	0 / 103 (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
Injury, poisoning and procedural complications			
Joint Injury			
subjects affected / exposed	0 / 103 (0.00%)	0 / 105 (0.00%)	0 / 103 (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
Tendon Injury			
subjects affected / exposed	1 / 103 (0.97%)	0 / 105 (0.00%)	0 / 103 (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 / 103 (0.00%)	0 / 105 (0.00%)	0 / 103 (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			
Atrioventricular Block Second Degree			
subjects affected / exposed	0 / 103 (0.00%)	1 / 105 (0.95%)	0 / 103 (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
Ventricular Tachycardia			
subjects affected / exposed	0 / 103 (0.00%)	0 / 105 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Mammoplasty			
subjects affected / exposed	1 / 103 (0.97%)	0 / 105 (0.00%)	0 / 103 (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
Nervous system disorders			
Multiple Sclerosis Relapse	Additional description: Not all MS relapses are added as AEs/SAEs		

subjects affected / exposed	7 / 103 (6.80%)	5 / 105 (4.76%)	4 / 103 (3.88%)
occurrences causally related to treatment / all	0 / 7	0 / 5	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Macular oedema			
subjects affected / exposed	1 / 103 (0.97%)	0 / 105 (0.00%)	0 / 103 (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
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	0 / 103 (0.00%)	0 / 105 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Enlargement			
subjects affected / exposed	0 / 103 (0.00%)	0 / 105 (0.00%)	0 / 103 (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
Psychiatric disorders			
Confusional State			
subjects affected / exposed	1 / 103 (0.97%)	0 / 105 (0.00%)	0 / 103 (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
Neurosis			
subjects affected / exposed	0 / 103 (0.00%)	1 / 105 (0.95%)	0 / 103 (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
Renal and urinary disorders			
Cystitis Noninfective			
subjects affected / exposed	0 / 103 (0.00%)	1 / 105 (0.95%)	0 / 103 (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	MT-1303 0.4mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 104 (5.77%)		

number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Joint Injury			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tendon Injury			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wrist Fracture			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrioventricular Block Second Degree			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ventricular Tachycardia			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			

Mammoplasty			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Multiple Sclerosis Relapse	Additional description: Not all MS relapses are added as AEs/SAEs		
subjects affected / exposed	2 / 104 (1.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Macular oedema			
subjects affected / exposed	0 / 104 (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 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine Enlargement			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional State			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neurosis			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Cystitis Noninfective			

subjects affected / exposed	0 / 104 (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	Placebo	MT-1303 0.1mg	MT-1303 0.2mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 103 (64.08%)	59 / 105 (56.19%)	69 / 103 (66.99%)
Nervous system disorders			
Headache	Additional description: Number of occurrences were not reported		
subjects affected / exposed	4 / 103 (3.88%)	10 / 105 (9.52%)	10 / 103 (9.71%)
occurrences (all)	0	0	0
Multiple Sclerosis Relapse	Additional description: Number of occurrences were not reported		
subjects affected / exposed	8 / 103 (7.77%)	7 / 105 (6.67%)	4 / 103 (3.88%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea	Additional description: Number of occurrences were not reported		
subjects affected / exposed	3 / 103 (2.91%)	6 / 105 (5.71%)	0 / 103 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis	Additional description: Number of occurrences were not reported		
subjects affected / exposed	8 / 103 (7.77%)	9 / 105 (8.57%)	7 / 103 (6.80%)
occurrences (all)	0	0	0
Influenza	Additional description: Number of occurrences were not reported		
subjects affected / exposed	3 / 103 (2.91%)	1 / 105 (0.95%)	6 / 103 (5.83%)
occurrences (all)	0	0	0
Upper Respiratory Tract Infection	Additional description: Number of occurrences were not reported		
subjects affected / exposed	7 / 103 (6.80%)	3 / 105 (2.86%)	2 / 103 (1.94%)
occurrences (all)	0	0	0

Non-serious adverse events	MT-1303 0.4mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 104 (55.77%)		
Nervous system disorders			

Headache	Additional description: Number of occurrences were not reported		
subjects affected / exposed	10 / 104 (9.62%)		
occurrences (all)	0		
Multiple Sclerosis Relapse	Additional description: Number of occurrences were not reported		
subjects affected / exposed	3 / 104 (2.88%)		
occurrences (all)	0		
Gastrointestinal disorders			
Diarrhoea	Additional description: Number of occurrences were not reported		
subjects affected / exposed	4 / 104 (3.85%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis	Additional description: Number of occurrences were not reported		
subjects affected / exposed	10 / 104 (9.62%)		
occurrences (all)	0		
Influenza	Additional description: Number of occurrences were not reported		
subjects affected / exposed	4 / 104 (3.85%)		
occurrences (all)	0		
Upper Respiratory Tract Infection	Additional description: Number of occurrences were not reported		
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported