

**Clinical trial results:****A Phase II, Open-label, Multicentre Study to Evaluate the Long-term Safety and Efficacy of MT-1303 in Subjects with Moderate to Severe Active Crohn's Disease who have Completed the MT-1303-E13 Study Summary**

EudraCT number	2014-002557-19
Trial protocol	CZ HU SK NL IT PL
Global end of trial date	24 August 2017

Results information

Result version number	v1 (current)
This version publication date	24 August 2018
First version publication date	24 August 2018

Trial information**Trial identification**

Sponsor protocol code	MT-1303-E14
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02389790
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	12 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 August 2017
Global end of trial reached?	Yes
Global end of trial date	24 August 2017
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 moderate to severe active Crohn's disease (CD). Secondary objectives were to evaluate the long term effects of MT-1303 on clinical outcomes in subjects with moderate to severe active CD and explore the pharmacodynamic effects 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-E14 study could be terminated. 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 could be translated into clinical benefit.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 August 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: 2
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Israel: 1

Country: Number of subjects enrolled	Ukraine: 11
Country: Number of subjects enrolled	Japan: 4
Worldwide total number of subjects	46
EEA total number of subjects	30

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)	46
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a follow on study from a previous study MT-1303-E13

Pre-assignment

Screening details:

There was no screening period for this study. Subject eligibility was confirmed at Visit 7 (Week 14) in MT-1303-E13 and eligible subjects who wished to continue in the open-label extension were entered at Visit 1 (Week 0) in E14.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This is an open label study

Arms

Are arms mutually exclusive?	Yes
Arm title	MT-1303/MT-1303

Arm description:

Subjects received once daily oral 0.4 mg MT-1303 capsules during the double-blind MT-1303-E13 study, and received once daily oral 0.4 mg MT-1303 capsules during the MT-1303-E14 extension study.

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

Arm title	placebo/MT-1303
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Arm description:

Subjects received once daily oral placebo capsules during the double-blind MT-1303-E13 study, and received once daily oral 0.4 mg MT-1303 capsules during the MT-1303-E14 extension study.

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

Number of subjects in period 1	MT-1303/MT-1303	placebo/MT-1303
Started	21	25
Completed	14	12
Not completed	7	13
Consent withdrawn by subject	3	6
Physician decision	1	-
ALT/AST >5 x ULN, 2 or more consecutive visits	-	1
Adverse event, non-fatal	1	2
Pregnancy	-	1
Insufficient control of disease condition	1	-
Lack of efficacy	1	3

Baseline characteristics

Reporting groups

Reporting group title	MT-1303/MT-1303
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Reporting group description:

Subjects received once daily oral 0.4 mg MT-1303 capsules during the double-blind MT-1303-E13 study, and received once daily oral 0.4 mg MT-1303 capsules during the MT-1303-E14 extension study.

Reporting group title	placebo/MT-1303
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Reporting group description:

Subjects received once daily oral placebo capsules during the double-blind MT-1303-E13 study, and received once daily oral 0.4 mg MT-1303 capsules during the MT-1303-E14 extension study.

Reporting group values	MT-1303/MT-1303	placebo/MT-1303	Total
Number of subjects	21	25	46
Age categorical			
Units: Subjects			
Adults (18-64 years)	21	25	46
Age continuous			
Units: years			
arithmetic mean	36.4	34.9	
standard deviation	± 8.5	± 11.1	-
Gender categorical			
Units: Subjects			
Female	8	9	17
Male	13	16	29

End points

End points reporting groups

Reporting group title	MT-1303/MT-1303
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Reporting group description:

Subjects received once daily oral 0.4 mg MT-1303 capsules during the double-blind MT-1303-E13 study, and received once daily oral 0.4 mg MT-1303 capsules during the MT-1303-E14 extension study.

Reporting group title	placebo/MT-1303
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Reporting group description:

Subjects received once daily oral placebo capsules during the double-blind MT-1303-E13 study, and received once daily oral 0.4 mg MT-1303 capsules during the MT-1303-E14 extension study.

Primary: Safety

End point title	Safety ^[1]
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End point description:

The primary endpoint was safety and the data are provided in the AE section

End point type	Primary
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End point timeframe:

All of Study

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: The primary endpoint was safety and the data are provided in the AE section

End point values	MT-1303/MT-1303	placebo/MT-1303		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	25		
Units: Adverse Events				
number (not applicable)				
subjects affected by serious adverse events	1	8		
subjects affected by non-serious adverse events	12	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects who achieved a 70-point decrease from MT-1303-E13 baseline in CDAI score (CAI 70) at Protocol scheduled visits

End point title	Proportion of subjects who achieved a 70-point decrease from MT-1303-E13 baseline in CDAI score (CAI 70) at Protocol scheduled visits
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End point description:

End point type	Secondary
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End point timeframe:

Weeks 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36

End point values	MT-1303/MT-1303	placebo/MT-1303		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	25		
Units: percent				
number (not applicable)				
week 0	83.3	86.4		
week 2	84.2	76.5		
week 4	81	81.0		
week 8	70.6	88.9		
week 12	76.5	81.3		
week 16	82.4	78.6		
week 20	87.5	92.3		
week 24	93.8	100.0		
week 28	88.2	100.0		
week 32	92.9	90.0		
week 36	81.8	80.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects who achieved a 100-point decrease from MT-1303-E13 baseline in CDAI score (CDAI 100) at Protocol scheduled visits.

End point title	Proportion of subjects who achieved a 100-point decrease from MT-1303-E13 baseline in CDAI score (CDAI 100) at Protocol scheduled visits.
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End point description:

End point type	Secondary
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End point timeframe:

Weeks 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36

End point values	MT-1303/MT-1303	placebo/MT-1303		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	23		
Units: percent				
number (not applicable)				
week 0	66.7	81.8		
week 2	68.4	64.7		
week 4	71.4	76.2		

week 8	64.7	83.3		
week 12	70.6	81.3		
week 16	76.5	71.4		
week 20	75	92.3		
week 24	87.5	90		
week 28	76.5	91.7		
week 32	85.7	90		
week 36	81.8	80		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects who achieve clinical remission (CDAI <150) at Protocol scheduled visits.

End point title	Proportion of subjects who achieve clinical remission (CDAI <150) at Protocol scheduled visits.
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End point description:

End point type	Secondary
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End point timeframe:

Weeks 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36

End point values	MT-1303/MT-1303	placebo/MT-1303		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	23		
Units: percent				
number (not applicable)				
week 0	38.9	72.7		
week 2	47.4	52.9		
week 4	52.4	47.6		
week 8	52.9	61.1		
week 12	52.9	75		
week 16	58.8	64.3		
week 20	68.8	69.2		
week 24	75	80		
week 28	58.8	75		
week 32	85.7	50		
week 36	81.8	70		

Statistical analyses

No statistical analyses for this end point

Secondary: CDAI Score at Protocol scheduled visits

End point title	CDAI Score at Protocol scheduled visits
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End point description:

End point type	Secondary
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End point timeframe:

Weeks 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36

End point values	MT-1303/MT-1303	placebo/MT-1303		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	23		
Units: score on scale				
arithmetic mean (standard deviation)				
week 0	155.7 (± 77.7)	136.8 (± 82.9)		
week 2	162.8 (± 78.7)	127.7 (± 71.7)		
week 4	158.2 (± 84.3)	151.4 (± 73.2)		
week 8	162.8 (± 91.7)	113.7 (± 73.9)		
week 12	153.8 (± 78.8)	117.3 (± 67.1)		
week 16	144.7 (± 72.3)	117.1 (± 87)		
week 20	138.1 (± 78.2)	111.8 (± 62)		
week 24	126.8 (± 71.4)	110.2 (± 44.4)		
week 28	151.2 (± 75.3)	116.8 (± 51)		
week 32	112.6 (± 77)	124.7 (± 58.7)		
week 36	112.6 (± 87)	137 (± 67.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects in corticosteroid free remission at End of Treatment.

End point title	Proportion of subjects in corticosteroid free remission at End of Treatment.
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End point description:

End point type	Secondary
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End point timeframe:

Weeks 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, and 36 Last observation carried forward (LOCF)

End point values	MT-1303/MT-1303	placebo/MT-1303		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	23		
Units: percent				
number (not applicable)				
week 0	0.0	25.0		
week 2	0.0	0.0		
week 4	12.5	0.0		
week 8	28.6	20.0		
week 12	28.6	25.0		
week 16	14.3	0.0		
week 20	57.1	33.3		
week 24	42.9	50.0		
week 28	42.9	33.3		
week 32	50.0	0.0		
week 36	66.7	50.0		
week 36 LOCF	50.0	25.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Lymphocyte counts at Protocol scheduled visits

End point title	Lymphocyte counts at Protocol scheduled visits
End point description:	
End point type	Secondary
End point timeframe:	
Weeks 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48	

End point values	MT-1303/MT-1303	placebo/MT-1303		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	23		
Units: X 10 ⁹ /L				
arithmetic mean (standard deviation)				
week 0	0.656 (± 0.271)	1.708 (± 0.793)		
week 2	0.748 (± 0.307)	0.824 (± 0.314)		
week 4	0.772 (± 0.328)	0.704 (± 0.265)		
week 8	0.685 (± 0.307)	0.622 (± 0.247)		
week 12	0.728 (± 0.362)	0.568 (± 0.219)		
week 16	0.723 (± 0.358)	0.607 (± 0.274)		

week 20	0.767 (± 0.373)	0.612 (± 0.281)		
week 24	0.634 (± 0.18)	0.593 (± 0.302)		
week 28	0.694 (± 0.37)	0.645 (± 0.289)		
week 32	0.621 (± 0.184)	0.668 (± 0.368)		
week 36	0.628 (± 0.307)	0.579 (± 0.268)		
week 40	0.918 (± 0.282)	0.924 (± 0.418)		
week 44	1.182 (± 0.326)	1.131 (± 0.369)		
week 48	1.386 (± 0.313)	1.171 (± 0.489)		

Statistical analyses

No statistical analyses for this end point

Secondary: C-reactive protein at Protocol scheduled visits

End point title	C-reactive protein at Protocol scheduled visits
End point description:	
End point type	Secondary
End point timeframe:	
Weeks 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36	

End point values	MT-1303/MT-1303	placebo/MT-1303		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	24		
Units: mg/L				
median (full range (min-max))				
week 0	3.45 (0.61 to 47.8)	13.1 (0.20 to 49.90)		
week 2	6.135 (0.76 to 30.60)	8.25 (0.85 to 43.70)		
week 4	6.82 (1.35 to 37.80)	15.4 (0.25 to 72.60)		
week 8	5.2 (1.11 to 41.50)	9.155 (0.80 to 37.70)		
week 12	6.29 (1.03 to 36.30)	10.165 (3.97 to 55.70)		
week 16	7.84 (1.00 to 55.00)	9.87 (0.81 to 39.40)		
week 20	4.3 (0.84 to 31.50)	10.3 (0.55 to 33.80)		
week 24	7.845 (0.80 to 33.5)	10.135 (1.30 to 35.30)		

week 28	10.3 (1.19 to 47.50)	9.805 (1.25 to 45.60)		
week 32	9.82 (0.95 to 24.60)	7.295 (1.14 to 46.40)		
week 36	14.50 (0.95 to 62.50)	10.56 (0.87 to 36.50)		

Statistical analyses

No statistical analyses for this end point

Secondary: Faecal calprotectin at Protocol scheduled visits

End point title	Faecal calprotectin at Protocol scheduled visits
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End point description:

End point type	Secondary
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End point timeframe:

Weeks 12 and 36

End point values	MT-1303/MT-1303	placebo/MT-1303		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	24		
Units: mg/kg				
median (full range (min-max))				
week 12	766 (30 to 2278)	1356.5 (55 to 9546)		
week 36	283 (30 to 2051)	878 (30 to 3324)		

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.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	MT-1303/MT-1303
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Reporting group description:

Subjects received once daily oral 0.4 mg MT-1303 capsules during the double-blind MT-1303-E13 study, and received once daily oral 0.4 mg MT-1303 capsules during the MT-1303-E14 extension study.

Reporting group title	placebo/MT-1303
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Reporting group description:

Subjects received once daily oral placebo capsules during the double-blind MT-1303-E13 study, and received once daily oral 0.4 mg MT-1303 capsules during the MT-1303-E14 extension study.

Serious adverse events	MT-1303/MT-1303	placebo/MT-1303	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 21 (4.76%)	8 / 25 (32.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Endoscopy small intestine			
subjects affected / exposed	1 / 21 (4.76%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	0 / 21 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Vagal nerve stimulator removal			

subjects affected / exposed	0 / 21 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Crohn's disease			
subjects affected / exposed	0 / 21 (0.00%)	2 / 25 (8.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal stenosis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 21 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 21 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Granuloma skin			
subjects affected / exposed	0 / 21 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 21 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			

subjects affected / exposed	0 / 21 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal abscess			
subjects affected / exposed	0 / 21 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 21 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	MT-1303/MT-1303	placebo/MT-1303	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 21 (57.14%)	13 / 25 (52.00%)	
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	2 / 21 (9.52%)	2 / 25 (8.00%)	
occurrences (all)	2	3	
Protein urine present			
subjects affected / exposed	2 / 21 (9.52%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 21 (14.29%)	2 / 25 (8.00%)	
occurrences (all)	6	4	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	2 / 21 (9.52%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Lymphopenia			
subjects affected / exposed	3 / 21 (14.29%)	1 / 25 (4.00%)	
occurrences (all)	3	1	
Gastrointestinal disorders			

Abdominal pain subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	3 / 25 (12.00%) 3	
Anal fistula subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	3 / 25 (12.00%) 4	
Aphthous ulcer subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	2 / 25 (8.00%) 2	
Crohn's disease subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 3	2 / 25 (8.00%) 2	
Vomiting subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	2 / 25 (8.00%) 2	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	2 / 25 (8.00%) 2	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	3 / 25 (12.00%) 4	
Infections and infestations Pharyngitis subjects affected / exposed occurrences (all) Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2 3 / 21 (14.29%) 3	0 / 25 (0.00%) 0 2 / 25 (8.00%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 December 2015	Inclusion criterion 1 was removed. Section 6.6.3, Section 8, Section 10.1, and were updated. Other minor administrative changes were made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported