



## Clinical trial results:

### A Phase II, Multicentre, Randomised, Double-Blind, Parallel Group, Placebo Controlled Study to Evaluate Safety, Tolerability and Clinical Efficacy of MT 1303 in Subjects with Moderate to Severe Active Crohn's Disease

#### Summary

EudraCT number	2014-002556-77
Trial protocol	CZ HU SK NL IT PL
Global end of trial date	10 October 2016

#### Results information

Result version number	v1 (current)
This version publication date	26 October 2017
First version publication date	26 October 2017

#### Trial information

##### Trial identification

Sponsor protocol code	MT-1303-E13
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02378688
WHO universal trial number (UTN)	-

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 (MTPE), 0044 (0)2070655000, regulatory@mt-pharma-eu.com
Scientific contact	General Information, Mitsubishi Tanabe Pharma Europe Ltd (MTPE), 0044 (0)2070655000, 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	15 December 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	10 October 2016
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objectives of the trial were to evaluate the safety and tolerability of MT-1303 in subjects with moderate to severe active Crohn's disease (CD) and to evaluate the clinical efficacy of MT-1303 in subjects with moderate to severe active CD. Secondary objectives were to explore the pharmacokinetics (PK) and pharmacodynamics (PD) of MT-1303 in subjects with moderate to severe active CD.

Protection of trial subjects:

The study was conducted in accordance with the 2013 (Fortaleza) revision of the 1964 Declaration of Helsinki, Good Clinical Practice (GCP) as required by the International Conference on Harmonisation (ICH) guidelines, applicable regional and local legislation, and standard operating procedures in place at Mitsubishi Tanabe Pharma Europe Ltd (MTPE). Before implementing the study, the Protocol and all other appropriate documents were reviewed and approved by an Independent Ethics Committee (IEC) and regulatory authorities. The study was carefully designed to minimise the identified and potential risks to subjects; all subjects underwent screening procedures aimed at minimising the likelihood and impact of any such risks. In addition, regular safety monitoring during the treatment and safety Follow-up Periods for all subjects ensured that any unanticipated effects of study participation were identified promptly and managed appropriately. At the level of the individual subject, the Protocol stated well-defined criteria for intensive Cardiovascular Safety Monitoring, including extended monitoring and permanent discontinuation of study medication. In addition, an independent Data and Safety Monitoring Board (DSMB) reviewed selected data across the study, at regular, predefined intervals. The DSMB was empowered to make recommendations regarding continuation, termination or modification of the study, as appropriate. In particular, if it became clear that continuing treatment with MT-1303 was not clinically or ethically justified, the MT 1303-E13 study could be terminated. Given that this was a proof-of-concept study, there were no guaranteed benefits for subjects; however, there was an expectation that subjects treated with MT-1303 would experience a selective reduction in lymphocytes which may be translated into clinical benefit.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 March 2015
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	Netherlands: 4
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Slovakia: 8
Country: Number of subjects enrolled	Czech Republic: 6
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 4

Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Japan: 5
Country: Number of subjects enrolled	Ukraine: 17
Worldwide total number of subjects	78
EEA total number of subjects	55

Notes:

<b>Subjects enrolled per age group</b>	
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)	78
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Up to 4 weeks 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, Carer, Assessor

Blinding implementation details:

Lymphocyte count and white blood cell differential were not provided to any site/study personnel 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
<b>Arm title</b>	Placebo

Arm description:

Placebo oral capsules administered once daily from Week 0 to Week 14.

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

Dosage and administration details:

One placebo capsule administered orally once daily from Week 0 to Week 14.

<b>Arm title</b>	MT-1303 0.4 mg
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Arm description:

MT-1303 0.4 mg oral capsules administered once daily from Week 0 to Week 14.

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:

One 0.4 mg MT-1303 capsule administered orally once daily from Week 0 to Week 14.

<b>Number of subjects in period 1</b>	Placebo	MT-1303 0.4 mg
Started	38	40
Completed	33	28
Not completed	5	12
Consent withdrawn by subject	2	4
Adverse event, non-fatal	2	3
False positive serum HCG	-	1
Lack of efficacy	1	3
Protocol deviation	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo oral capsules administered once daily from Week 0 to Week 14.

Reporting group title	MT-1303 0.4 mg
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Reporting group description:

MT-1303 0.4 mg oral capsules administered once daily from Week 0 to Week 14.

Reporting group values	Placebo	MT-1303 0.4 mg	Total
Number of subjects	38	40	78
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)	38	40	78
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	32.1	35.2	
standard deviation	± 10.2	± 8.93	-
Gender categorical			
Units: Subjects			
Female	13	16	29
Male	25	24	49

### Subject analysis sets

Subject analysis set title	Placebo - ITT
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

Placebo oral capsules administered once daily from Week 0 to Week 14.

Subject analysis set title	MT-1303 0.4 mg - ITT
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

MT-1303 0.4 mg oral capsules administered once daily from Week 0 to Week 14.

Subject analysis set title	MT-1303 0.4 mg - PK pop
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

MT-1303 0.4 mg oral capsules administered once daily from Week 0 to Week 14.

<b>Reporting group values</b>	Placebo - ITT	MT-1303 0.4 mg - ITT	MT-1303 0.4 mg - PK pop
Number of subjects	37	39	38
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)	37	39	38
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	32.4	35.5	35.7
standard deviation	± 10.2	± 8.9	± 8.9
Gender categorical Units: Subjects			
Female	13	16	15
Male	24	23	23

## End points

### End points reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo oral capsules administered once daily from Week 0 to Week 14.

Reporting group title	MT-1303 0.4 mg
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Reporting group description:

MT-1303 0.4 mg oral capsules administered once daily from Week 0 to Week 14.

Subject analysis set title	Placebo - ITT
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

Placebo oral capsules administered once daily from Week 0 to Week 14.

Subject analysis set title	MT-1303 0.4 mg - ITT
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

MT-1303 0.4 mg oral capsules administered once daily from Week 0 to Week 14.

Subject analysis set title	MT-1303 0.4 mg - PK pop
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

MT-1303 0.4 mg oral capsules administered once daily from Week 0 to Week 14.

### Primary: Proportion of Subjects Achieving a 100-Point Decrease from Baseline in CDAI Score (CDAI 100) at Week 12

End point title	Proportion of Subjects Achieving a 100-Point Decrease from Baseline in CDAI Score (CDAI 100) at Week 12
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End point description:

End point type	Primary
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End point timeframe:

Week 12

End point values	Placebo - ITT	MT-1303 0.4 mg - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	39		
Units: Percent				
number (confidence interval 95%)	54.1 (38.4 to 69.0)	48.7 (33.9 to 63.8)		

## Statistical analyses



<b>Statistical analysis title</b>	Logistic Regression Model (NRI)
Statistical analysis description: Logistic regression model with treatment as a fixed effect and baseline CDAI score and previous exposure to anti-TNF- $\alpha$ agents as covariates.	
Comparison groups	Placebo - ITT v MT-1303 0.4 mg - ITT
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.598 <sup>[1]</sup>
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	1.98

Notes:

[1] - p-values were computed using Cochran Mantel Haenszel test stratified by previous exposure to anti-TNF- $\alpha$  agents.

### Secondary: Proportion of Subjects Achieving a 70-Point Decrease from Baseline in CDAI Score (CDAI 70)

End point title	Proportion of Subjects Achieving a 70-Point Decrease from Baseline in CDAI Score (CDAI 70)
End point description:	
End point type	Secondary
End point timeframe: Weeks 2, 4, 8, 12 and 14	

End point values	Placebo - ITT	MT-1303 0.4 mg - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	39		
Units: Percent				
number (not applicable)				
Week 2	32.4	43.6		
Week 4	62.2	43.6		
Week 8	56.8	51.3		
Week 12	64.9	53.8		
Week 14	64.9	53.8		

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Proportion of Subjects Achieving a 100-Point Decrease from Baseline in CDAI Score (CDAI 100)**

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End point title	Proportion of Subjects Achieving a 100-Point Decrease from Baseline in CDAI Score (CDAI 100)
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End point description:

End point type	Secondary
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End point timeframe:

Weeks 2, 4, 8, 12 and 14

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End point values	Placebo - ITT	MT-1303 0.4 mg - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	39		
Units: Percent				
number (not applicable)				
Week 2	18.9	20.5		
Week 4	51.4	30.8		
Week 8	45.9	41		
Week 12	54.1	48.7		
Week 14	59.5	41		

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Proportion of Subjects Achieving Clinical Remission (CDAI score of <150)**

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End point title	Proportion of Subjects Achieving Clinical Remission (CDAI score of <150)
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End point description:

End point type	Secondary
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End point timeframe:

Weeks 2, 4, 8, 12 and 14

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End point values	Placebo - ITT	MT-1303 0.4 mg - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	39		
Units: Percent				
number (not applicable)				
Week 2	8.1	10.3		

Week 4	27	15.4		
Week 8	32.4	25.6		
Week 12	40.5	28.2		
Week 14	51.4	17.9		

## Statistical analyses

No statistical analyses for this end point

## Secondary: CDAI Score by Week

End point title	CDAI Score by Week
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End point description:

End point type	Secondary
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End point timeframe:

Weeks 2, 4, 8, 12 and 14

End point values	Placebo - ITT	MT-1303 0.4 mg - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	39		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline	307 (± 63.2)	305.1 (± 50.7)		
Week 2	252.2 (± 77.3)	239.8 (± 75.8)		
Week 4	214 (± 90.7)	233.8 (± 79.4)		
Week 8	180.6 (± 84.2)	205.6 (± 83.6)		
Week 12	170 (± 115)	182.4 (± 102.7)		
Week 14	167 (± 98.8)	161.3 (± 69.8)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Decrease from Baseline in CDAI Score by Week

End point title	Percent Decrease from Baseline in CDAI Score by Week
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End point description:

End point type	Secondary
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End point timeframe:

Weeks 2, 4, 8, 12 and 14

End point values	Placebo - ITT	MT-1303 0.4 mg - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	39		
Units: Percent				
arithmetic mean (standard deviation)				
Week 2	16.81 (± 22.32)	21.53 (± 21.84)		
Week 4	29.39 (± 31.6)	21.12 (± 30.26)		
Week 8	39.37 (± 27.6)	32.2 (± 28.97)		
Week 12	44.74 (± 35.2)	40.63 (± 34.15)		
Week 14	43.55 (± 32.76)	47.78 (± 22.68)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Concentrations of MT-1303 and its Active Metabolite MT-1303-P by Week

End point title	Plasma Concentrations of MT-1303 and its Active Metabolite MT-1303-P by Week
End point description:	
End point type	Secondary
End point timeframe:	
Pre-dose to Week 26	

End point values	MT-1303 0.4 mg - PK pop			
Subject group type	Subject analysis set			
Number of subjects analysed	38			
Units: ng/mL				
arithmetic mean (standard deviation)				
MT-1303, Week 0	0.000 (± 0.000)			
MT-1303-P, Week 0	0.001 (± 0.008)			
MT-1303, Week 2	1.990 (± 0.958)			
MT-1303-P, Week 2	3.569 (± 1.574)			
MT-1303, Week 4	2.829 (± 1.115)			

MT-1303-P, Week 4	5.099 ( $\pm$ 1.897)			
MT-1303, Week 8	3.309 ( $\pm$ 1.105)			
MT-1303-P, Week 8	6.036 ( $\pm$ 2.180)			
MT-1303, Week 12	3.479 ( $\pm$ 1.137)			
MT-1303-P, Week 12	6.139 ( $\pm$ 2.380)			
MT-1303, Week 14	3.493 ( $\pm$ 1.147)			
MT-1303-P, Week 14	6.620 ( $\pm$ 2.396)			
MT-1303, Week 18	0.742 ( $\pm$ 0.387)			
MT-1303-P, Week 18	1.196 ( $\pm$ 0.793)			
MT-1303, Week 22	0.292 ( $\pm$ 0.164)			
MT-1303-P, Week 22	0.429 ( $\pm$ 0.339)			
MT-1303, Week 26	0.109 ( $\pm$ 0.085)			
MT-1303-P, Week 26	0.183 ( $\pm$ 0.181)			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All adverse events occurring from the signing of the informed consent form until the end of the safety Follow-up Period or the withdrawal of the subject from the study were documented, regardless of the relationship to study drug.

Adverse event reporting additional description:

During the study visits, regular questioning of each subject was done 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 were reported.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	19

### Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo oral capsules administered once daily from Week 0 to Week 14.

Reporting group title	MT-1303 0.4 mg
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Reporting group description:

MT-1303 0.4 mg oral capsules administered once daily from Week 0 to Week 14.

Serious adverse events	Placebo	MT-1303 0.4 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 38 (2.63%)	6 / 39 (15.38%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Crohn's disease			
subjects affected / exposed	0 / 38 (0.00%)	3 / 39 (7.69%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastrointestinal infection			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Placebo	MT-1303 0.4 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 38 (55.26%)	26 / 39 (66.67%)	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 38 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 38 (15.79%)	4 / 39 (10.26%)	
occurrences (all)	6	4	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	2 / 38 (5.26%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
Pyrexia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Crohn's disease			
subjects affected / exposed	1 / 38 (2.63%)	6 / 39 (15.38%)	
occurrences (all)	1	6	
Abdominal pain			
subjects affected / exposed	1 / 38 (2.63%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
Diarrhoea			
subjects affected / exposed	2 / 38 (5.26%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
Reproductive system and breast disorders			



Dysmenorrhoea subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	0 / 39 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	2 / 39 (5.13%) 2	
Skin and subcutaneous tissue disorders Dermatitis allergic subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	2 / 39 (5.13%) 2	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)  Back pain subjects affected / exposed occurrences (all)  Myalgia subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 3  2 / 38 (5.26%) 2  0 / 38 (0.00%) 0	2 / 39 (5.13%) 2  0 / 39 (0.00%) 0  2 / 39 (5.13%) 2	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	3 / 39 (7.69%) 3	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 December 2015	Exclusion criteria were modified to decrease the prohibited period for adalimumab from 8 weeks prior to Screening to 4 weeks, to permit the prior use of vedolizumab (with a 16 week washout period prior to Visit 1) and to prohibit the use of parenteral nutrition including the use of a central venous catheter. All patients (including non-responders) were allowed into the long term extension study MT-1303- E14. The addition of a database lock after the last patient last dose to facilitate timely data analysis and decision making without comprising the validity of the study was added. Changes to company process regarding adverse events management were also reflected.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported