Clinical trial results:
A Multicenter, Randomized, Double-Blind Study of the Human Anti-TNF Monoclonal Antibody Adalimumab in Pediatric Subjects With Moderate to Severe Ulcerative Colitis

Summary

EudraCT number	2013-003032-77
Trial protocol	GB IT HU BE AT SK ES CZ PL FR
Global end of trial date	07 February 2020

Results information

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

Trial information

Trial identification

Sponsor protocol code	M11-290

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02065557
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)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 February 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the study is to demonstrate the efficacy and safety, and to assess the pharmacokinetics of adalimumab administered subcutaneously in pediatric subjects with moderate-to-severe UC.

Protection of trial subjects:

The study was conducted in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki.

Prior to the initiation of any screening or study-specific procedures, the investigator or his or her representative explained the nature of the study to the subject or his or her representative and answered all questions regarding this study. Pediatric subjects were included in all discussions, and their verbal or written assent was obtained. The informed consent statement was reviewed and signed and dated by the subject's parent or legal guardian, the person who administered the informed consent, and any other signatories according to local requirements. If a subject became of legal age during the study, that subject was reconsented.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 October 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: 1
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Japan: 8
Country: Number of subjects enrolled	Poland: 66
Country: Number of subjects enrolled	Slovakia: 6
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	101
EEA total number of subjects	79

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)	19
Adolescents (12-17 years)	82
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Prior to Protocol Amendment 4, subjects were randomized 3:2 at baseline to adalimumab induction high dose or adalimumab induction standard dose. At Week 8, those demonstrating a clinical response per Partial Mayo Score (PMS) were randomized 2:2:1 to adalimumab maintenance standard dose, adalimumab maintenance high dose, or maintenance placebo.

Pre-assignment

Screening details:

After Protocol Amendment 4, subjects received adalimumab induction high dose open-label. At Week 8, those demonstrating a clinical response per PMS were randomized in a 1:1 ratio to adalimumab maintenance standard dose or adalimumab maintenance high dose. "Integrated Study" data includes data from both the Main Study and the Japan Sub-Study.

Period 1

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

Blinding implementation details:

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of 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	Integrated Study: Induction Standard Dose (I-SD)

Arm description:

Subjects randomized to receive adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and matching placebo at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.

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

Dosage and administration details:

subcutaneous injection

Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled injector
Routes of administration	Subcutaneous use

Dosage and administration details:

subcutaneous injection

Arm title	Integrated Study: Induction High Dose (I-HD)

Arm description:

Subjects randomized to receive adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.

Arm type	Experimental

Investigational medicinal product name	adalimumab
Investigational medicinal product code	
Other name	Humira
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

subcutaneous injection

Arm title	Integrated Study: Induction High Dose Open Label (I-HD-OL)

Arm description:

(After Amendment 4) subjects assigned to open-label adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.

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

Dosage and administration details:

subcutaneous injection

Number of subjects in period 1	Integrated Study: Induction Standard Dose (I-SD)	Integrated Study: Induction High Dose (I-HD)	Integrated Study: Induction High Dose Open Label (I-HD-OL)
Started	32	51	18
Enrolled in Main Study	30	47	16
Enrolled in Japan Substudy	2 [1]	4 [2]	2 [3]
Completed	22	43	16
Not completed	10	8	2
Consent withdrawn by subject	2	1	-
Non-responder at Week 8	4	4	-
Adverse event	1	1	-
Requires alternative/prohibited therapy	1	1	1
Lack of efficacy	2	1	1

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: Subjects who were enrolled in the Japan substudy.

[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: Subjects who were enrolled in the Japan substudy.

[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: Subjects who were enrolled in the Japan substudy.

Period 2

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

Blinding implementation details:

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of 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	Integrated Study: Maintenance Placebo (M-PL)

Arm description:

(Prior to Amendment 4) subjects demonstrating a clinical response per PMS (defined as a decrease in PMS ≥ 2 points and ≥ 30% from Baseline) at Week 8 randomized to maintenance placebo. Subjects were to continue their blinded treatment during the maintenance period until Week 52 unless they had ≥ 2 flares and got open label adalimumab rescue therapy after the second flare.

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled injector
Routes of administration	Subcutaneous use

Dosage and administration details:

subcutaneous injection

Investigational medicinal product name	adalimumab
Investigational medicinal product code	
Other name	Humira
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

subcutaneous injection

Arm title	Integrated Study: Maintenance Standard Dose (M-SD)

Arm description:

Subjects demonstrating a clinical response per PMS (defined as a decrease in PMS ≥ 2 points and ≥ 30% from Baseline) at Week 8 randomized to adalimumab maintenance standard dose (0.6 mg/kg [maximum dose of 40 mg] every other week). Subjects were to continue their blinded treatment during the maintenance period until Week 52 unless they had ≥ 2 flares and got open label rescue therapy after second flare.

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

Dosage and administration details:

subcutaneous injection

Arm title	Integrated Study: Maintenance High Dose (M-HD)

Arm description:

Subjects demonstrating a clinical response per PMS (defined as a decrease in PMS ≥ 2 points and ≥ 30% from Baseline) at Week 8 randomized to adalimumab maintenance high dose (0.6 mg/kg [maximum dose of 40 mg] every week). Subjects were to continue their blinded treatment during the

maintenance period until Week 52 unless they had ≥ 2 flares and got open label rescue therapy after second flare.

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

Dosage and administration details:

subcutaneous injection

Number of subjects in period 2	Integrated Study: Maintenance Placebo (M-PL)	Integrated Study: Maintenance Standard Dose (M-SD)	Integrated Study: Maintenance High Dose (M-HD)
Started	12	33	36
Completed	11	25	32
Not completed	1	8	4
Consent withdrawn by subject	-	2	1
Subject non-compliance	-	-	1
Requires alternative/prohibited therapy	1	1	-
Lack of efficacy	-	5	2

Baseline characteristics

Reporting groups	
Reporting group title	Integrated Study: Induction Standard Dose (I-SD)
Reporting group description:	
Subjects randomized to receive adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and matching placebo at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.	
Reporting group title	Integrated Study: Induction High Dose (I-HD)
Reporting group description:	
Subjects randomized to receive adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.	
Reporting group title	Integrated Study: Induction High Dose Open Label (I-HD-OL)
Reporting group description:	
(After Amendment 4) subjects assigned to open-label adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.	

Reporting group values	Integrated Study: Induction Standard Dose (I-SD)	Integrated Study: Induction High Dose (I-HD)	Integrated Study: Induction High Dose Open Label (I-HD-OL)
Number of subjects	32	51	18
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	14.7	13.8	13.8
standard deviation	± 2.66	± 3.06	± 2.82
Gender categorical Units: Subjects			
Female	15	23	13
Male	17	28	5
Race Units: Subjects			
White	28	45	15
Black	1	2	0
Asian	3	4	2
Multiple	0	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	1	2	1
Japanese	2	4	2
No ethnicity	29	45	15
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).			
Units: score on a scale			

arithmetic mean	7.8	7.7	7.7
standard deviation	± 1.22	± 1.25	± 1.09
Partial Mayo Score (PMS)			
The PMS (Mayo score without endoscopy) ranges from 0 (normal or inactive disease) to 9 (severe disease) and is calculated as the sum of 3 subscores (stool frequency, rectal bleeding and physician's global assessment), each of which ranges from 0 (normal) to 3 (severe disease).			
Units: score on a scale			
arithmetic mean	5.7	5.5	5.5
standard deviation	± 1.14	± 1.24	± 1.06
Endoscopy Subscore			
The endoscopy subscore of the FMS ranges from 0 (normal) to 3 (severe disease).			
Units: score on a scale			
arithmetic mean	2.1	2.2	2.2
standard deviation	± 0.34	± 0.40	± 0.43
Rectal Bleeding Subscore			
The rectal bleeding subscore of the FMS ranges from 0 (normal) to 3 (severe disease).			
Units: score on a scale			
arithmetic mean	1.4	1.5	1.4
standard deviation	± 0.93	± 0.88	± 0.97
Physicians Global Assessment Subscore			
The physicians global assessment subscore of the FMS ranges from 0 (normal) to 3 (severe disease).			
Units: score on a scale			
arithmetic mean	2.2	2.2	2.2
standard deviation	± 0.40	± 0.43	± 0.38
Stool Frequency Subscore			
The stool frequency subscore of the FMS ranges from 0 (normal) to 3 (severe disease).			
Units: score on a scale			
arithmetic mean	2.1	1.8	1.9
standard deviation	± 0.78	± 0.88	± 0.73

Reporting group values	Total		
Number of subjects	101		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	51		
Male	50		
Race Units: Subjects			
White	88		
Black	3		
Asian	9		
Multiple	1		
Ethnicity Units: Subjects			
Hispanic or Latino	4		

Japanese	8		
No ethnicity	89		

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).			
Units: score on a scale			
arithmetic mean			
standard deviation	-		
Partial Mayo Score (PMS)			
The PMS (Mayo score without endoscopy) ranges from 0 (normal or inactive disease) to 9 (severe disease) and is calculated as the sum of 3 subscores (stool frequency, rectal bleeding and physician's global assessment), each of which ranges from 0 (normal) to 3 (severe disease).			
Units: score on a scale			
arithmetic mean			
standard deviation	-		
Endoscopy Subscore			
The endoscopy subscore of the FMS ranges from 0 (normal) to 3 (severe disease).			
Units: score on a scale			
arithmetic mean			
standard deviation	-		
Rectal Bleeding Subscore			
The rectal bleeding subscore of the FMS ranges from 0 (normal) to 3 (severe disease).			
Units: score on a scale			
arithmetic mean			
standard deviation	-		
Physicians Global Assessment Subscore			
The physicians global assessment subscore of the FMS ranges from 0 (normal) to 3 (severe disease).			
Units: score on a scale			
arithmetic mean			
standard deviation	-		
Stool Frequency Subscore			
The stool frequency subscore of the FMS ranges from 0 (normal) to 3 (severe disease).			
Units: score on a scale			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Integrated Study: Induction Standard Dose (I-SD)

Reporting group description:

Subjects randomized to receive adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and matching placebo at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.

Reporting group title	Integrated Study: Induction High Dose (I-HD)

Reporting group description:

Subjects randomized to receive adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.

Reporting group title	Integrated Study: Induction High Dose Open Label (I-HD-OL)

Reporting group description:

(After Amendment 4) subjects assigned to open-label adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.

Reporting group title	Integrated Study: Maintenance Placebo (M-PL)

Reporting group description:

(Prior to Amendment 4) subjects demonstrating a clinical response per PMS (defined as a decrease in PMS ≥ 2 points and ≥ 30% from Baseline) at Week 8 randomized to maintenance placebo. Subjects were to continue their blinded treatment during the maintenance period until Week 52 unless they had ≥ 2 flares and got open label adalimumab rescue therapy after the second flare.

Reporting group title	Integrated Study: Maintenance Standard Dose (M-SD)

Reporting group description:

Subjects demonstrating a clinical response per PMS (defined as a decrease in PMS ≥ 2 points and ≥ 30% from Baseline) at Week 8 randomized to adalimumab maintenance standard dose (0.6 mg/kg [maximum dose of 40 mg] every other week). Subjects were to continue their blinded treatment during the maintenance period until Week 52 unless they had ≥ 2 flares and got open label rescue therapy after second flare.

Reporting group title	Integrated Study: Maintenance High Dose (M-HD)

Reporting group description:

Subjects demonstrating a clinical response per PMS (defined as a decrease in PMS ≥ 2 points and ≥ 30% from Baseline) at Week 8 randomized to adalimumab maintenance high dose (0.6 mg/kg [maximum dose of 40 mg] every week). Subjects were to continue their blinded treatment during the maintenance period until Week 52 unless they had ≥ 2 flares and got open label rescue therapy after second flare.

Subject analysis set title	Main Study: I-SD
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects randomized to receive adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and matching placebo at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.

Intent-to-Treat (ITT): all subjects who received at least 1 dose of study drug during the Induction period; analyzed as enrolled/randomized.

Subject analysis set title	Main Study: I-HD
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects randomized to receive adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.

Intent-to-Treat (ITT): all subjects who received at least 1 dose of study drug during the Induction period; analyzed as enrolled/randomized.

Subject analysis set title	Main Study: I-SD + I-HD
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Combined I-SD + I-HD arms (see above).

Intent-to-Treat (ITT): all subjects who received at least 1 dose of study drug during the Induction period; analyzed as enrolled/randomized.

Subject analysis set title	Main Study: I-HD-OL
Subject analysis set type	Intention-to-treat

Subject analysis set description:

(After Amendment 4) subjects assigned to open-label adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.

Intent-to-Treat (ITT): all subjects who received at least 1 dose of study drug during the Induction period; analyzed as enrolled/randomized.

Subject analysis set title	Integrated Study (Main + Japan Sub- Study): I-SD
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects randomized to receive adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and matching placebo at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.

Intent-to-Treat (ITT): all subjects who received at least 1 dose of study drug during the Induction period; analyzed as enrolled/randomized.

Subject analysis set title	Integrated Study (Main + Japan Sub- Study): I-HD
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects randomized to receive adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.

Intent-to-Treat (ITT): all subjects who received at least 1 dose of study drug during the Induction period; analyzed as enrolled/randomized.

Subject analysis set title	Integrated Study (Main + Japan Sub- Study): I-SD + I-HD
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Combined I-SD + I-HD arms (see above).

Intent-to-Treat (ITT): all subjects who received at least 1 dose of study drug during the Induction period; analyzed as enrolled/randomized.

Subject analysis set title	Integrated Study (Main + Japan Sub- Study): I-HD-OL
Subject analysis set type	Intention-to-treat

Subject analysis set description:

(After Amendment 4) subjects assigned to open-label adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.

Intent-to-Treat (ITT): all subjects who received at least 1 dose of study drug during the Induction period; analyzed as enrolled/randomized.

Subject analysis set title	Main Study: M-PL
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

(Prior to Amendment 4) subjects demonstrating a clinical response per PMS (defined as a decrease in PMS ≥ 2 points and ≥ 30% from Baseline) at Week 8 randomized to maintenance placebo. Subjects were to continue their blinded treatment during the maintenance period until Week 52 unless they had ≥ 2 flares and got open label rescue therapy after the second flare.

Modified intent-to-treat (mITT): all Week 8 PMS responders who were re-randomized at Week 8 and received at least 1 dose of study drug during the Maintenance period; analyzed as randomized/enrolled at the beginning of the Maintenance phase.

Subject analysis set title	Main Study: M-SD
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Subjects demonstrating a clinical response per PMS (defined as a decrease in PMS ≥ 2 points and ≥ 30% from Baseline) at Week 8 randomized to adalimumab maintenance standard dose (0.6 mg/kg [maximum dose of 40 mg] eow). Subjects were to continue their blinded treatment during the maintenance period until Week 52 unless they had ≥ 2 flares and got open label rescue therapy after the second flare.

Modified intent-to-treat (mITT): all Week 8 PMS responders who were re-randomized at Week 8 and received at least 1 dose of study drug during the Maintenance period; analyzed as randomized/enrolled at the beginning of the Maintenance phase.

Subject analysis set title	Main Study: M-HD
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Subjects demonstrating a clinical response per PMS (defined as a decrease in PMS ≥ 2 points and ≥ 30% from Baseline) at Week 8 randomized to adalimumab maintenance high dose (0.6 mg/kg [maximum dose of 40 mg] ew). Subjects were to continue their blinded treatment during the maintenance period until Week 52 unless they had ≥ 2 flares and got open label rescue therapy after the second flare.

Modified intent-to-treat (mITT): all Week 8 PMS responders who were re-randomized at Week 8 and received at least 1 dose of study drug during the Maintenance period; analyzed as randomized/enrolled at the beginning of the Maintenance phase.

Subject analysis set title	Main Study: M-SD + M-HD
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Combined M-SD + M-HD arms (see above).

Modified intent-to-treat (mITT): all Week 8 PMS responders who were re-randomized at Week 8 and received at least 1 dose of study drug during the Maintenance period; analyzed as randomized/enrolled at the beginning of the Maintenance phase.

Subject analysis set title	Integrated Study (Main + Japan Sub- Study): M-PL
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

(Prior to Amendment 4) subjects demonstrating a clinical response per PMS (defined as a decrease in PMS ≥ 2 points and ≥ 30% from Baseline) at Week 8 randomized to maintenance placebo. Subjects were to continue their blinded treatment during the maintenance period until Week 52 unless they had ≥ 2 flares and got open label rescue therapy after the second flare.

Modified intent-to-treat (mITT): all Week 8 PMS responders who were re-randomized at Week 8 and received at least 1 dose of study drug during the Maintenance period; analyzed as randomized/enrolled at the beginning of the Maintenance phase.

Subject analysis set title	Integrated Study (Main + Japan Sub- Study): M-SD
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Subjects demonstrating a clinical response per PMS (defined as a decrease in PMS ≥ 2 points and ≥ 30% from Baseline) at Week 8 randomized to adalimumab maintenance standard dose (0.6 mg/kg [maximum dose of 40 mg] eow). Subjects were to continue their blinded treatment during the maintenance period until Week 52 unless they had ≥ 2 flares and got open label rescue therapy after the second flare.

Modified intent-to-treat (mITT): all Week 8 PMS responders who were re-randomized at Week 8 and received at least 1 dose of study drug during the Maintenance period; analyzed as randomized/enrolled at the beginning of the Maintenance phase.

Subject analysis set title	Integrated Study (Main + Japan Sub- Study): M-HD
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Subjects demonstrating a clinical response per PMS (defined as a decrease in PMS ≥ 2 points and ≥ 30% from Baseline) at Week 8 randomized to adalimumab maintenance high dose (0.6 mg/kg [maximum dose of 40 mg] ew). Subjects were to continue their blinded treatment during the maintenance period until Week 52 unless they had ≥ 2 flares and got open label rescue therapy after the second flare.

Modified intent-to-treat (mITT): all Week 8 PMS responders who were re-randomized at Week 8 and

received at least 1 dose of study drug during the Maintenance period; analyzed as randomized/enrolled at the beginning of the Maintenance phase.

Subject analysis set title	Integrated Study (Main + Japan Sub- Study): M-SD + M-HD
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Combined M-SD + M-HD arms (see above).

Modified intent-to-treat (mITT): all Week 8 PMS responders who were re-randomized at Week 8 and received at least 1 dose of study drug during the Maintenance period; analyzed as randomized/enrolled at the beginning of the Maintenance phase.

Primary: Co-Primary Endpoint 1: Percentage of Subjects Who Achieved Clinical Remission as Measured by Partial Mayo Score (PMS) at Week 8 - Induction Period

End point title	Co-Primary Endpoint 1: Percentage of Subjects Who Achieved Clinical Remission as Measured by Partial Mayo Score (PMS) at Week 8 - Induction Period[1]

End point description:

The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The PMS (Mayo score without endoscopy) ranges from 0 (normal or inactive disease) to 9 (severe disease) and is calculated as the sum of 3 subscores (stool frequency, rectal bleeding and physician's global assessment), each of which ranges from 0 (normal) to 3 (severe disease). A negative change in PMS indicates improvement. Clinical remission was defined as a PMS ≤ 2 and no individual subscore > 1.

Non-responder imputation: missing data imputed as not having met the endpoint.

End point type	Primary

End point timeframe:

Week 8

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analyses for this endpoint are presented in the attached document.

End point values	Main Study: I-SD	Main Study: I-HD	Main Study: I-SD + I-HD	Main Study: I-HD-OL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	47	77	16
Units: percentage of subjects				
number (confidence interval 95%)	43.3 (25.46 to 62.57)	59.6 (44.27 to 73.63)	53.2 (41.52 to 64.71)	68.8 (41.34 to 88.98)

End point values	Integrated Study (Main + Japan Sub-Study): I-SD	Integrated Study (Main + Japan Sub-Study): I-HD	Integrated Study (Main + Japan Sub-Study): I-SD + I-HD	Integrated Study (Main + Japan Sub-Study): I-HD-OL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	51	83	18
Units: percentage of subjects				
number (confidence interval 95%)	40.6 (23.70 to 59.36)	58.8 (44.17 to 72.42)	51.8 (40.56 to 62.92)	66.7 (40.99 to 86.66)

Attachments (see zip file)	Statistical Analysis for Co-Primary Endpoint 1.docx

Statistical analyses

No statistical analyses for this end point

Primary: Co-Primary Endpoint 2: Percentage of Subjects With Clinical Remission Per Full Mayo Score (FMS) at Week 52 in Week 8 Responders Per PMS - Maintenance Period

End point title	Co-Primary Endpoint 2: Percentage of Subjects With Clinical Remission Per Full Mayo Score (FMS) at Week 52 in Week 8 Responders Per PMS - Maintenance Period[2]

End point description:

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). The PMS (Mayo score without endoscopy) ranges from 0 (normal or inactive disease) to 9 (severe disease) and is calculated as the sum of 3 subscores (stool frequency, rectal bleeding and physician's global assessment). Negative changes indicate improvement. PMS responders are defined as those with a decrease in PMS ≥ 2 points and ≥ 30% from Baseline. Clinical remission per FMS is defined as Mayo Score ≤ 2 and no individual subscore > 1.

Non-responder imputation: missing data imputed as not having met the endpoint.

End point type	Primary

End point timeframe:

Week 52

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analyses for this endpoint are presented in the attached document.

End point values	Main Study: M-PL	Main Study: M-SD	Main Study: M-HD	Main Study: M-SD + M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	31	31	62
Units: percentage of subjects				
number (confidence interval 95%)	33.3 (9.92 to 65.11)	29.0 (14.22 to 48.04)	45.2 (27.32 to 63.97)	37.1 (25.16 to 50.31)

End point values	Integrated Study (Main + Japan Sub-Study): M-PL	Integrated Study (Main + Japan Sub-Study): M-SD	Integrated Study (Main + Japan Sub-Study): M-HD	Integrated Study (Main + Japan Sub-Study): M-SD + M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	33	35	68
Units: percentage of subjects				
number (confidence interval 95%)	33.3 (9.92 to 65.11)	27.3 (13.30 to 45.52)	42.9 (26.32 to 60.65)	35.3 (24.08 to 47.83)

Attachments (see zip file)	Statistical Analysis for Co-Primary Endpoint 2.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Ranked Secondary Endpoint 1: Percentage of Subjects With Clinical Response Per FMS at Week 52 in Week 8 Responders Per PMS - Maintenance Period

End point title	Ranked Secondary Endpoint 1: Percentage of Subjects With Clinical Response Per FMS at Week 52 in Week 8 Responders Per PMS - Maintenance Period

End point description:

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). The PMS (Mayo score without endoscopy) ranges from 0 (normal or inactive disease) to 9 (severe disease) and is calculated as the sum of 3 subscores (stool frequency, rectal bleeding and physician's global assessment). Negative changes indicate improvement. PMS responders are defined as those with a decrease in PMS ≥ 2 points and ≥ 30% from Baseline. Clinical response per FMS is defined as a decrease in FMS ≥ 3 points and ≥ 30% from Baseline.

Non-responder imputation: missing data imputed as not having met the endpoint.

End point type	Secondary

End point timeframe:

Week 52

End point values	Main Study: M-PL	Main Study: M-SD	Main Study: M-HD	Main Study: M-SD + M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	31	31	62
Units: percentage of participants				
number (confidence interval 95%)	33.3 (9.92 to 65.11)	61.3 (42.19 to 78.15)	67.7 (48.63 to 83.32)	64.5 (51.34 to 76.26)

End point values	Integrated Study (Main + Japan Sub-Study): M-PL	Integrated Study (Main + Japan Sub-Study): M-SD	Integrated Study (Main + Japan Sub-Study): M-HD	Integrated Study (Main + Japan Sub-Study): M-SD + M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	33	35	68
Units: percentage of participants				
number (confidence interval 95%)	33.3 (9.92 to 65.11)	57.6 (39.22 to 74.52)	65.7 (47.79 to 80.87)	61.8 (49.18 to 73.29)

Attachments (see zip file)	Statistical Analysis for Ranked Secondary Endpoint 1.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Ranked Secondary Endpoint 2: Percentage of Subjects With Mucosal Healing at Week 52 in Week 8 Responders Per PMS - Maintenance Period

End point title	Ranked Secondary Endpoint 2: Percentage of Subjects With Mucosal Healing at Week 52 in Week 8 Responders Per PMS - Maintenance Period

End point description:

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). The PMS (Mayo score without endoscopy) ranges from 0 (normal or inactive disease) to 9 (severe disease) and is calculated as the sum of 3 subscores (stool frequency, rectal bleeding and physician's global assessment). Negative changes indicate improvement. PMS responders are defined as those subjects with a decrease in PMS ≥ 2 points and ≥ 30% from Baseline. Mucosal healing per Mayo endoscopy subscore is defined as a subscore of ≤ 1.

Non-responder imputation: missing data imputed as not having met the endpoint.

End point type	Secondary

End point timeframe:

Week 52

End point values	Main Study: M-PL	Main Study: M-SD	Main Study: M-HD	Main Study: M-SD + M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	31	31	62
Units: percentage of subjects				
number (confidence interval 95%)	33.3 (9.92 to 65.11)	38.7 (21.85 to 57.81)	51.6 (33.06 to 69.85)	45.2 (32.48 to 58.32)

End point values	Integrated Study (Main + Japan Sub-Study): M-PL	Integrated Study (Main + Japan Sub-Study): M-SD	Integrated Study (Main + Japan Sub-Study): M-HD	Integrated Study (Main + Japan Sub-Study): M-SD + M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	33	35	68
Units: percentage of subjects				
number (confidence interval 95%)	33.3 (9.92 to 65.11)	36.4 (20.40 to 54.88)	48.6 (31.38 to 66.01)	42.6 (30.72 to 55.23)

Attachments (see zip file)	Statistical Analysis for Ranked Secondary Endpoint 2.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Ranked Secondary Endpoint 3: Percentage of Subjects With Clinical Remission Per FMS at Week 52 in Week 8 Remitters Per PMS - Maintenance Period

End point title	Ranked Secondary Endpoint 3: Percentage of Subjects With Clinical Remission Per FMS at Week 52 in Week 8 Remitters Per PMS - Maintenance Period

End point description:

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). The PMS (Mayo score without endoscopy) ranges from 0 (normal or inactive disease) to 9 (severe disease) and is calculated as the sum of 3 subscores (stool frequency, rectal bleeding and physician's global assessment). Negative changes indicate improvement. PMS remitters are defined as those subjects with a PMS ≤ 2 and no individual subscore > 1. Clinical remission per FMS is defined as Mayo Score ≤ 2 and no individual subscore > 1.

Non-responder imputation: missing data imputed as not having met the endpoint.

End point type	Secondary

End point timeframe:

Week 52

End point values	Main Study: M-PL	Main Study: M-SD	Main Study: M-HD	Main Study: M-SD + M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8[3]	21[4]	22[5]	43[6]
Units: percentage of subjects				
number (confidence interval 95%)	37.5 (8.52 to 75.51)	42.9 (21.82 to 65.98)	45.5 (24.39 to 67.79)	44.2 (29.08 to 60.12)

Notes:

[3] - mITT subjects who were also Week 8 remitters

[4] - mITT subjects who were also Week 8 remitters

[5] - mITT subjects who were also Week 8 remitters

[6] - mITT subjects who were also Week 8 remitters

End point values	Integrated Study (Main + Japan Sub-Study): M-PL	Integrated Study (Main + Japan Sub-Study): M-SD	Integrated Study (Main + Japan Sub-Study): M-HD	Integrated Study (Main + Japan Sub-Study): M-SD + M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8[7]	21[8]	25[9]	46[10]
Units: percentage of subjects				
number (confidence interval 95%)	37.5 (8.52 to 75.51)	42.9 (21.82 to 65.98)	44.0 (24.40 to 65.07)	43.5 (28.93 to 58.89)

Notes:

[7] - mITT subjects who were also Week 8 remitters

[8] - mITT subjects who were also Week 8 remitters

[9] - mITT subjects who were also Week 8 remitters

[10] - mITT subjects who were also Week 8 remitters

Attachments (see zip file)	Statistical Analysis for Ranked Secondary Endpoint 3.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Ranked Secondary Endpoint 4: Percentage of Subjects With Corticosteroid-Free Clinical Remission Per FMS at Week 52 in Week 8 Responders Per PMS - Maintenance Period

End point title	Ranked Secondary Endpoint 4: Percentage of Subjects With Corticosteroid-Free Clinical Remission Per FMS at Week 52 in

	Week 8 Responders Per PMS - Maintenance Period

End point description:

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). The PMS (Mayo score without endoscopy) ranges from 0 (normal or inactive disease) to 9 (severe disease) and is calculated as the sum of 3 subscores (stool frequency, rectal bleeding and physician's global assessment). Negative changes indicate improvement. PMS responders are defined as those with a decrease in PMS ≥ 2 points and ≥ 30% from baseline. Among subjects receiving systemic corticosteroids at Baseline, corticosteroid-free clinical remission per FMS at Week 52 is defined as having discontinued systemic corticosteroids prior to Week 52 and being in FMS clinical remission at Week 52 (defined as Mayo Score ≤ 2 and no individual subscore > 1).

Non-responder imputation: missing data imputed as not having met the endpoint.

End point type	Secondary

End point timeframe:

Week 52

End point values	Main Study: M-PL	Main Study: M-SD	Main Study: M-HD	Main Study: M-SD + M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5[11]	13[12]	16[13]	29[14]
Units: percentage of stubjects				
number (confidence interval 95%)	40.0 (5.27 to 85.34)	30.8 (9.09 to 61.43)	31.3 (11.02 to 58.66)	31.0 (15.28 to 50.83)

Notes:

[11] - mITT subjects receiving systemic corticosteroids at baseline.

[12] - mITT subjects receiving systemic corticosteroids at baseline.

[13] - mITT subjects receiving systemic corticosteroids at baseline.

[14] - mITT subjects receiving systemic corticosteroids at baseline.

End point values	Integrated Study (Main + Japan Sub-Study): M-PL	Integrated Study (Main + Japan Sub-Study): M-SD	Integrated Study (Main + Japan Sub-Study): M-HD	Integrated Study (Main + Japan Sub-Study): M-SD + M-HD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5[15]	15[16]	17[17]	32[18]
Units: percentage of stubjects				
number (confidence interval 95%)	40.0 (5.27 to 85.34)	26.7 (7.79 to 55.10)	35.3 (14.21 to 61.67)	31.3 (16.12 to 50.01)

Notes:

[15] - mITT subjects receiving systemic corticosteroids at baseline.

[16] - mITT subjects receiving systemic corticosteroids at baseline.

[17] - mITT subjects receiving systemic corticosteroids at baseline.

[18] - mITT subjects receiving systemic corticosteroids at baseline.

Attachments (see zip file)	Statistical Analysis for Ranked Secondary Endpoint 4.docx

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

See time frame specifics detailed for each reporting group in their respective descriptions below.

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAEs) are presented.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Integrated Study (Main + Japan Sub- Study): I-SD

Reporting group description:

Subjects randomized to receive adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and matching placebo at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and 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 52.8 days.

Reporting group title	Integrated Study (Main + Japan Sub- Study): I-HD

Reporting group description:

Subjects randomized to receive adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and 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 55.4 days.

Reporting group title	Integrated Study (Main + Japan Sub- Study): I-HD-OL

Reporting group description:

(After Amendment 4) subjects assigned to open-label adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and 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 53.8 days.

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

Reporting group description:

Subjects demonstrating a clinical response per PMS (defined as a decrease in PMS ≥ 2 points and ≥ 30% from Baseline) at Week 8 randomized to adalimumab maintenance standard dose (0.6 mg/kg [maximum dose of 40 mg] eow). Subjects were to continue their blinded treatment during the maintenance period until Week 52 unless they had ≥ 2 flares and got open label adalimumab rescue therapy after the second flare.

TEAEs during maintenance period: events with an onset date on or after first dose date of study drug in maintenance period and prior to re-randomization due to first disease flare if applicable and up to 70 days after the last dose date of the study drug in maintenance period. Events with an onset date on or after the first dose date in long-term follow-up study M10-870 (NCT02632175) are excluded. Mean duration of treatment was 226.8 days.

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

Reporting group description:

Subjects demonstrating a clinical response per PMS (defined as a decrease in PMS ≥ 2 points and ≥ 30% from Baseline) at Week 8 randomized to adalimumab maintenance high dose (0.6 mg/kg [maximum dose of 40 mg] ew). Subjects were to continue their blinded treatment during the maintenance period until Week 52 unless they had ≥ 2 flares and got open label adalimumab rescue therapy after the second flare.

TEAEs during maintenance period: events with an onset date on or after first dose date of study drug in maintenance period and prior to re-randomization due to first disease flare if applicable and up to 70 days after the last dose date of the study drug in maintenance period. Events with an onset date on or after the first dose date in long-term follow-up study M10-870 (NCT02632175) are excluded. Mean duration of treatment was 241.0 days.

Reporting group title	Integrated Study (Main + Japan Sub- Study): M-PL

Reporting group description:

(Prior to Amendment 4) subjects demonstrating a clinical response per PMS (defined as a decrease in PMS ≥ 2 points and ≥ 30% from Baseline) at Week 8 randomized to maintenance placebo. Subjects were to continue their blinded treatment during the maintenance period until Week 52 unless they had ≥ 2 flares and got open label adalimumab rescue therapy after the second flare.

TEAEs during maintenance period: events with an onset date on or after first dose date of study drug in maintenance period and prior to re-randomization due to first disease flare if applicable and up to 70 days after the last dose date of the study drug in maintenance period. Events with an onset date on or after the first dose date in long-term follow-up study M10-870 (NCT02632175) are excluded. Mean duration of treatment was 184.2 days.

Reporting group title	Integrated Study (Main + Japan Sub- Study): Any Adalimumab

Reporting group description:

Subjects receiving any adalimumab during Induction or Maintenance Phase.

Any Adalimumab TEAEs: events with an onset date on or after first dose date of adalimumab and up to 70 days after the last dose date of adalimumab and prior to the first dose date in M10-870 if applicable, whichever comes first. For subjects who received placebo during the maintenance period, TEAE collection period ends 70 days after last induction dose of adalimumab and re-starts with their next adalimumab dose, if applicable. Mean duration of treatment was 256.3 days.

Serious adverse events	Integrated Study (Main + Japan Sub-Study): I-SD	Integrated Study (Main + Japan Sub-Study): I-HD	Integrated Study (Main + Japan Sub-Study): I-HD-OL
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 32 (15.63%)	4 / 51 (7.84%)	1 / 18 (5.56%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
HAND FRACTURE			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (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
WRIST FRACTURE			
subjects affected / exposed	0 / 32 (0.00%)	1 / 51 (1.96%)	0 / 18 (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
Cardiac disorders			
PERICARDITIS			

subjects affected / exposed	1 / 32 (3.13%)	0 / 51 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
HEADACHE			
subjects affected / exposed	1 / 32 (3.13%)	0 / 51 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOSS OF CONSCIOUSNESS			
subjects affected / exposed	1 / 32 (3.13%)	0 / 51 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	2 / 32 (6.25%)	0 / 51 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
COLITIS ULCERATIVE			
subjects affected / exposed	2 / 32 (6.25%)	2 / 51 (3.92%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 2	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPEPSIA			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (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
ENTERITIS			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (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
PANCREATITIS			
subjects affected / exposed	0 / 32 (0.00%)	1 / 51 (1.96%)	0 / 18 (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

Skin and subcutaneous tissue disorders			
ERYTHEMA NODOSUM			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (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
PSORIASIS			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (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
Infections and infestations			
ENTERITIS INFECTIOUS			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (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
GASTROENTERITIS			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (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
MENINGITIS ASEPTIC			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (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
PHARYNGITIS			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (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
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (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

Serious adverse events	Integrated Study (Main + Japan Sub-Study): M-SD	Integrated Study (Main + Japan Sub-Study): M-HD	Integrated Study (Main + Japan Sub-Study): M-PL
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 33 (15.15%)	5 / 36 (13.89%)	1 / 12 (8.33%)

number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
HAND FRACTURE			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	0 / 12 (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
WRIST FRACTURE			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
PERICARDITIS			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	0 / 12 (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
Nervous system disorders			
HEADACHE			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	0 / 12 (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
LOSS OF CONSCIOUSNESS			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	0 / 12 (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	1 / 33 (3.03%)	0 / 36 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
COLITIS ULCERATIVE			
subjects affected / exposed	3 / 33 (9.09%)	0 / 36 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

DYSPEPSIA			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	0 / 12 (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
ENTERITIS			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	0 / 12 (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
PANCREATITIS			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	0 / 12 (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 / 33 (0.00%)	1 / 36 (2.78%)	0 / 12 (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
PSORIASIS			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
ENTERITIS INFECTIOUS			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	0 / 12 (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
GASTROENTERITIS			
subjects affected / exposed	2 / 33 (6.06%)	0 / 36 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENINGITIS ASEPTIC			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	0 / 12 (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

PHARYNGITIS			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Integrated Study (Main + Japan Sub-Study): Any Adalimumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 101 (21.78%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
HAND FRACTURE			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
WRIST FRACTURE			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
PERICARDITIS			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
HEADACHE			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
LOSS OF CONSCIOUSNESS			

subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
COLITIS ULCERATIVE			
subjects affected / exposed	10 / 101 (9.90%)		
occurrences causally related to treatment / all	1 / 11		
deaths causally related to treatment / all	0 / 0		
DYSPEPSIA			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
ENTERITIS			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PANCREATITIS			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
ERYTHEMA NODOSUM			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PSORIASIS			
subjects affected / exposed	0 / 101 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
ENTERITIS INFECTIOUS			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
GASTROENTERITIS			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
MENINGITIS ASEPTIC			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
PHARYNGITIS			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Integrated Study (Main + Japan Sub-Study): I-SD	Integrated Study (Main + Japan Sub-Study): I-HD	Integrated Study (Main + Japan Sub-Study): I-HD-OL
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 32 (40.63%)	16 / 51 (31.37%)	14 / 18 (77.78%)
Investigations			
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	0 / 32 (0.00%)	1 / 51 (1.96%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
HEPATIC ENZYME INCREASED			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

MONOCYTE COUNT DECREASED			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
JOINT INJURY			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
HEADACHE			
subjects affected / exposed	4 / 32 (12.50%)	5 / 51 (9.80%)	4 / 18 (22.22%)
occurrences (all)	4	7	6
TREMOR			
subjects affected / exposed	0 / 32 (0.00%)	1 / 51 (1.96%)	1 / 18 (5.56%)
occurrences (all)	0	2	1
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 32 (3.13%)	3 / 51 (5.88%)	1 / 18 (5.56%)
occurrences (all)	1	3	1
NEUTROPENIA			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
THROMBOCYTOSIS			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	0 / 32 (0.00%)	1 / 51 (1.96%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
INFLAMMATION			

subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
PERIPHERAL SWELLING			
subjects affected / exposed	1 / 32 (3.13%)	0 / 51 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
PYREXIA			
subjects affected / exposed	2 / 32 (6.25%)	1 / 51 (1.96%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Eye disorders			
NONINFECTIVE CONJUNCTIVITIS			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 32 (0.00%)	2 / 51 (3.92%)	2 / 18 (11.11%)
occurrences (all)	0	2	2
ABDOMINAL PAIN UPPER			
subjects affected / exposed	1 / 32 (3.13%)	2 / 51 (3.92%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
COLITIS ULCERATIVE			
subjects affected / exposed	2 / 32 (6.25%)	0 / 51 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
CONSTIPATION			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
DIARRHOEA			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 32 (0.00%)	1 / 51 (1.96%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
NAUSEA			
subjects affected / exposed	0 / 32 (0.00%)	3 / 51 (5.88%)	1 / 18 (5.56%)
occurrences (all)	0	3	1
VOMITING			

subjects affected / exposed	0 / 32 (0.00%)	1 / 51 (1.96%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	0 / 32 (0.00%)	1 / 51 (1.96%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
EPISTAXIS			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
OROPHARYNGEAL PAIN			
subjects affected / exposed	1 / 32 (3.13%)	1 / 51 (1.96%)	2 / 18 (11.11%)
occurrences (all)	1	1	2
RHINITIS ALLERGIC			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
RHINORRHOEA			
subjects affected / exposed	0 / 32 (0.00%)	1 / 51 (1.96%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
WHEEZING			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
DERMATITIS			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
HANGNAIL			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
RASH			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Renal and urinary disorders			
GLYCOSURIA			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			

ARTHRALGIA			
subjects affected / exposed	1 / 32 (3.13%)	0 / 51 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
MUSCULOSKELETAL PAIN			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
GASTROENTERITIS			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
INFLUENZA			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
NASOPHARYNGITIS			
subjects affected / exposed	2 / 32 (6.25%)	2 / 51 (3.92%)	1 / 18 (5.56%)
occurrences (all)	2	2	2
PHARYNGITIS			
subjects affected / exposed	2 / 32 (6.25%)	1 / 51 (1.96%)	1 / 18 (5.56%)
occurrences (all)	2	1	1
RESPIRATORY TRACT INFECTION VIRAL			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
STREPTOCOCCAL INFECTION			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
TOOTH ABSCESS			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 32 (0.00%)	3 / 51 (5.88%)	0 / 18 (0.00%)
occurrences (all)	0	4	0
VIRAL INFECTION			

subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
VULVOVAGINAL MYCOTIC INFECTION			
subjects affected / exposed	0 / 32 (0.00%)	0 / 51 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

Non-serious adverse events	Integrated Study (Main + Japan Sub-Study): M-SD	Integrated Study (Main + Japan Sub-Study): M-HD	Integrated Study (Main + Japan Sub-Study): M-PL
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 33 (45.45%)	20 / 36 (55.56%)	10 / 12 (83.33%)
Investigations			
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	3 / 33 (9.09%)	0 / 36 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
HEPATIC ENZYME INCREASED			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
MONOCYTE COUNT DECREASED			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
JOINT INJURY			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nervous system disorders			
HEADACHE			
subjects affected / exposed	6 / 33 (18.18%)	2 / 36 (5.56%)	2 / 12 (16.67%)
occurrences (all)	6	2	2
TREMOR			

subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	2 / 33 (6.06%)	1 / 36 (2.78%)	1 / 12 (8.33%)
occurrences (all)	2	1	1
NEUTROPENIA			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
THROMBOCYTOSIS			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	2 / 33 (6.06%)	0 / 36 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
INFLAMMATION			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
PERIPHERAL SWELLING			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
PYREXIA			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
NONINFECTIVE CONJUNCTIVITIS			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	1 / 33 (3.03%)	1 / 36 (2.78%)	1 / 12 (8.33%)
occurrences (all)	3	1	1
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 33 (0.00%)	2 / 36 (5.56%)	0 / 12 (0.00%)
occurrences (all)	0	2	0

COLITIS ULCERATIVE			
subjects affected / exposed	3 / 33 (9.09%)	4 / 36 (11.11%)	2 / 12 (16.67%)
occurrences (all)	3	4	2
CONSTIPATION			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
DIARRHOEA			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
NAUSEA			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
VOMITING			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	0 / 33 (0.00%)	2 / 36 (5.56%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
EPISTAXIS			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
OROPHARYNGEAL PAIN			
subjects affected / exposed	2 / 33 (6.06%)	1 / 36 (2.78%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
RHINITIS ALLERGIC			
subjects affected / exposed	0 / 33 (0.00%)	2 / 36 (5.56%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
RHINORRHOEA			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
WHEEZING			

subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
DERMATITIS			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
HANGNAIL			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
RASH			
subjects affected / exposed	1 / 33 (3.03%)	2 / 36 (5.56%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Renal and urinary disorders			
GLYCOSURIA			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
MUSCULOSKELETAL PAIN			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
GASTROENTERITIS			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
INFLUENZA			
subjects affected / exposed	0 / 33 (0.00%)	2 / 36 (5.56%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
NASOPHARYNGITIS			
subjects affected / exposed	3 / 33 (9.09%)	4 / 36 (11.11%)	1 / 12 (8.33%)
occurrences (all)	4	4	1

PHARYNGITIS			
subjects affected / exposed	2 / 33 (6.06%)	1 / 36 (2.78%)	1 / 12 (8.33%)
occurrences (all)	2	1	3
RESPIRATORY TRACT INFECTION VIRAL			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
STREPTOCOCCAL INFECTION			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
TOOTH ABSCESS			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 33 (6.06%)	4 / 36 (11.11%)	2 / 12 (16.67%)
occurrences (all)	3	4	2
VIRAL INFECTION			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
VULVOVAGINAL MYCOTIC INFECTION			
subjects affected / exposed	0 / 33 (0.00%)	0 / 36 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Integrated Study (Main + Japan Sub-Study): Any Adalimumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 101 (64.36%)		
Investigations			
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	5 / 101 (4.95%)		
occurrences (all)	5		
HEPATIC ENZYME INCREASED			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
MONOCYTE COUNT DECREASED			

subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	3		
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
JOINT INJURY			
subjects affected / exposed	0 / 101 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
HEADACHE			
subjects affected / exposed	19 / 101 (18.81%)		
occurrences (all)	28		
TREMOR			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	9 / 101 (8.91%)		
occurrences (all)	9		
NEUTROPENIA			
subjects affected / exposed	0 / 101 (0.00%)		
occurrences (all)	0		
THROMBOCYTOSIS			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
INFLAMMATION			

subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
PERIPHERAL SWELLING			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
PYREXIA			
subjects affected / exposed	5 / 101 (4.95%)		
occurrences (all)	5		
Eye disorders			
NONINFECTIVE CONJUNCTIVITIS			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	6 / 101 (5.94%)		
occurrences (all)	11		
ABDOMINAL PAIN UPPER			
subjects affected / exposed	4 / 101 (3.96%)		
occurrences (all)	5		
COLITIS ULCERATIVE			
subjects affected / exposed	11 / 101 (10.89%)		
occurrences (all)	14		
CONSTIPATION			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
DIARRHOEA			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	3		
NAUSEA			
subjects affected / exposed	4 / 101 (3.96%)		
occurrences (all)	4		
VOMITING			

subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	4 / 101 (3.96%)		
occurrences (all)	6		
EPISTAXIS			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
OROPHARYNGEAL PAIN			
subjects affected / exposed	7 / 101 (6.93%)		
occurrences (all)	8		
RHINITIS ALLERGIC			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	3		
RHINORRHOEA			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
WHEEZING			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
DERMATITIS			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
HANGNAIL			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
RASH			
subjects affected / exposed	4 / 101 (3.96%)		
occurrences (all)	4		
Renal and urinary disorders			
GLYCOSURIA			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			

ARTHRALGIA			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
MUSCULOSKELETAL PAIN			
subjects affected / exposed	0 / 101 (0.00%)		
occurrences (all)	0		
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
GASTROENTERITIS			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
INFLUENZA			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
NASOPHARYNGITIS			
subjects affected / exposed	12 / 101 (11.88%)		
occurrences (all)	18		
PHARYNGITIS			
subjects affected / exposed	9 / 101 (8.91%)		
occurrences (all)	10		
RESPIRATORY TRACT INFECTION VIRAL			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
STREPTOCOCCAL INFECTION			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	2		
TOOTH ABSCESS			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	10 / 101 (9.90%)		
occurrences (all)	13		
VIRAL INFECTION			

subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
VULVOVAGINAL MYCOTIC INFECTION			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 September 2013	Major changes included: revised the time points of blood sampling measurements for adalimumab concentrations and anti-adalimumab antibodies; revised exclusion criteria and prohibited therapy to clarify that rectal medication for bowel preparation prior to endoscopy was permitted; revised exclusion criteria and concomitant therapy in terms of the number of days that subjects needed to be on stable dose of oral aminosalicylates prior to Baseline; revised study procedures to clarify the process of adjudication to evaluate subject's eligibility for the study and to clarify that subjects who prematurely discontinue from the study before or at Week 26 do not have to undergo an endoscopy at the Premature Discontinuation Visit; ePRO and data collection process details were added.
02 April 2014	Major changes included: added information about a Japan Substudy with inclusion of approximately 20 subjects; revised steroid tapering requirements; replaced inadequate response criteria with disease flare criteria; clarified Inclusion Criterion 2 regarding the diagnosis of ulcerative colitis confirmed by endoscopy; revised Inclusion Criterion 3 regarding methotrexate dosing requirement; added information of antibiotics use in prior therapy and concomitant therapy.
28 August 2015	Major changes included: revised steroid tapering requirements to allow tapering schedule based on investigator's discretion; revised time point to allow increasing dose of corticosteroid after corticosteroid taper was initiated;revised time point allowing initiation of treatment with corticosteroids, immunosuppressants or aminosalicylates; revised disease flare criteria and time point that rescue therapy based on disease flare could be initiated; updated Inclusion Criterion 2 to clarify the requirement for endoscopy during the Screening period; revised Inclusion Criterion 3 to add guidance on use of 6-Thioguanine nucleotide levels and revised the required timeline for previous treatment with corticosteroids or immunosuppressants; clarified Exclusion Criterion 24 regarding Hepatitis B; added fecal transplantation within 30 days prior to the Baseline visit to Exclusion Criterion 26; added vedolizumab to the list of prohibited medications; removed stool sample collection for fecal calprotectin and microbiota; removed the collection of serum bone markers; added information about the use of NRI.
02 November 2017	Major changes included: ceased randomization to double-blind induction treatment and enrollment into the standard induction dose group (all subsequent subjects who enter the study were to receive open-label high induction dose); ceased randomization to the internal placebo arm from the maintenance period and modified study endpoints and statistical analyses to reflect said change; reduced the number of planned subjects from approximately 225 (and approximately 20 subjects in the Japan Substudy) to approximately 85 subjects (and up to approximately 20 subjects in the Japan Substudy).
20 November 2018	Major changes included: modified statistical analyses and ranking of study endpoints; reflected final sample size of 93 subjects (and up to approximately 9 subjects in the Japan Substudy).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported