Clinical trial results:
A Double-Blind, Randomized, Multicenter Study of Higher Versus Standard Adalimumab Dosing Regimens for Induction and Maintenance Therapy in Subjects With Moderately to Severely Active Ulcerative Colitis

Summary

EudraCT number	2013-001682-16
Trial protocol	DE HU BE IT SK NL ES DK AT CZ PL
Global end of trial date	11 November 2019

Results information

Result version number	v1 (current)
This version publication date	13 November 2020
First version publication date	13 November 2020

Trial information

Trial identification

Sponsor protocol code	M14-033

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02065622
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6 4UB
Public contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	
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	11 November 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate safety and efficacy of two adalimumab dosing regimens for induction and maintenance (standard and higher dosing) in achieving clinical remission in subjects with moderately to severely active ulcerative colitis.

Protection of trial subjects:

Subject and/or legal guardian read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 March 2014
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	Austria: 30
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Canada: 71
Country: Number of subjects enrolled	Czech Republic: 3
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 42
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	Israel: 23
Country: Number of subjects enrolled	Italy: 67
Country: Number of subjects enrolled	Japan: 100
Country: Number of subjects enrolled	Netherlands: 15
Country: Number of subjects enrolled	Poland: 236
Country: Number of subjects enrolled	Romania: 5
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	Ukraine: 75
Country: Number of subjects enrolled	United Kingdom: 33
Country: Number of subjects enrolled	United States: 178

Worldwide total number of subjects	952
EEA total number of subjects	500

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)	914
From 65 to 84 years	38
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study included a Main Study (120 sites in 19 countries) and a Japan Sub-Study (22 sites in Japan).

After a 3-week screening period, participants were randomized 3:2 to an 8-week double-blind (DB) Induction Period with 2 adalimumab dosing regimens (Induction Standard Dose [I-SD] or Induction Higher Dose [I-HD]).

Pre-assignment

Screening details:

At Week 8, participants in Main Study were re-randomized (2:2:1) into 44-week DB Maintenance Period with 3 adalimumab dosing regimens (M-SD, M-HD, or an exploratory Therapeutic Drug Monitoring [TDM] Regimen). Participants in Japan Sub-study were re-randomized (1:1) into 44-week DB Maintenance Period with 2 adalimumab dosing regimens (M-SD, M-HD).

Period 1

Period 1 title	Induction Study
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of the AbbVie Drug Supply Management Team) the Investigator, study site personnel and the subject will remain blinded to each subject's treatment throughout the blinded period of the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Induction (Main Study + Japan Substudy): I-SD

Arm description:

Induction Standard Dose (I-SD): Double-blind adalimumab regimen of 160 mg at Week 0 followed by 80 mg at Week 2, 40 mg at Week 4, and 40 mg at Week 6.

Arm type	Experimental
Investigational medicinal product name	adalimumab
Investigational medicinal product code	
Other name	Humira
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Double-blind adalimumab regimen of 160 mg at Week 0 followed by 80 mg at Week 2, 40 mg at Week 4, and 40 mg at Week 6.

Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

In order to retain blinding, all subjects in the Standard Induction Dose Regimen will receive matching placebo injections in addition to the adalimumab injection at Weeks 1, 2 and 3.

Arm title	Induction (Main Study + Japan Substudy): I-HD

Arm description:

Induction Higher Dose (I-HD): Double-blind adalimumab regimen of 160 mg at Weeks 0, 1, 2, and 3 followed by 40 mg at Week 4 and 40 mg at Week 6.

Arm type	Experimental
Investigational medicinal product name	adalimumab
Investigational medicinal product code	
Other name	Humira
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Double-blind adalimumab regimen of 160 mg at Weeks 0, 1, 2, and 3 followed by 40 mg at Week 4 and 40 mg at Week 6.

Number of subjects in period 1	Induction (Main Study + Japan Substudy): I-SD	Induction (Main Study + Japan Substudy): I-HD
Started	379	573
Enrolled in Main Study	340	512 [1]
Enrolled in Japan Sub-Study	39 [2]	61 [3]
Completed	332	514
Not completed	47	59
Adverse event	13	19
Requires Alternative/ Prohibited Therapy	4	5
Subject Noncompliance	1	1
Lost to follow-up	1	-
Withdrawal by subject	3	5
Lack of efficacy	22	27
Other, Not Specified	3	2

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Enrolled in Main Study

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Enrolled in Japan Sub-Study

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Enrolled in Japan Sub-Study

Period 2

Period 2 title	Maintenance Study
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

All AbbVie personally with direct oversight of the conduct and management of the trial (with the exception of the AbbVie Drug Supply Management Team) the Investigator, study site personnel and the subject remained blinded to each subject's treatment throughout the blinded period of the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Maintenance (Main Study + Japan Sub-study): M-SD

Arm description:

Maintenance Standard Dose (M-SD): Double-blind adalimumab 40 mg every other week (eow), for 44 weeks.

Arm type	Experimental
Investigational medicinal product name	adalimumab
Investigational medicinal product code	
Other name	Humira
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Double-blind adalimumab 40 mg every other week (eow), for 44 weeks.

Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Matching Placebo was administered every other week, starting at Week 9 until Week 51.

Arm title	Maintenance (Main Study + Japan Sub-study): M-HD

Arm description:

Maintenance Higher Dose (M-HD): Double-blind adalimumab 40 mg every week (ew) for 44 weeks.

Arm type	Experimental
Investigational medicinal product name	adalimumab
Investigational medicinal product code	
Other name	Humira
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Double-blind adalimumab 40 mg every week (ew) for 44 weeks.

Arm title	Maintenance (Main Study): TDM Regimen

Arm description:

Exploratory Therapeutic Drug Monitoring (TDM) Regimen: Double-blind adalimumab 40 mg eow at Week 8 and Week 10, with possible dose adjustments at Weeks 12, 24, and 37 based on criteria assessing blinded adalimumab serum concentration and rectal bleeding subscore assessments. Per protocol, the TDM Regimen arm was used to analyze exploratory outcome measures only.

Arm type	Experimental
Investigational medicinal product name	adalimumab
Investigational medicinal product code	
Other name	Humira
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Double-blind adalimumab 40 mg eow at Week 8 and Week 10, with possible dose adjustments at Weeks 12, 24, and 37 based on criteria assessing blinded adalimumab serum concentration and rectal bleeding subscore assessments.

Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection

Routes of administration	Subcutaneous use

Dosage and administration details:

In order to retain blinding, all subjects in the TDM Regimen will receive matching placebo injections in addition to the adalimumab injection at Weeks 9 and 11.

Number of subjects in period 2	Maintenance (Main Study + Japan Sub-study): M-SD	Maintenance (Main Study + Japan Sub-study): M-HD	Maintenance (Main Study): TDM Regimen
Started	345	350	151
Completed	221	246	105
Not completed	124	104	46
Subject Non-Compliance	1	3	2
Unknown Reason	-	1	-
Adverse event	25	22	11
Requires Alternative/ Prohibited Therapy	7	3	4
Lost to follow-up	4	1	1
Withdrawal by subject	11	5	7
Lack of efficacy	70	55	19
Other, Not Specified	6	14	2

Baseline characteristics

Reporting groups	
Reporting group title	Induction (Main Study + Japan Substudy): I-SD
Reporting group description:	
Induction Standard Dose (I-SD): Double-blind adalimumab regimen of 160 mg at Week 0 followed by 80 mg at Week 2, 40 mg at Week 4, and 40 mg at Week 6.	
Reporting group title	Induction (Main Study + Japan Substudy): I-HD
Reporting group description:	
Induction Higher Dose (I-HD): Double-blind adalimumab regimen of 160 mg at Weeks 0, 1, 2, and 3 followed by 40 mg at Week 4 and 40 mg at Week 6.	

Reporting group values	Induction (Main Study + Japan Substudy): I-SD	Induction (Main Study + Japan Substudy): I-HD	Total
Number of subjects	379	573	952
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	40.2	40.5	
standard deviation	± 13.14	± 12.89	-
Gender categorical Units: Subjects			
Female	166	239	405
Male	213	334	547
Race Units: Subjects			
White	326	484	810
Black or African American	8	16	24
Asian	44	70	114
Native Hawaiian/ Other Pacific Islander	0	1	1
Multiracial	1	1	2
Missing	0	1	1
Ethnicity Units: Subjects			
Hispanic or Latino	19	28	47
Japanese	39	61	100
Other, Not Specified	321	484	805
Region Units: Subjects			
United States	65	113	178
Non-United States	314	460	774
Full Mayo Score (FMS)			
The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The FMS ranges from 0 (normal or inactive disease) to 12 (severe disease) and is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, endoscopy, and physician's global assessment), each of which ranges from 0 (normal) to 3 (severe disease). Measure Analysis Population Description: participants with an assessment (n=379, 570)			

Units: units on a scale			
arithmetic mean	8.69	8.87	
standard deviation	± 1.509	± 1.571	-
FMS: Rectal Bleeding Subscore			
The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The FMS ranges from 0 (normal or inactive disease) to 12 (severe disease) and is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, endoscopy, and physician's global assessment), each of which ranges from 0 (normal) to 3 (severe disease). Measure Analysis Population Description: participants with an assessment (n=379, 570).			
Units: units on a scale			
arithmetic mean	1.68	1.75	
standard deviation	± 0.955	± 0.967	-

End points

End points reporting groups

Reporting group title	Induction (Main Study + Japan Substudy): I-SD
Reporting group description:	
Induction Standard Dose (I-SD): Double-blind adalimumab regimen of 160 mg at Week 0 followed by 80 mg at Week 2, 40 mg at Week 4, and 40 mg at Week 6.	
Reporting group title	Induction (Main Study + Japan Substudy): I-HD
Reporting group description:	
Induction Higher Dose (I-HD): Double-blind adalimumab regimen of 160 mg at Weeks 0, 1, 2, and 3 followed by 40 mg at Week 4 and 40 mg at Week 6.	
Reporting group title	Maintenance (Main Study + Japan Sub-study): M-SD
Reporting group description:	
Maintenance Standard Dose (M-SD): Double-blind adalimumab 40 mg every other week (eow), for 44 weeks.	
Reporting group title	Maintenance (Main Study + Japan Sub-study): M-HD
Reporting group description:	
Maintenance Higher Dose (M-HD): Double-blind adalimumab 40 mg every week (ew) for 44 weeks.	
Reporting group title	Maintenance (Main Study): TDM Regimen
Reporting group description:	
Exploratory Therapeutic Drug Monitoring (TDM) Regimen: Double-blind adalimumab 40 mg eow at Week 8 and Week 10, with possible dose adjustments at Weeks 12, 24, and 37 based on criteria assessing blinded adalimumab serum concentration and rectal bleeding subscore assessments. Per protocol, the TDM Regimen arm was used to analyze exploratory outcome measures only.	
Subject analysis set title	Induction (Main Study): I-SD
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Induction Standard Dose: Double-blind adalimumab regimen of 160 mg at Week 0 followed by 80 mg at Week 2, 40 mg at Week 4, and 40 mg at Week 6.	
Subject analysis set title	Induction (Main Study): I-HD
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Induction Higher Dose: Double-blind adalimumab regimen of 160 mg at Weeks 0, 1, 2, and 3 followed by 40 mg at Week 4 and 40 mg at Week 6.	
Subject analysis set title	Induction (Main Study + Japan Substudy): I-SD
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Induction Standard Dose: Double-blind adalimumab regimen of 160 mg at Week 0 followed by 80 mg at Week 2, 40 mg at Week 4, and 40 mg at Week 6.	
Subject analysis set title	Induction (Main Study + Japan Substudy): I-HD
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Induction Higher Dose: Double-blind adalimumab regimen of 160 mg at Weeks 0, 1, 2, and 3 followed by 40 mg at Week 4 and 40 mg at Week 6.	
Subject analysis set title	Maintenance (Main Study): M-SD
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Maintenance Standard Dose: Double-blind adalimumab 40 mg every other week (eow), for 44 weeks.	
Subject analysis set title	Maintenance (Main Study): M-HD
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Maintenance Higher Dose: Double-blind adalimumab 40 mg every week (ew) for 44 weeks.	
Subject analysis set title	Maintenance (Main Study + Japan Sub-study): M-SD
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Maintenance Standard Dose: Double-blind adalimumab 40 mg every other week (eow), for 44 weeks.

Subject analysis set title	Maintenance (Main Study + Japan Sub-study): M-HD
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Maintenance Higher Dose: Double-blind adalimumab 40 mg every week (ew) for 44 weeks.

Primary: Induction Period Primary Endpoint: Percentage of Participants With Clinical Remission Per Full Mayo Score (FMS) at Week 8

End point title	Induction Period Primary Endpoint: Percentage of Participants With Clinical Remission Per Full Mayo Score (FMS) at Week 8

End point description:

The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The FMS ranges from 0 (normal or inactive disease) to 12 (severe disease) and is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, endoscopy [confirmed by a central reader], and physician's global assessment), each of which ranges from 0 (normal) to 3 (severe disease). Negative changes indicate improvement. Clinical remission per FMS is defined as Mayo Score ≤ 2 and no individual subscore > 1.

Induction Study Intent-to-Treat (ITT) set: all participants who were randomized at Baseline. Non-responder imputation.

End point type	Primary

End point timeframe:

Week 8

End point values	Induction (Main Study): I-SD	Induction (Main Study): I-HD	Induction (Main Study + Japan Substudy): I-SD	Induction (Main Study + Japan Substudy): I-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	340	512	379	573
Units: percentage of participants				
number (not applicable)	10.9	13.3	11.6	13.8

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel test adjusted for previous infliximab use and baseline corticosteroid use.

Comparison groups	Induction (Main Study): I-SD v Induction (Main Study): I-HD

Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.269
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	7

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction (Main Study): I-SD v Induction (Main Study): I-HD
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.447 [1]
Method	Breslow-Day test

Notes:

[1] - Breslow-Day test of homogeneity across strata.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel test adjusted for previous infliximab use and baseline corticosteroid use.

Comparison groups	Induction (Main Study + Japan Substudy): I-HD v Induction (Main Study + Japan Substudy): I-SD
Number of subjects included in analysis	952
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.301
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	6.6

Statistical analysis title	Statistical Analysis 4
Comparison groups	Induction (Main Study + Japan Substudy): I-SD v Induction (Main Study + Japan Substudy): I-HD

Number of subjects included in analysis	952
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.502 [2]
Method	Breslow-Day test

Notes:

[2] - Breslow-Day test of homogeneity across strata.

Primary: Maintenance Period Primary Endpoint: Percentage of Week 8 Responders (Per FMS) With Clinical Remission (Per FMS) at Week 52

End point title	Maintenance Period Primary Endpoint: Percentage of Week 8 Responders (Per FMS) With Clinical Remission (Per FMS) at Week 52

End point description:

The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The FMS ranges from 0 (normal or inactive disease) to 12 (severe disease) and is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, endoscopy [confirmed by a central reader], and physician's global assessment), each of which ranges from 0 (normal) to 3 (severe disease). Negative changes indicate improvement. Week 8 responders (per FMS) are defined as participants with a decrease in Full Mayo score of ≥ 3 points and ≥ 30% from Baseline plus a decrease from baseline in the rectal bleeding subscore (RBS) ≥ 1 or an absolute RBS ≤ 1. Clinical remission per FMS is defined as Mayo Score ≤ 2 and no individual subscore > 1.

ITT-Responder population (I-ITT-RP): all participants in the Induction ITT population who achieve Week 8 response based on the FMS utilizing the endoscopy subscore provided by the central reader. Non-responder imputation.

End point type	Primary

End point timeframe:

Week 52

End point values	Maintenance (Main Study): M-SD	Maintenance (Main Study): M-HD	Maintenance (Main Study + Japan Sub-study): M-SD	Maintenance (Main Study + Japan Sub-study): M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	145	152	163	175
Units: percentage of participants				
number (not applicable)	29.0	39.5	30.1	41.1

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study): M-SD v Maintenance (Main Study): M-HD

Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.069
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	9.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	20.6

Statistical analysis title	Statistical Analysis 2
Comparison groups	Maintenance (Main Study): M-SD v Maintenance (Main Study): M-HD
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.085 [3]
Method	Breslow-Day test

Notes:

[3] - Breslow-Day test of homogeneity across strata.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study + Japan Sub-study): M-HD v Maintenance (Main Study + Japan Sub-study): M-SD
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.045
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	10.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	20.4

Statistical analysis title	Statistical Analysis 4
Comparison groups	Maintenance (Main Study + Japan Sub-study): M-SD v Maintenance (Main Study + Japan Sub-study): M-HD

Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.106 [4]
Method	Breslow-Day test

Notes:

[4] - Breslow-Day test of homogeneity across strata.

Secondary: Induction Period Ranked Secondary Endpoint 2: Percentage of Participants With Fecal Calprotectin < 150 mg/kg at Week 8

End point title	Induction Period Ranked Secondary Endpoint 2: Percentage of Participants With Fecal Calprotectin < 150 mg/kg at Week 8

End point description:

Induction Study Intent-to-Treat (ITT) set: all participants who were randomized at Baseline. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 8

End point values	Induction (Main Study): I-SD	Induction (Main Study): I-HD	Induction (Main Study + Japan Substudy): I-SD	Induction (Main Study + Japan Substudy): I-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	340	512	379	573
Units: percentage of participants				
number (not applicable)	27.1	31.1	26.9	30.5

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel test adjusted for previous infliximab use and baseline corticosteroid use.

Comparison groups	Induction (Main Study): I-SD v Induction (Main Study): I-HD
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	8.6

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel test adjusted for previous infliximab use and baseline corticosteroid use.

Comparison groups	Induction (Main Study + Japan Substudy): I-SD v Induction (Main Study + Japan Substudy): I-HD
Number of subjects included in analysis	952
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.254
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	8.4

Secondary: Induction Period Ranked Secondary Endpoint 1: Percentage of Participants With Endoscopic Improvement at Week 8

End point title	Induction Period Ranked Secondary Endpoint 1: Percentage of Participants With Endoscopic Improvement at Week 8

End point description:

The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The FMS ranges from 0 (normal or inactive disease) to 12 (severe disease) and is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, endoscopy [confirmed by a central reader], and physician's global assessment), each of which ranges from 0 (normal) to 3 (severe disease). Negative changes indicate improvement. Endoscopic improvement is defined as an endoscopy subscore of 0 or 1.

Induction Study Intent-to-Treat (ITT) set: all participants who were randomized at Baseline. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 8

End point values	Induction (Main Study): I-SD	Induction (Main Study): I-HD	Induction (Main Study + Japan Substudy): I-SD	Induction (Main Study + Japan Substudy): I-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	340	512	379	573
Units: percentage of participants				
number (not applicable)	27.1	31.1	26.9	30.5

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel test adjusted for previous infliximab use and baseline corticosteroid use.

Comparison groups	Induction (Main Study): I-SD v Induction (Main Study): I-HD
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.181
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	10.5

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel test adjusted for previous infliximab use and baseline corticosteroid use.

Comparison groups	Induction (Main Study + Japan Substudy): I-SD v Induction (Main Study + Japan Substudy): I-HD
Number of subjects included in analysis	952
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	3.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	9.7

Secondary: Induction Period Ranked Secondary Endpoint 3: Percentage of Participants With Inflammatory Bowel Disease Questionnaire (IBDQ) Response (Increase of IBDQ ≥ 16 From Baseline) at Week 8

End point title	Induction Period Ranked Secondary Endpoint 3: Percentage of Participants With Inflammatory Bowel Disease Questionnaire (IBDQ) Response (Increase of IBDQ ≥ 16 From Baseline) at Week 8

End point description:

The IBDQ is a self-administered 32-item questionnaire to evaluate quality of life across 4 dimensional scores: bowel, systemic, social and emotional. Responses to each question range from 1 (severe problem) to 7 (normal health). Total IBDQ score is the sum of the responses to the individual IBDQ questions, and ranges from 32 to 224 with higher scores indicating a better quality of life.

Induction Study Intent-to-Treat (ITT) set: all participants who were randomized at Baseline. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 8

End point values	Induction (Main Study): I-SD	Induction (Main Study): I-HD	Induction (Main Study + Japan Substudy): I-SD	Induction (Main Study + Japan Substudy): I-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	340	512	379	573
Units: percentage of participants				
number (not applicable)	60.9	67.2	60.7	65.3

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel test adjusted for previous infliximab use and baseline corticosteroid use.

Comparison groups	Induction (Main Study): I-SD v Induction (Main Study): I-HD

Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	13.1

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel test adjusted for previous infliximab use and baseline corticosteroid use.

Comparison groups	Induction (Main Study + Japan Substudy): I-SD v Induction (Main Study + Japan Substudy): I-HD
Number of subjects included in analysis	952
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.131
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	11

Secondary: Induction Period Ranked Secondary Endpoint 4: Percentage of Participants With Clinical Response Per FMS at Week 8

End point title	Induction Period Ranked Secondary Endpoint 4: Percentage of Participants With Clinical Response Per FMS at Week 8

End point description:

The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The FMS ranges from 0 (normal or inactive disease) to 12 (severe disease) and is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, endoscopy [confirmed by a central reader], and physician's global assessment), each of which ranges from 0 (normal) to 3 (severe disease). Negative changes indicate improvement. Clinical response is defined as a decrease in FMS of ≥ 3 points and ≥ 30% from baseline, plus a decrease in the rectal bleeding subscore (RBS) ≥ 1 or an absolute RBS ≤ 1.

Induction Study Intent-to-Treat (ITT) set: all participants who were randomized at Baseline. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 8

End point values	Induction (Main Study): I-SD	Induction (Main Study): I-HD	Induction (Main Study + Japan Substudy): I-SD	Induction (Main Study + Japan Substudy): I-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	340	512	379	573
Units: percentage of participants				
number (not applicable)	40.0	47.1	38.8	47.3

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel test adjusted for previous infliximab use and baseline corticosteroid use.

Comparison groups	Induction (Main Study): I-SD v Induction (Main Study): I-HD
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	7.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	14.1

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel test adjusted for previous infliximab use and baseline corticosteroid use.

Comparison groups	Induction (Main Study + Japan Substudy): I-SD v Induction (Main Study + Japan Substudy): I-HD
Number of subjects included in analysis	952
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	8.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.3
upper limit	15.1

Secondary: Induction Period Ranked Secondary Endpoint 5: Percentage of Participants With Endoscopic Remission at Week 8

End point title	Induction Period Ranked Secondary Endpoint 5: Percentage of Participants With Endoscopic Remission at Week 8

End point description:

The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The FMS ranges from 0 (normal or inactive disease) to 12 (severe disease) and is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, endoscopy [confirmed by a central reader], and physician's global assessment), each of which ranges from 0 (normal) to 3 (severe disease). Negative changes indicate improvement. Endoscopic remission is defined as an endoscopy subscore of 0.

Induction Study Intent-to-Treat (ITT) set: all participants who were randomized at Baseline. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 8

End point values	Induction (Main Study): I-SD	Induction (Main Study): I-HD	Induction (Main Study + Japan Substudy): I-SD	Induction (Main Study + Japan Substudy): I-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	340	512	379	573
Units: percentage of participants				
number (not applicable)	10.0	13.1	10.0	12.9

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel test adjusted for previous infliximab use and baseline corticosteroid use.

Comparison groups	Induction (Main Study): I-HD v Induction (Main Study): I-SD
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	3.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	7.6

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel test adjusted for previous infliximab use and baseline corticosteroid use.

Comparison groups	Induction (Main Study + Japan Substudy): I-SD v Induction (Main Study + Japan Substudy): I-HD
Number of subjects included in analysis	952
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.166
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	7.1

Secondary: Induction Period Ranked Secondary Endpoint 6: Percentage of Participants Achieving Response in IBDQ Bowel Symptom Domain at Week 8

End point title	Induction Period Ranked Secondary Endpoint 6: Percentage of Participants Achieving Response in IBDQ Bowel Symptom Domain at Week 8

End point description:

The IBDQ is a self-administered 32-item questionnaire to evaluate quality of life across 4 dimensional scores: bowel, systemic, social and emotional. Responses to each question range from 1 (severe problem) to 7 (normal health). The range for Bowel Symptom domain score is 10 (severe problem) to 70 (normal health). Response in IBDQ Bowel Symptom domain is defined as an increase of IBDQ Bowel Symptom domain score ≥ 6.

Induction Study Intent-to-Treat (ITT) set: all participants who were randomized at Baseline. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 8

End point values	Induction (Main Study): I-SD	Induction (Main Study): I-HD	Induction (Main Study + Japan Substudy): I-SD	Induction (Main Study + Japan Substudy): I-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	340	512	379	573
Units: percentage of participants				
number (not applicable)	63.2	71.3	63.1	69.8

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel test adjusted for previous infliximab use and baseline corticosteroid use.

Comparison groups	Induction (Main Study): I-SD v Induction (Main Study): I-HD
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	8.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.9
upper limit	14.7

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel test adjusted for previous infliximab use and baseline corticosteroid use.

Comparison groups	Induction (Main Study + Japan Substudy): I-SD v Induction (Main Study + Japan Substudy): I-HD
Number of subjects included in analysis	952
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	7

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	13

Secondary: Induction Period Ranked Secondary Endpoint 7: Percentage of Participants Achieving Response in IBDQ Fatigue Item at Week 8

End point title	Induction Period Ranked Secondary Endpoint 7: Percentage of Participants Achieving Response in IBDQ Fatigue Item at Week 8

End point description:

The IBDQ is a self-administered 32-item questionnaire to evaluate quality of life across 4 dimensional scores: bowel, systemic, social and emotional. Responses to each question range from 1 (severe problem) to 7 (normal health). The IBDQ Fatigue item score range is from 1 (severe problem) to 7 (normal health). Response is defined as an increase of IBDQ Fatigue item score ≥ 1.

Induction Study Intent-to-Treat (ITT) set: all participants who were randomized at Baseline. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 8

End point values	Induction (Main Study): I-SD	Induction (Main Study): I-HD	Induction (Main Study + Japan Substudy): I-SD	Induction (Main Study + Japan Substudy): I-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	340	512	379	573
Units: percentage of participants				
number (not applicable)	57.1	61.1	57.5	59.9

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel test adjusted for previous infliximab use and baseline corticosteroid use.

Comparison groups	Induction (Main Study): I-SD v Induction (Main Study): I-HD
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.218
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	4.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	10.9

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel test adjusted for previous infliximab use and baseline corticosteroid use.

Comparison groups	Induction (Main Study + Japan Substudy): I-SD v Induction (Main Study + Japan Substudy): I-HD
Number of subjects included in analysis	952
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.456
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	8.8

Secondary: Maintenance Period Ranked Secondary Endpoint 1: Percentage of Week 8 Responders (Per FMS) With Endoscopic Improvement at Week 52

End point title	Maintenance Period Ranked Secondary Endpoint 1: Percentage of Week 8 Responders (Per FMS) With Endoscopic Improvement at Week 52

End point description:

The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The FMS ranges from 0 (normal or inactive disease) to 12 (severe disease) and is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, endoscopy [confirmed by a central reader], and physician's global assessment), each of which ranges from 0 (normal) to 3 (severe disease). Negative changes indicate improvement. Week 8 responders are defined as participants with a decrease in FMS of ≥ 3 points and ≥ 30% from Baseline plus a decrease in the rectal bleeding subscore (RBS) ≥ 1 or an absolute RBS ≤ 1. Endoscopic improvement is defined as an endoscopy subscore of 0 or 1.

ITT-Responder population (I-ITT-RP): all participants in the Induction ITT population who achieve Week 8 response based on the FMS utilizing the endoscopy subscore provided by the central reader. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 52

End point values	Maintenance (Main Study): M-SD	Maintenance (Main Study): M-HD	Maintenance (Main Study + Japan Sub-study): M-SD	Maintenance (Main Study + Japan Sub-study): M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	145	152	163	175
Units: percentage of participants				
number (not applicable)	41.4	51.3	41.7	52.0

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study): M-SD v Maintenance (Main Study): M-HD
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.098
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	9.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	20.8

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study + Japan Sub-study): M-SD v Maintenance (Main Study + Japan Sub-study): M-HD
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.066
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	9.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	20.5

Secondary: Maintenance Period Ranked Secondary Endpoint 2: Percentage of Week 8 Responders With Steroid Usage at Baseline and Steroid Free at Least 90 Days at Week 52

End point title	Maintenance Period Ranked Secondary Endpoint 2: Percentage of Week 8 Responders With Steroid Usage at Baseline and Steroid Free at Least 90 Days at Week 52

End point description:

The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The FMS ranges from 0 (normal or inactive disease) to 12 (severe disease) and is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, endoscopy [confirmed by a central reader], and physician's global assessment), each of which ranges from 0 (normal) to 3 (severe disease). Negative changes indicate improvement. Week 8 responders, per FMS, are defined as participants with a decrease in FMS of ≥ 3 points and ≥ 30% from Baseline plus a decrease in the rectal bleeding subscore (RBS) ≥ 1 or an absolute RBS ≤ 1.

I-ITT-RP: participants in the Induction ITT population who achieve Week 8 response based on the FMS utilizing the endoscopy subscore provided by the central reader. Participants with steroid use at Baseline. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 52

End point values	Maintenance (Main Study): M-SD	Maintenance (Main Study): M-HD	Maintenance (Main Study + Japan Sub-study): M-SD	Maintenance (Main Study + Japan Sub-study): M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	92	95	103	108
Units: percentage of participants				
number (not applicable)	53.3	74.7	54.4	74.1

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study): M-SD v Maintenance (Main Study): M-HD

Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	21.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.6
upper limit	35.4

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study + Japan Sub-study): M-SD v Maintenance (Main Study + Japan Sub-study): M-HD
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	19.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.6
upper limit	32.7

Secondary: Maintenance Period Ranked Secondary Endpoint 3: Percentage of Week 8 Responders With Steroid Usage at Baseline and Steroid Free at Least 90 Days and With Clinical Remission at Week 52

End point title	Maintenance Period Ranked Secondary Endpoint 3: Percentage of Week 8 Responders With Steroid Usage at Baseline and Steroid Free at Least 90 Days and With Clinical Remission at Week 52

End point description:

The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The FMS ranges from 0 (normal or inactive disease) to 12 (severe disease) and is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, endoscopy [confirmed by a central reader], and physician's global assessment), each of which ranges from 0 (normal) to 3 (severe disease). Negative changes indicate improvement. Week 8 responders, per FMS, are defined as participants with a decrease in FMS of ≥ 3 points and ≥ 30% from Baseline plus a decrease in the rectal bleeding subscore (RBS) ≥ 1 or an absolute RBS ≤ 1. Clinical remission is defined as FMS ≤ 2 with no subscore > 1.

I-ITT-RP: participants in the Induction ITT population who achieve Week 8 response based on the FMS utilizing the endoscopy subscore provided by the central reader. Participants with steroid use at

Baseline. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 52

End point values	Maintenance (Main Study): M-SD	Maintenance (Main Study): M-HD	Maintenance (Main Study + Japan Sub-study): M-SD	Maintenance (Main Study + Japan Sub-study): M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	92	95	103	108
Units: percentage of participants				
number (not applicable)	27.2	38.9	28.2	39.8

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study): M-SD v Maintenance (Main Study): M-HD
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.093
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	11.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	25

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study + Japan Sub-study): M-SD v Maintenance (Main Study + Japan Sub-study): M-HD

Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.088
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	11.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	23.8

Secondary: Maintenance Period Ranked Secondary Endpoint 4: Percentage of Week 8 Remitters (Per FMS) With Clinical Remission (Per FMS) at Week 52

End point title	Maintenance Period Ranked Secondary Endpoint 4: Percentage of Week 8 Remitters (Per FMS) With Clinical Remission (Per FMS) at Week 52

End point description:

The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The FMS ranges from 0 (normal or inactive disease) to 12 (severe disease) and is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, endoscopy [confirmed by a central reader], and physician's global assessment), each of which ranges from 0 (normal) to 3 (severe disease). Negative changes indicate improvement. Week 8 remitters are defined as participants with clinical remission (per FMS) at Week 8. Clinical remission is defined as a FMS ≤ 2 with no subscore > 1. Endoscopy subscore provided by the central reader.

ITT-Remitter (ITT-RM) Population included all participants in the ITT population who achieved Week 8 remission based on the FMS utilizing the endoscopy subscore provided by the central reader. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 52

End point values	Maintenance (Main Study): M-SD	Maintenance (Main Study): M-HD	Maintenance (Main Study + Japan Sub-study): M-SD	Maintenance (Main Study + Japan Sub-study): M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	42	45	52
Units: percentage of participants				
number (not applicable)	40.5	57.1	44.4	55.8

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the

treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study): M-SD v Maintenance (Main Study): M-HD
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.161
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	15.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	38.2

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study + Japan Sub-study): M-SD v Maintenance (Main Study + Japan Sub-study): M-HD
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.312
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	10.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.8
upper limit	30.6

Secondary: Maintenance Period Ranked Secondary Endpoint 5: Percentage of Week 8 Remitters (Per FMS) With Endoscopic Improvement at Week 52

End point title	Maintenance Period Ranked Secondary Endpoint 5: Percentage of Week 8 Remitters (Per FMS) With Endoscopic Improvement at Week 52

End point description:

The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The FMS ranges from 0 (normal or inactive disease) to 12 (severe disease) and is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, endoscopy [confirmed by a central reader], and physician's global assessment), each of which ranges from 0 (normal) to 3 (severe disease). Negative changes indicate improvement. Week 8 remitters are defined as participants with clinical remission (per FMS) at Week 8. Clinical remission is defined as a FMS ≤ 2 with no subscore > 1. Endoscopic improvement is defined as an endoscopy subscore of 0 or 1. Endoscopy subscore provided by the central reader.

ITT-Remitter (ITT-RM) Population included all participants in the ITT population who achieved Week 8 remission based on the FMS utilizing the endoscopy subscore provided by the central reader. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 52

End point values	Maintenance (Main Study): M-SD	Maintenance (Main Study): M-HD	Maintenance (Main Study + Japan Sub-study): M-SD	Maintenance (Main Study + Japan Sub-study): M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	42	45	52
Units: percentage of participants				
number (not applicable)	51.4	64.3	55.6	61.5

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study): M-HD v Maintenance (Main Study): M-SD
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.272
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	12.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.7
upper limit	34.4

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study + Japan Sub-study): M-SD v Maintenance (Main Study + Japan Sub-study): M-HD

Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.6
upper limit	25.2

Secondary: Maintenance Period Ranked Secondary Endpoint 6: Percentage of Week 8 Remitters (Per FMS) With Steroid Usage at Baseline and Steroid Free at Least 90 Days at Week 52

End point title	Maintenance Period Ranked Secondary Endpoint 6: Percentage of Week 8 Remitters (Per FMS) With Steroid Usage at Baseline and Steroid Free at Least 90 Days at Week 52

End point description:

The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The FMS ranges from 0 (normal or inactive disease) to 12 (severe disease) and is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, endoscopy [confirmed by a central reader], and physician's global assessment), each of which ranges from 0 (normal) to 3 (severe disease). Negative changes indicate improvement. Week 8 remitters are defined as participants with clinical remission (per FMS) at Week 8. Clinical remission is defined as a FMS ≤ 2 with no subscore > 1.

ITT-RM Population: participants in ITT population who achieved Week 8 remission based on the FMS utilizing the endoscopy subscore provided by the central reader. Participants with steroid use at Baseline. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 52

End point values	Maintenance (Main Study): M-SD	Maintenance (Main Study): M-HD	Maintenance (Main Study + Japan Sub-study): M-SD	Maintenance (Main Study + Japan Sub-study): M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	26	27	32	35
Units: percentage of participants				
number (not applicable)	53.8	77.8	56.3	71.4

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the

treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study): M-SD v Maintenance (Main Study): M-HD
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.074
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	23.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	49.9

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study + Japan Sub-study): M-SD v Maintenance (Main Study + Japan Sub-study): M-HD
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.5
upper limit	38.4

Secondary: Maintenance Period Ranked Secondary Endpoint 7: Percentage of Week 8 Remitters (Per FMS) With Steroid Usage at Baseline and Steroid Free at Least 90 Days and With Clinical Remission (Per FMS) at Week 52

End point title	Maintenance Period Ranked Secondary Endpoint 7: Percentage of Week 8 Remitters (Per FMS) With Steroid Usage at Baseline and Steroid Free at Least 90 Days and With Clinical Remission (Per FMS) at Week 52

End point description:

The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The FMS ranges from 0 (normal or inactive disease) to 12 (severe disease) and is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, endoscopy [confirmed by a central reader], and physician's global assessment), each of which ranges from 0 (normal) to 3 (severe disease). Negative changes indicate improvement. Week 8 remitters are defined as participants with clinical remission (per FMS) at Week 8. Clinical remission is defined as a FMS ≤ 2 with no subscore > 1.

ITT-RM Population: all participants in the ITT population who achieved Week 8 remission based on the FMS utilizing the endoscopy subscore provided by the central reader. Participants with steroid usage. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 52

End point values	Maintenance (Main Study): M-SD	Maintenance (Main Study): M-HD	Maintenance (Main Study + Japan Sub-study): M-SD	Maintenance (Main Study + Japan Sub-study): M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	26	27	32	35
Units: percentage of participants				
number (not applicable)	34.6	55.6	37.5	51.4

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study): M-SD v Maintenance (Main Study): M-HD
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.151
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	20
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	47.3

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study + Japan Sub-study): M-SD v Maintenance (Main Study + Japan Sub-study): M-HD

Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.299
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	12.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.3
upper limit	36.8

Secondary: Maintenance Period Ranked Secondary Endpoint 8: Percentage of Week 8 Responders (Per FMS) With IBDQ Response (Increase of IBDQ ≥ 16 From Baseline) at Week 52

End point title	Maintenance Period Ranked Secondary Endpoint 8: Percentage of Week 8 Responders (Per FMS) With IBDQ Response (Increase of IBDQ ≥ 16 From Baseline) at Week 52

End point description:

The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The FMS ranges from 0 (normal or inactive disease) to 12 (severe disease) and is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, endoscopy [confirmed by a central reader], and physician's global assessment), each of which ranges from 0 (normal) to 3 (severe disease). Negative changes indicate improvement. Week 8 responders are defined as participants with a decrease in FMS of ≥ 3 points and ≥ 30% from Baseline plus a decrease in the rectal bleeding subscore (RBS) ≥ 1 or an absolute RBS ≤ 1. The IBDQ is a self-administered 32-item questionnaire to evaluate quality of life across 4 dimensional scores: bowel, systemic, social and emotional. Responses to each question range from 1 (severe problem) to 7 (normal health). Total IBDQ score is the sum of responses to the individual IBDQ questions, and ranges from 32 to 224 with higher scores indicating a better quality of life.

End point type	Secondary

End point timeframe:

Week 52

End point values	Maintenance (Main Study): M-SD	Maintenance (Main Study): M-HD	Maintenance (Main Study + Japan Sub-study): M-SD	Maintenance (Main Study + Japan Sub-study): M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	145[5]	152[6]	163[7]	175[8]
Units: percentage of participants				
number (not applicable)	62.1	66.4	62.6	65.7

Notes:

[5] - ITT-Responder population (ITT-RP). Non-responder imputation.

[6] - ITT-Responder population (ITT-RP). Non-responder imputation.

[7] - ITT-Responder population (ITT-RP). Non-responder imputation.

[8] - ITT-Responder population (ITT-RP). Non-responder imputation.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study): M-SD v Maintenance (Main Study): M-HD
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.422
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	15.3

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study + Japan Sub-study): M-SD v Maintenance (Main Study + Japan Sub-study): M-HD
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.513
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.8
upper limit	13.6

Secondary: Maintenance Period Ranked Secondary Endpoint 9: Percentage of Week 8 Non-Responders With Clinical Remission (Per FMS) at Week 52

End point title	Maintenance Period Ranked Secondary Endpoint 9: Percentage of Week 8 Non-Responders With Clinical Remission (Per FMS) at Week 52

End point description:

The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The FMS ranges from 0 (normal or inactive disease) to 12 (severe disease) and is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, endoscopy [confirmed by a central reader], and physician's global

assessment), each of which ranges from 0 (normal) to 3 (severe disease). Negative changes indicate improvement. Week 8 non-responders are defined as participants not meeting the criteria of response (defined as a decrease in FMS of ≥ 3 points and ≥ 30% from baseline, plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS ≤ 1) at Week 8. Clinical remission is defined as a FMS ≤ 2 with no subscore > 1.

ITT-Non-Responder (ITT-NRP) Population: all participants in ITT who did not achieve Week 8 response based on the Full Mayo Score utilizing the endoscopy subscore provided by the central reader. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 52

End point values	Maintenance (Main Study): M-SD	Maintenance (Main Study): M-HD	Maintenance (Main Study + Japan Sub-study): M-SD	Maintenance (Main Study + Japan Sub-study): M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	157	152	182	175
Units: percentage of participants				
number (not applicable)	12.1	15.8	12.1	16.0

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study): M-SD v Maintenance (Main Study): M-HD
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.351
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	11.4

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for

induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study + Japan Sub-study): M-SD v Maintenance (Main Study + Japan Sub-study): M-HD
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.292
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	11.1

Secondary: Maintenance Period Ranked Secondary Endpoint 10: Percentage of Week 8 Non-Remitters With Clinical Remission (Per FMS) at Week 52

End point title	Maintenance Period Ranked Secondary Endpoint 10: Percentage of Week 8 Non-Remitters With Clinical Remission (Per FMS) at Week 52

End point description:

The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The FMS ranges from 0 (normal or inactive disease) to 12 (severe disease) and is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, endoscopy [confirmed by a central reader], and physician's global assessment), each of which ranges from 0 (normal) to 3 (severe disease). Negative changes indicate improvement. Week 8 non-remitters are defined as participants not meeting the criteria of clinical remission at Week 8. Clinical remission is defined as a FMS ≤ 2 with no subscore > 1.

ITT-Non-Remitter (ITT-NRM) Population: all participants in ITT who did not achieve Week 8 remission based on the FMS utilizing the endoscopy subscore provided by the central reader. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 52

End point values	Maintenance (Main Study): M-SD	Maintenance (Main Study): M-HD	Maintenance (Main Study + Japan Sub-study): M-SD	Maintenance (Main Study + Japan Sub-study): M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	265	262	300	298
Units: percentage of participants				
number (not applicable)	17.4	22.9	17.0	23.8

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study): M-SD v Maintenance (Main Study): M-HD
Number of subjects included in analysis	527
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.121
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	12.1

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study + Japan Sub-study): M-SD v Maintenance (Main Study + Japan Sub-study): M-HD
Number of subjects included in analysis	598
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.046
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	12.8

Secondary: Maintenance Period Ranked Secondary Endpoint 11: Percentage of Week 8 Responders (Per FMS) With Endoscopic Subscore of 0 at Week 52

End point title	Maintenance Period Ranked Secondary Endpoint 11: Percentage of Week 8 Responders (Per FMS) With Endoscopic Subscore of 0 at Week 52

End point description:

The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The FMS ranges from 0 (normal or inactive disease) to 12 (severe disease) and is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, endoscopy [confirmed by a central reader], and physician's global

assessment), each of which ranges from 0 (normal) to 3 (severe disease). Negative changes indicate improvement. Week 8 responders (per Full Mayo score) are defined as participants with a decrease in Full Mayo score of ≥ 3 points and ≥ 30% from Baseline plus a decrease in the rectal bleeding subscore (RBS) ≥ 1 or an absolute RBS ≤ 1. Endoscopic remission is defined as an endoscopy subscore of 0.

ITT-RP: participants in the Induction ITT population who achieve Week 8 response based on the FMS utilizing the endoscopy subscore provided by the central reader. Participants who were remitters at Week 8. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 52

End point values	Maintenance (Main Study): M-SD	Maintenance (Main Study): M-HD	Maintenance (Main Study + Japan Sub-study): M-SD	Maintenance (Main Study + Japan Sub-study): M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	145	152	163	175
Units: percentage of participants				
number (not applicable)	27.6	35.5	27.0	35.4

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study): M-SD v Maintenance (Main Study): M-HD
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.159
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	7.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	17.9

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study + Japan Sub-study): M-SD v Maintenance (Main Study + Japan Sub-study): M-HD
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.109
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	17.9

Secondary: Maintenance Period Ranked Secondary Endpoint 12: Percentage of Week 8 Remitters (Per FMS) With Endoscopic Subscore of 0 at Week 52

End point title	Maintenance Period Ranked Secondary Endpoint 12: Percentage of Week 8 Remitters (Per FMS) With Endoscopic Subscore of 0 at Week 52

End point description:

The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The FMS ranges from 0 (normal or inactive disease) to 12 (severe disease) and is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, endoscopy [confirmed by a central reader], and physician's global assessment), each of which ranges from 0 (normal) to 3 (severe disease). Negative changes indicate improvement. Week 8 remitters are defined as participants with clinical remission (per FMS) at Week 8. Clinical remission is defined as a FMS ≤ 2 with no subscore > 1. Endoscopic remission is defined as an endoscopy subscore of 0.

ITT-Remitter (ITT-RM) Population: all participants in ITT who achieved Week 8 remission based on the Full Mayo Score utilizing the endoscopy subscore provided by the central reader. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 52

End point values	Maintenance (Main Study): M-SD	Maintenance (Main Study): M-HD	Maintenance (Main Study + Japan Sub-study): M-SD	Maintenance (Main Study + Japan Sub-study): M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	42	45	52
Units: percentage of participants				
number (not applicable)	45.9	47.6	42.2	44.2

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study): M-SD v Maintenance (Main Study): M-HD
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.903
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21
upper limit	23.8

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study + Japan Sub-study): M-SD v Maintenance (Main Study + Japan Sub-study): M-HD
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.901
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.8
upper limit	21.3

Secondary: Maintenance Period Ranked Secondary Endpoint 13: Percentage of Week 8 Responders (Per FMS) With Response in IBDQ Bowel Symptom Domain at Week 52

End point title	Maintenance Period Ranked Secondary Endpoint 13: Percentage of Week 8 Responders (Per FMS) With Response in IBDQ Bowel Symptom Domain at Week 52

End point description:

The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The FMS ranges from 0 (normal or inactive disease) to 12 (severe disease) and is calculated as the sum of 4 subscores (stool

frequency, rectal bleeding, endoscopy [confirmed by a central reader], and physician's global assessment), each of which ranges from 0 (normal) to 3 (severe disease). Negative changes indicate improvement. Week 8 responders are defined as participants with a decrease in FMS of ≥ 3 points and ≥ 30% from Baseline plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS ≤ 1. The IBDQ is a self-administered 32-item questionnaire to evaluate quality of life across 4 dimensional scores: bowel, systemic, social and emotional. Responses to each question range from 1 (severe problem) to 7 (normal health). Bowel Symptom domain score range is 10 (severe problem) to 70 (normal health). Response is defined as increase of Bowel Symptom domain score ≥ 6 from baseline.

End point type	Secondary

End point timeframe:

Week 52

End point values	Maintenance (Main Study): M-SD	Maintenance (Main Study): M-HD	Maintenance (Main Study + Japan Sub-study): M-SD	Maintenance (Main Study + Japan Sub-study): M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	145[9]	152[10]	163[11]	175[12]
Units: percentage of participants				
number (not applicable)	62.1	69.7	62.6	71.4

Notes:

[9] - ITT-Responder population (ITT-RP). Non-responder imputation.

[10] - ITT-Responder population (ITT-RP). Non-responder imputation.

[11] - ITT-Responder population (ITT-RP). Non-responder imputation.

[12] - ITT-Responder population (ITT-RP). Non-responder imputation.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study): M-SD v Maintenance (Main Study): M-HD
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	7.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	18.4

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.

Comparison groups	Maintenance (Main Study + Japan Sub-study): M-SD v Maintenance (Main Study + Japan Sub-study): M-HD
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.076
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	9.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	19.1

Secondary: Maintenance Period Ranked Secondary Endpoint 14: Percentage of Week 8 Responders (Per FMS) With Response in IBDQ Fatigue Item at Week 52

End point title	Maintenance Period Ranked Secondary Endpoint 14: Percentage of Week 8 Responders (Per FMS) With Response in IBDQ Fatigue Item at Week 52

End point description:

The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The FMS ranges from 0 (normal or inactive disease) to 12 (severe disease) and is calculated as the sum of 4 subscores (stool frequency, rectal bleeding, endoscopy [confirmed by a central reader], and physician's global assessment), each of which ranges from 0 (normal) to 3 (severe disease). Negative changes indicate improvement. Week 8 responders are defined as participants with a decrease in FMS of ≥ 3 points and ≥ 30% from Baseline plus a decrease in the rectal bleeding subscore (RBS) ≥ 1 or an absolute RBS ≤ 1. The IBDQ is a self-administered 32-item questionnaire to evaluate quality of life across 4 dimensional scores: bowel, systemic, social and emotional. Responses to each question range from 1 (severe problem) to 7 (normal health). Response in IBDQ fatigue item (range 1 [severe problem] to 7 [normal health]) is defined as increase of IBDQ fatigue item ≥ 1 from baseline.

End point type	Secondary

End point timeframe:

Week 52

End point values	Maintenance (Main Study): M-SD	Maintenance (Main Study): M-HD	Maintenance (Main Study + Japan Sub-study): M-SD	Maintenance (Main Study + Japan Sub-study): M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	145[13]	152[14]	163[15]	175[16]
Units: percentage of participants				
number (not applicable)	53.8	61.2	55.2	59.4

Notes:

[13] - ITT-Responder population (ITT-RP). Non-responder imputation.

[14] - ITT-Responder population (ITT-RP). Non-responder imputation.

[15] - ITT-Responder population (ITT-RP). Non-responder imputation.

[16] - ITT-Responder population (ITT-RP). Non-responder imputation.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.	
Comparison groups	Maintenance (Main Study): M-SD v Maintenance (Main Study): M-HD
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.207
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	7.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	18.6

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Adjusted risk difference, 95% confidence interval for the difference in the proportions between the treatment groups and P-value were calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen and week 8 remission status.	
Comparison groups	Maintenance (Main Study + Japan Sub-study): M-SD v Maintenance (Main Study + Japan Sub-study): M-HD
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	14.8

Adverse events

Adverse events information

Timeframe for reporting adverse events:

See time frame specifics detailed for each reporting group in their respective descriptions below. Treatment-emergent adverse events (TEAEs) are presented.

Adverse event reporting additional description:

Participants were contacted 70 days following study drug discontinuation for an assessment of any new or ongoing adverse events, except those participants who continued on adalimumab therapy after the end of study participation.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Induction (Main Study + Japan Substudy): I-SD

Reporting group description:

Induction Standard Dose: Double-blind adalimumab regimen of 160 mg at Week 0 followed by 80 mg at Week 2, 40 mg at Week 4, and 40 mg at Week 6.

TEAEs during induction period: events with an onset date on or after first dose date of study drug in induction period and up to 70 days after last dose date of the study drug in induction period and prior to first dose date of study drug in maintenance period. Mean duration of treatment was 57.5 days.

Reporting group title	Induction (Main Study + Japan Substudy): I-HD

Reporting group description:

Induction Higher Dose: Double-blind adalimumab regimen of 160 mg at Weeks 0, 1, 2, and 3 followed by 40 mg at Week 4 and 40 mg at Week 6.

TEAEs during induction period: events with an onset date on or after first dose date of study drug in induction period and up to 70 days after last dose date of the study drug in induction period and prior to first dose date of study drug in maintenance period. Mean duration of treatment was 55.0 days.

Reporting group title	Maintenance (Main Study + Japan Sub-study): M-SD

Reporting group description:

Maintenance Standard Dose: Double-blind adalimumab 40 mg every other week (eow), for 44 weeks.

TEAEs during maintenance period: events with an onset date on or after first dose date of study drug in maintenance period and up to 70 days after the last dose date of the study drug in maintenance period. Mean duration of treatment was 251.5 days.

Reporting group title	Maintenance (Main Study + Japan Sub-study): M-HD

Reporting group description:

Maintenance Higher Dose: Double-blind adalimumab 40 mg every week (ew) for 44 weeks.

TEAEs during maintenance period: events with an onset date on or after first dose date of study drug in maintenance period and up to 70 days after the last dose date of the study drug in maintenance period. Mean duration of treatment was 263.1 days.

Reporting group title	Maintenance (Main Study): TDM Regimen

Reporting group description:

Double-blind adalimumab 40 mg eow at Week 8 and Week 10, with possible dose adjustments at Weeks 12, 24, and 37 based on criteria assessing blinded adalimumab serum concentration and rectal bleeding subscore (RBS) assessments.

TEAEs during maintenance period: events with an onset date on or after first dose date of study drug in maintenance period and up to 70 days after the last dose date of the study drug in maintenance period. Mean duration of treatment was 255.9 days.

Serious adverse events	Induction (Main Study + Japan Substudy): I-SD	Induction (Main Study + Japan Substudy): I-HD	Maintenance (Main Study + Japan Sub-study): M-SD
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 573 (3.84%)	19 / 379 (5.01%)	44 / 345 (12.75%)
number of deaths (all causes)	2	0	2
number of deaths resulting from adverse events	1	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BLADDER CANCER			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
FIBROMATOSIS			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
MALIGNANT MELANOMA			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
MALIGNANT MELANOMA IN SITU			
subjects affected / exposed	0 / 573 (0.00%)	1 / 379 (0.26%)	0 / 345 (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
NON-SMALL CELL LUNG CANCER			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
OESOPHAGEAL ADENOCARCINOMA			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
SQUAMOUS CELL CARCINOMA OF THE CERVIX			

subjects affected / exposed	0 / 573 (0.00%)	1 / 379 (0.26%)	0 / 345 (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
UTERINE LEIOMYOMA			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THROMBOPHLEBITIS			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
WOUND DRAINAGE			
subjects affected / exposed	1 / 573 (0.17%)	0 / 379 (0.00%)	0 / 345 (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
General disorders and administration site conditions			
GAIT DISTURBANCE			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
subjects affected / exposed	1 / 573 (0.17%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
PROSTATOMEGALY			

subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
EMPHYSEMA			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
NASAL POLYPS			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NASAL SEPTUM DEVIATION			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
SINUS POLYP			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
BINGE DRINKING			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
BIPOLAR DISORDER			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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

Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WEIGHT DECREASED			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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			
HUMERUS FRACTURE			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
MENISCUS INJURY			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
PATELLA FRACTURE			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
POST PROCEDURAL HAEMORRHAGE			

subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
RADIUS FRACTURE			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
RIB FRACTURE			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER LIMB FRACTURE			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC ARREST			
subjects affected / exposed	1 / 573 (0.17%)	0 / 379 (0.00%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CORONARY ARTERY DISEASE			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOCARDIAL ISCHAEMIA			

subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
ALTERED STATE OF CONSCIOUSNESS			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
HYPOAESTHESIA			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
ISCHAEMIC STROKE			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
MONONEUROPATHY			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	2 / 573 (0.35%)	3 / 379 (0.79%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IRON DEFICIENCY ANAEMIA			

subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
LYMPHADENOPATHY			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
THROMBOCYTOSIS			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
Eye disorders			
EYELID PTOSIS			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
OPTIC ATROPHY			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	1 / 573 (0.17%)	1 / 379 (0.26%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANOGENITAL DYSPLASIA			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
COLITIS			

subjects affected / exposed	1 / 573 (0.17%)	0 / 379 (0.00%)	2 / 345 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLITIS ULCERATIVE			
subjects affected / exposed	13 / 573 (2.27%)	12 / 379 (3.17%)	16 / 345 (4.64%)
occurrences causally related to treatment / all	0 / 13	0 / 17	0 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
subjects affected / exposed	0 / 573 (0.00%)	1 / 379 (0.26%)	0 / 345 (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
DUODENAL ULCER PERFORATION			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
HAEMORRHOIDS			
subjects affected / exposed	1 / 573 (0.17%)	0 / 379 (0.00%)	0 / 345 (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
LARGE INTESTINAL STENOSIS			
subjects affected / exposed	1 / 573 (0.17%)	0 / 379 (0.00%)	0 / 345 (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
MALLORY-WEISS SYNDROME			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
NAUSEA			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS ACUTE			

subjects affected / exposed	1 / 573 (0.17%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL HAEMORRHAGE			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
VOMITING			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
BILE DUCT STONE			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
HEPATITIS			
subjects affected / exposed	1 / 573 (0.17%)	0 / 379 (0.00%)	0 / 345 (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
PORTOSPLENOMESENTERIC VENOUS THROMBOSIS			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
Skin and subcutaneous tissue disorders			

ERYTHEMA NODOSUM			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
EXCESSIVE SKIN			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
LINEAR IGA DISEASE			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NIGHT SWEATS			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PEMPHIGOID			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
SUBCORNEAL PUSTULAR DERMATOSIS			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
HAEMATURIA			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEPHROTIC SYNDROME			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

RENAL FAILURE			
subjects affected / exposed	1 / 573 (0.17%)	0 / 379 (0.00%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY RETENTION			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOARTHRITIS			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 573 (0.17%)	0 / 379 (0.00%)	0 / 345 (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
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
BRONCHITIS			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
CLOSTRIDIUM DIFFICILE INFECTION			
subjects affected / exposed	1 / 573 (0.17%)	0 / 379 (0.00%)	3 / 345 (0.87%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

CYTOMEGALOVIRUS COLITIS			
subjects affected / exposed	1 / 573 (0.17%)	0 / 379 (0.00%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ERYSIPELAS			
subjects affected / exposed	0 / 573 (0.00%)	1 / 379 (0.26%)	0 / 345 (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
EXTERNAL EAR CELLULITIS			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL INFECTION			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HERPES ZOSTER			
subjects affected / exposed	0 / 573 (0.00%)	1 / 379 (0.26%)	0 / 345 (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
INFECTION			
subjects affected / exposed	1 / 573 (0.17%)	0 / 379 (0.00%)	0 / 345 (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
OTITIS EXTERNA			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PELVIC INFLAMMATORY DISEASE			

subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
PERINEAL ABSCESS			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERITONSILLAR ABSCESS			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
PNEUMONIA			
subjects affected / exposed	0 / 573 (0.00%)	1 / 379 (0.26%)	2 / 345 (0.58%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
STERNITIS			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TUBERCULOSIS			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
TUBERCULOSIS OF INTRATHORACIC LYMPH NODES			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
VARICELLA			

subjects affected / exposed	1 / 573 (0.17%)	0 / 379 (0.00%)	0 / 345 (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
VIRAL INFECTION			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIABETES MELLITUS			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPONATRAEMIA			
subjects affected / exposed	0 / 573 (0.00%)	0 / 379 (0.00%)	0 / 345 (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
HYPOVOLAEMIA			
subjects affected / exposed	1 / 573 (0.17%)	0 / 379 (0.00%)	0 / 345 (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

Serious adverse events	Maintenance (Main Study + Japan Sub-study): M-HD	Maintenance (Main Study): TDM Regimen	
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 350 (12.57%)	15 / 151 (9.93%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	2	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BLADDER CANCER			

subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FIBROMATOSIS			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALIGNANT MELANOMA			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALIGNANT MELANOMA IN SITU			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NON-SMALL CELL LUNG CANCER			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGEAL ADENOCARCINOMA			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
SQUAMOUS CELL CARCINOMA OF THE CERVIX			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UTERINE LEIOMYOMA			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
HYPERTENSION			

subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOPHLEBITIS			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
WOUND DRAINAGE			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
GAIT DISTURBANCE			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
PROSTATOMEGALY			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
EMPHYSEMA			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NASAL POLYPS			

subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NASAL SEPTUM DEVIATION			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	2 / 350 (0.57%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SINUS POLYP			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
BINGE DRINKING			
subjects affected / exposed	0 / 350 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BIPOLAR DISORDER			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WEIGHT DECREASED			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (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			
HUMERUS FRACTURE			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENISCUS INJURY			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PATELLA FRACTURE			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL HAEMORRHAGE			
subjects affected / exposed	0 / 350 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RADIUS FRACTURE			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RIB FRACTURE			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

UPPER LIMB FRACTURE			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ARREST			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY DISEASE			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL ISCHAEMIA			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
ALTERED STATE OF CONSCIOUSNESS			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY			

subjects affected / exposed	0 / 350 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOAESTHESIA			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ISCHAEMIC STROKE			
subjects affected / exposed	0 / 350 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MONONEUROPATHY			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	3 / 350 (0.86%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IRON DEFICIENCY ANAEMIA			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHADENOPATHY			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOSIS			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

EYELID PTOSIS			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OPTIC ATROPHY			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANOGENITAL DYSPLASIA			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS ULCERATIVE			
subjects affected / exposed	18 / 350 (5.14%)	6 / 151 (3.97%)	
occurrences causally related to treatment / all	1 / 21	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DUODENAL ULCER PERFORATION			

subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHOIDS			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARGE INTESTINAL STENOSIS			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALLORY-WEISS SYNDROME			
subjects affected / exposed	0 / 350 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS ACUTE			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RECTAL HAEMORRHAGE			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 350 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER GASTROINTESTINAL HAEMORRHAGE			

subjects affected / exposed	0 / 350 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
BILE DUCT STONE			
subjects affected / exposed	0 / 350 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATITIS			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PORTOSPLENOMESENTERIC VENOUS THROMBOSIS			
subjects affected / exposed	0 / 350 (0.00%)	1 / 151 (0.66%)	
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			
ERYTHEMA NODOSUM			
subjects affected / exposed	0 / 350 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EXCESSIVE SKIN			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LINEAR IGA DISEASE			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

NIGHT SWEATS			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PEMPHIGOID			
subjects affected / exposed	0 / 350 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBCORNEAL PUSTULAR DERMATOSIS			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
HAEMATURIA			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEPHROTIC SYNDROME			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY RETENTION			
subjects affected / exposed	0 / 350 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			

subjects affected / exposed	2 / 350 (0.57%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOARTHRITIS			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS			
subjects affected / exposed	0 / 350 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM DIFFICILE INFECTION			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYTOMEGALOVIRUS COLITIS			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYSIPELAS			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EXTERNAL EAR CELLULITIS			

subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL INFECTION			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTION			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OTITIS EXTERNA			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PELVIC INFLAMMATORY DISEASE			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERINEAL ABSCESS			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERITONSILLAR ABSCESS			

subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	4 / 350 (1.14%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
SEPSIS			
subjects affected / exposed	0 / 350 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
STERNITIS			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUBERCULOSIS			
subjects affected / exposed	1 / 350 (0.29%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUBERCULOSIS OF INTRATHORACIC LYMPH NODES			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VARICELLA			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIRAL INFECTION			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DEHYDRATION			

subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETES MELLITUS			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
subjects affected / exposed	1 / 350 (0.29%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOVOLAEMIA			
subjects affected / exposed	0 / 350 (0.00%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Induction (Main Study + Japan Substudy): I-SD	Induction (Main Study + Japan Substudy): I-HD	Maintenance (Main Study + Japan Sub-study): M-SD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	112 / 573 (19.55%)	74 / 379 (19.53%)	140 / 345 (40.58%)
Nervous system disorders			
HEADACHE			
subjects affected / exposed	48 / 573 (8.38%)	23 / 379 (6.07%)	17 / 345 (4.93%)
occurrences (all)	62	32	19
Gastrointestinal disorders			
COLITIS ULCERATIVE			
subjects affected / exposed	18 / 573 (3.14%)	20 / 379 (5.28%)	60 / 345 (17.39%)
occurrences (all)	18	22	70
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	10 / 573 (1.75%)	11 / 379 (2.90%)	11 / 345 (3.19%)
occurrences (all)	10	11	13
Musculoskeletal and connective tissue disorders			

ARTHRALGIA			
subjects affected / exposed	18 / 573 (3.14%)	11 / 379 (2.90%)	23 / 345 (6.67%)
occurrences (all)	19	11	27
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	29 / 573 (5.06%)	16 / 379 (4.22%)	47 / 345 (13.62%)
occurrences (all)	34	18	61
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	6 / 573 (1.05%)	3 / 379 (0.79%)	22 / 345 (6.38%)
occurrences (all)	6	3	25

Non-serious adverse events	Maintenance (Main Study + Japan Sub-study): M-HD	Maintenance (Main Study): TDM Regimen	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	141 / 350 (40.29%)	47 / 151 (31.13%)	
Nervous system disorders			
HEADACHE			
subjects affected / exposed	22 / 350 (6.29%)	8 / 151 (5.30%)	
occurrences (all)	36	9	
Gastrointestinal disorders			
COLITIS ULCERATIVE			
subjects affected / exposed	47 / 350 (13.43%)	23 / 151 (15.23%)	
occurrences (all)	58	29	
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	20 / 350 (5.71%)	4 / 151 (2.65%)	
occurrences (all)	24	6	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	23 / 350 (6.57%)	5 / 151 (3.31%)	
occurrences (all)	27	5	
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	46 / 350 (13.14%)	11 / 151 (7.28%)	
occurrences (all)	57	20	
UPPER RESPIRATORY TRACT INFECTION			

subjects affected / exposed occurrences (all)	19 / 350 (5.43%) 20	9 / 151 (5.96%) 10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 June 2014	Major changes included: updated the Study Designated Physician and contact information, clarified reference to the rectal bleeding subscore; updated biopsy language and clarified endoscopy to be colonoscopy or flexible sigmoidoscopy; added restratification details; updated inclusion criteria (IC) 4 to clarify methotrexate usage for entry into the study; updated IC 5 with additional clarification on the definition of intolerance of infliximab (IFX) for entry purposes; updated Ethics Committee (EC) 10 to add the definition of excluded medications; updated to clarify EC 16 also applied to subjects who previously received fecal microbial transplantation; updated to clarify that EC 19 also applied to subjects who previously received adalimumab; added trade name of vedolizumab; concomitant therapy updated to clarify the need for any immunosuppressants taken at Baseline to remain at stable doses throughout the study and to clarify that the taper schedule was a proposal and to clarify how changes in ulcerative colitis (UC) related medications during the study were to be handled with respect to efficacy and safety assessment; prohibited therapy updated to address marijuana use due to possible interference with subject self-assessments and align with clarification made to EC 16; updated timepoints as it is required to have the stool sample taken prior to bowel prep so this should be done during the Screening period not the Baseline visit; clarified procedures for stool collection of samples; provided further guidance around Unscheduled Visits; clarified that sites do not need to send endoscopy videos for central review if the site determines that the subject does not meet IC of an endoscopy subscore of 2 or 3 and additional information added for clarification of what sites should record in the electronic case report form (eCRF);
02 June 2014	(continued) updated to clarify collection requirements for the additional biopsy samples taken for histologic assessment, clarified that if a biopsy is taken for UC confirmation it will be processed, read locally, and added language to specify that the additional biopsies taken for histologic samples will not be read in real time by the central laboratory; updated requirements such that any positive test whether purified protein derivative (tuberculin) or interferon-γ release assays (IGRA) will be considered tuberculosis (TB) positive; added additional direction for chest x-ray (CXR) documentation; provided clarification on what were considered the baseline laboratory test values; added pH to urinalysis under clinical laboratory testing, updated to reflect that dipstick urinalyses are done and only sent on to central lab for microscopy efficacy variables will be based on the central reading endoscopy subscore and the procedure for handling missing data for continuous variables are described in the SAP; specified the endpoints for Interim Analysis are for Week 8; details added about Week 8 Mayo score will be utilizing the endoscopy subscore provided by the site; Appendix edited to allow determination of loss of response or intolerance to IFX to be based on the investigator's assessment; and added clarification that for the Japan Substudy, Unscheduled Visit procedures are only needed when subjects are coming in for assessment of their UC and removed details about immediate sending of PK samples at specific weeks because Japan Substudy does not have the TDM arm. when the dipstick is abnormal; provided the definition of "remission" and "response;" clarified that the presence of extraintestinal manifestations over time will be assessed as a nonranked secondary endpoint;

02 June 2014	(continued) efficacy variables will be based on the central reading endoscopy subscore and the procedure for handling missing data for continuous variables are described in the SAP; specified the endpoints for Interim Analysis are for Week 8; details added about Week 8 Mayo score will be utilizing the endoscopy subscore provided by the site; Appendix edited to allow determination of loss of response or intolerance to IFX to be based on the investigator's assessment; and added clarification that for the Japan Substudy, Unscheduled Visit procedures are only needed when subjects are coming in for assessment of their UC and removed details about immediate sending of PK samples at specific weeks because Japan Substudy does not have the TDM arm.
03 December 2015	Major changes included: added a secondary Sponsor/Emergency contact for sites in Japan; clarified language regarding stool collection instructions for the subject; clarified that PK testing is to remain blinded and local pharmacokinetic (PK) testing is not be performed; updated the list of approved adalimumab indications; clarified procedures for corticosteroid taper at Week 4; clarified sample collection for pharmacogenetic samples; clarified IC 4 regarding required 6 thioguanine nucleotide (TGN) level; clarified TB testing procedures at screening; clarified regarding shipment of adalimumab samples during specific weeks; updated language regarding adverse event (AE) reporting and the 24 hour AbbVie Medical Escalation Hotline; updated language regarding protocol deviations; added language regarding sample withdrawal; added language around public disclosure; and added Japan requirements for reporting AEs and Japan's Regional Medical Monitor contact information.
16 June 2016	Major changes included: updated to include updated names of statistical groups due to statistical changes in protocol; updated terminology from "arm" to "regimen," "dosing regimen" or "treatment group" as appropriate and introduce terminology Induction Study and Maintenance Study; added clarification that both Main and Substudy have an Induction Study and a Maintenance Study; updated with new study enrollment numbers; added language to clarify collection of pharmacogenetic sample; clarified corticosteroid language; added clarification to serum concentration in TDM regimen to mean adalimumab serum concentration; added clarification to the results when testing for hepatitis B surface antibody; updated to convey that 840 subjects will be enrolled at up to 125 sites in the Main Study; updates made to total number of PK samples; clarified concomitant therapy assessment rules; clarified language on how previous TB medications should be collected and added to the eCRF; primary, secondary, and additional variables explained for the Induction Study and Maintenance Study; treatments administered were updated to reflect Week 52 or Premature Discontinuation; treatment compliance clarified that instruction is for home dosing; added clarification that medications for AEs/serious adverse events (SAEs) should be collected during 70-day follow-up phone call and that all 70 day follow-up phone call data is to be entered in the eCRF and recorded in source documentation; additional information added on the SAP between the Main Study and Substudy; added language about the method and interpretation between the dosing regimens; clarified statistical analysis delineating between Induction and Maintenance Studies; updated noting that interim analysis may be performed via a database cut; updated to provide scientific justification of the increase in the number of subjects; updated power of statistical analyses;
16 June 2016	(continued) updated to collect date of last study drug administration, collect reason if 70 day follow-up call was not performed, and added additional help text; deleted Japan Substudy planned methods of statistical analysis from Appendix K; and interim analyses for the Japan Substudy was updated noting that interim analysis will be performed only if performed for the Main Study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported