Clinical trial results:
A Multicenter, Randomized, Double-Blind Study to Evaluate Higher Versus Standard Adalimumab Dosing Regimens for Induction and Maintenance Therapy in Subjects With Moderately to Severely Active Crohn's Disease and Evidence of Mucosal Ulceration

Summary

EudraCT number	2013-001746-33
Trial protocol	DE BE IT SK NL ES DK AT FR
Global end of trial date	30 January 2020

Results information

Result version number	v1 (current)
This version publication date	05 February 2021
First version publication date	05 February 2021

Trial information

Trial identification

Sponsor protocol code	M14-115

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02065570
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 January 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the efficacy and safety of 2 adalimumab induction regimens in achieving clinical remission (CDAI < 150) at Week 4 and endoscopic response defined as decrease in SES-CD > 50% from Baseline (or for a Baseline SES-CD of 4, at least a 2-point reduction from Baseline) at Week 12, in subjects with moderately to severely active CD and evidence of mucosal ulceration at Baseline.

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	01 May 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Canada: 64
Country: Number of subjects enrolled	Czechia: 41
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Israel: 35
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Netherlands: 19
Country: Number of subjects enrolled	Poland: 72
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	Ukraine: 29
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	United States: 142

Worldwide total number of subjects	514
EEA total number of subjects	237

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)	499
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were randomized in a 3:2 ratio at Baseline to receive a higher induction adalimumab regimen or standard induction adalimumab regimen during the double-blind Induction Study.

Pre-assignment

Screening details:

At Week 12, participants were re-randomized in a 1:1 ratio to a double-blind exploratory treatment regimen (adalimumab clinically adjusted [CA] regimen or adalimumab therapeutic drug monitoring [TDM] regimen).

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

Blinding implementation details:

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie's 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	Induction: Standard Induction Dose

Arm description:

Participants randomized to receive blinded adalimumab 160 mg at Baseline and matching placebo at Week 1, adalimumab 80 mg and matching placebo at Week 2, matching placebo at Week 3, and then adalimumab 40 mg every other week (eow) starting at Week 4 through Week 12.

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:

Subjects assigned to the standard induction regimen received blinded adalimumab 160 mg (4 syringes) at Baseline. Subjects received adalimumab 80 mg (2 syringes) at Week 2. At Week 4, subjects receive adalimumab 40 mg (1 syringe) eow through Week 12.

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

Dosage and administration details:

Subjects assigned to the standard induction regimen received matching placebo (4 syringes) at Week 1. Subjects received matching placebo (2 syringes) at Week 2 and matching placebo (4 syringes) at Week 3.

Arm title	Induction: Higher Induction Dose

Arm description:

Participants randomized to receive blinded adalimumab 160 mg at Baseline, Week 1, Week 2, and Week 3. At Week 4, participants receive adalimumab 40 mg eow through Week 12.

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:

Subjects assigned to the higher induction regimen received blinded adalimumab 160 mg (4 syringes) at Baseline, Week 1, Week 2, and Week 3. At Week 4, subjects received 40 mg (1 syringe) eow through Week 12.

Number of subjects in period 1	Induction: Standard Induction Dose	Induction: Higher Induction Dose
Started	206	308
Completed	192	287
Not completed	14	21
Consent withdrawn by subject	2	3
Adverse Event	5	12
Other, not specified	6	5
Lost to follow-up	1	1

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

Blinding implementation details:

All AbbVie personally with direct oversight of the conduct and management of the trial (with the exception of AbbVie's 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: Clinically Adjusted (CA) Regimen

Arm description:

Participants randomized to the CA regimen receive adalimumab 40 mg eow beginning at Week 12. The adalimumab dose could be escalated to every week (ew) starting as early as Week 14 and up to Week 54 based on Crohn's Disease Activity Index (CDAI) or high-sensitivity C-reactive protein (hs-CRP) values, using results from the prior or current study visit. Once participants in the CA regimen are escalated, they remain on adalimumab 40 mg ew dosing.

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:

The adalimumab dose was be escalated to every week (ew) starting as early as Week 14 if the subject's CDAI was ≥ 220 or hs-CRP ≥ 10 mg/L
(using results from the prior or current visit). These subjects were also to be allowed to escalate at unscheduled visits that may occur only on Weeks 16, 18, 22, 24, 30, 32, 36, 38, 44, 46, 50, 52 and 54.

Arm title	Maintenance: Therapeutic Drug Monitoring (TDM) Regimen

Arm description:

At Weeks 14, 28 and 42, the adalimumab dose for participants randomized to the TDM are determined by protocol-established dose adjustment criteria. Doses are determined using blinded serum concentrations at the prior visit (Weeks 12, 26 and 40, respectively) as well as the CDAI or hs-CRP values from the current or prior study visit. Participants who meet criteria for dose escalation at Weeks 14, 28 or 42 receive 40 mg ew.

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:

Doses will be determined using blinded serum concentrations at the prior visit (Weeks 12, 26 and 40, respectively) as well as the CDAI or hs-CRP values from the current or prior visit.

Number of subjects in period 2[1]	Maintenance: Clinically Adjusted (CA) Regimen	Maintenance: Therapeutic Drug Monitoring (TDM) Regimen
Started	109	109
Completed	87	90
Not completed	22	19
Consent withdrawn by subject	1	4
Adverse Event	-	8
Other, not specified	11	5
Adverse Events	8	-
Lost to follow-up	2	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: All participants who entered the Maintenance Study.

Baseline characteristics

Reporting groups	
Reporting group title	Induction: Standard Induction Dose
Reporting group description:	
Participants randomized to receive blinded adalimumab 160 mg at Baseline and matching placebo at Week 1, adalimumab 80 mg and matching placebo at Week 2, matching placebo at Week 3, and then adalimumab 40 mg every other week (eow) starting at Week 4 through Week 12.	
Reporting group title	Induction: Higher Induction Dose
Reporting group description:	
Participants randomized to receive blinded adalimumab 160 mg at Baseline, Week 1, Week 2, and Week 3. At Week 4, participants receive adalimumab 40 mg eow through Week 12.	

Reporting group values	Induction: Standard Induction Dose	Induction: Higher Induction Dose	Total
Number of subjects	206	308	514
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	36.4	36.4	
standard deviation	± 12.79	± 13.02	-
Gender categorical Units: Subjects			
Female	109	158	267
Male	97	150	247
Ethnicity Units: Subjects			
Hispanic or Latino	5	10	15
Not Hispanic or Latino	0	0	0
Unknown or Not Reported	201	298	499
Race Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	5	6	11
Black or African American	18	11	29
White	182	288	470
More than one race	1	1	2
Unknown or Not Reported	0	1	1

End points

End points reporting groups

Reporting group title	Induction: Standard Induction Dose
Reporting group description:	
Participants randomized to receive blinded adalimumab 160 mg at Baseline and matching placebo at Week 1, adalimumab 80 mg and matching placebo at Week 2, matching placebo at Week 3, and then adalimumab 40 mg every other week (eow) starting at Week 4 through Week 12.	
Reporting group title	Induction: Higher Induction Dose
Reporting group description:	
Participants randomized to receive blinded adalimumab 160 mg at Baseline, Week 1, Week 2, and Week 3. At Week 4, participants receive adalimumab 40 mg eow through Week 12.	
Reporting group title	Maintenance: Clinically Adjusted (CA) Regimen
Reporting group description:	
Participants randomized to the CA regimen receive adalimumab 40 mg eow beginning at Week 12. The adalimumab dose could be escalated to every week (ew) starting as early as Week 14 and up to Week 54 based on Crohn's Disease Activity Index (CDAI) or high-sensitivity C-reactive protein (hs-CRP) values, using results from the prior or current study visit. Once participants in the CA regimen are escalated, they remain on adalimumab 40 mg ew dosing.	
Reporting group title	Maintenance: Therapeutic Drug Monitoring (TDM) Regimen
Reporting group description:	
At Weeks 14, 28 and 42, the adalimumab dose for participants randomized to the TDM are determined by protocol-established dose adjustment criteria. Doses are determined using blinded serum concentrations at the prior visit (Weeks 12, 26 and 40, respectively) as well as the CDAI or hs-CRP values from the current or prior study visit. Participants who meet criteria for dose escalation at Weeks 14, 28 or 42 receive 40 mg ew.	

Primary: Percentage of Participants Who Achieved Clinical Remission at Week 4

End point title	Percentage of Participants Who Achieved Clinical Remission at Week 4
End point description:	
Crohn's Disease Activity Index (CDAI) is used to assess the symptoms of participants with Crohn's Disease. Scores generally range from 0 to 600, where clinical remission of Crohn's disease is defined as CDAI < 150, and very severe disease is defined as CDAI > 450. Intent to Treat Population: all participants who were randomized. Non-responder imputation.	
End point type	Primary
End point timeframe:	
Week 4	

End point values	Induction: Standard Induction Dose	Induction: Higher Induction Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	308		
Units: percentage of participants				
number (not applicable)	43.7	43.5		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Risk difference = (adalimumab higher induction dose - adalimumab standard induction dose).

Comparison groups	Induction: Standard Induction Dose v Induction: Higher Induction Dose
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.939 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.1
upper limit	8.8

Notes:

[1] - Adjusted for previous infliximab use (or prior anti-TNF use for participants randomized under original protocol), hs-CRP at Baseline (<10 mg/L, >=10 mg/L) and Crohn's disease severity at Baseline (CDAI ≤ 300, CDAI > 300).

Primary: Percentage of Participants With Endoscopic Response at Week 12

End point title	Percentage of Participants With Endoscopic Response at Week 12

End point description:

Endoscopic response was scored using the Simplified Endoscopic Score for Crohn's Disease (SES-CD). The SES-CD evaluates 4 endoscopic variables (ulcer size ranging from 0 [none] to 3 [very large]; ulcerated surface ranging from 0 [none] to 3 [>30%]; affected surface ranging from 0 [none] to 3 [>75%], and narrowing ranging from 0 [none] to 3 [cannot be passed]) in 5 segments assessed during ileocolonoscopy (ileum, right colon, transverse colon, sigmoid and left colon, and rectum). The total score is the sum of the 4 endoscopic variable scores and range from 0 to 56, where higher scores indicate more severe disease. Endoscopic response was defined as SES-CD total score > 50% from Baseline (or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline) at Week 12.

Intent to Treat Population: all participants who were randomized. Non-responder imputation.

End point type	Primary

End point timeframe:

Week 12

End point values	Induction: Standard Induction Dose	Induction: Higher Induction Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	308		
Units: percentage of participants				
number (not applicable)	39.3	42.9		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Risk difference = (adalimumab higher induction dose - adalimumab standard induction dose).

Comparison groups	Induction: Higher Induction Dose v Induction: Standard Induction Dose
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.462 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.3
upper limit	11.7

Notes:

[2] - Adjusted for previous infliximab use (or prior anti-TNF use for participants randomized under original protocol), hs-CRP at Baseline (<10 mg/L, >=10 mg/L) and Crohn's disease severity at Baseline (CDAI ≤ 300, CDAI > 300).

Primary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs)[3]

End point description:

Adverse event (AE): any untoward medical occurrence that does not necessarily have a causal relationship with treatment. The investigator assessed the relationship of each event to the use of study drug (IP) as either probably related, possibly related, probably not related or not related. Serious AE (SAE) is an event that results in death, is life-threatening, requires or prolongs hospitalization, results in a congenital anomaly, persistent or significant disability/incapacity or is an important medical event that, based on medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above. TEAEs: any event that began or worsened in severity after the first dose of study drug in the induction or maintenance study. Events with unknown severity were counted as severe. Events with unknown relationship to study drug were counted as drug-related.

Safety Set: all participants who received >= 1 injection of study drug

End point type	Primary

End point timeframe:

From first dose of study drug until 70 days following last dose of study drug in the induction study (up to 12 weeks) or maintenance study (up to 56 weeks).

Notes:

[3] - 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: Descriptive statistics are presented per protocol.

End point values	Induction: Standard Induction Dose	Induction: Higher Induction Dose	Maintenance: Clinically Adjusted (CA) Regimen	Maintenance: Therapeutic Drug Monitoring (TDM) Regimen
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	206	308	109	109
Units: participants				
Any TEAE	133	185	77	76
TEAE: reasonable possibility of relationship to IP	54	75	29	33

Any severe TEAE	13	17	7	6
Any SAE	10	14	5	7
Any TEAE leading to discontinuation of IP	8	13	8	9
Any TEAE leading to death	0	0	0	0
Deaths	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Sustained Clinical Remission (Per CDAI) at Both Weeks 4 and 12

End point title	Percentage of Participants With Sustained Clinical Remission (Per CDAI) at Both Weeks 4 and 12

End point description:

CDAI is used to assess the symptoms of participants with Crohn's Disease. Scores generally range from 0 to 600, where clinical remission of Crohn's disease is defined as CDAI < 150, and very severe disease is defined as CDAI > 450.

Intent to Treat Population: all participants who were randomized. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 4 and Week 12

End point values	Induction: Standard Induction Dose	Induction: Higher Induction Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	308		
Units: percentage of participants				
number (not applicable)	35.0	39.0		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Risk difference = (adalimumab higher induction dose - adalimumab standard induction dose).

Comparison groups	Induction: Standard Induction Dose v Induction: Higher Induction Dose
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.269 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	4.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	12.8

Notes:

[4] - Adjusted for previous infliximab use (or prior anti-TNF use for participants randomized under original protocol), hs-CRP at Baseline (<10 mg/L, >=10 mg/L) and Crohn's disease severity at Baseline (CDAI ≤ 300, CDAI > 300).

Secondary: Percentage of Participants Who Achieve Clinical Response at Week 4 and Endoscopic Response at Week 12

End point title	Percentage of Participants Who Achieve Clinical Response at Week 4 and Endoscopic Response at Week 12

End point description:

Clinical response was scored using CDAI, which assesses the symptoms of participants with Crohn's Disease. Scores generally range from 0 to 600, where clinical remission of Crohn's disease is defined as CDAI < 150, and very severe disease is defined as CDAI > 450. Clinical response was defined as a decrease in CDAI ≥ 70 points from Baseline.
Endoscopic response was scored using the SES-CD, which evaluates 4 endoscopic variables (ulcer size ranging from 0 [none] to 3 [very large]; ulcerated surface ranging from 0 [none] to 3 [>30%]; affected surface ranging from 0 [none] to 3 [>75%], and narrowing ranging from 0 [none] to 3 [cannot be passed]) in 5 segments assessed during ileocolonoscopy. The total score is the sum of the 4 endoscopic variable scores and range from 0 to 56, where higher scores indicate more severe disease. Endoscopic response was defined as SES-CD total score >50% from Baseline (or for Baseline SES-CD of 4, at least a 2-point reduction from Baseline) at Week 12.

End point type	Secondary

End point timeframe:

Week 12

End point values	Induction: Standard Induction Dose	Induction: Higher Induction Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206[5]	308[6]		
Units: percentage of participants				
number (not applicable)	20.4	22.1		

Notes:

[5] - Intent to Treat Population: all participants who were randomized. Non-responder imputation.

[6] - Intent to Treat Population: all participants who were randomized. Non-responder imputation.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Risk difference = (adalimumab higher induction dose - adalimumab standard induction dose).

Comparison groups	Induction: Higher Induction Dose v Induction: Standard Induction Dose

Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.61 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.1
upper limit	8.7

Notes:

[7] - Adjusted for previous infliximab use (or prior anti-TNF use for participants randomized under original protocol), hs-CRP at Baseline (<10 mg/L, >=10 mg/L) and Crohn's disease severity at Baseline (CDAI ≤ 300, CDAI > 300).

Secondary: Percentage of Participants With Clinical Remission at Week 12

End point title	Percentage of Participants With Clinical Remission at Week 12

End point description:

Clinical remission was scored using the CDAI. CDAI assesses the symptoms of participants with Crohn's Disease. Scores generally range from 0 to 600, where clinical remission of Crohn's disease is defined as CDAI < 150, and very severe disease is defined as CDAI > 450.

Intent to Treat Population: all participants who were randomized. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 12

End point values	Induction: Standard Induction Dose	Induction: Higher Induction Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	308		
Units: percentage of participants				
number (not applicable)	51.5	62.3		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Risk difference = (adalimumab higher induction dose - adalimumab standard induction dose).

Comparison groups	Induction: Standard Induction Dose v Induction: Higher Induction Dose

Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	11.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.9
upper limit	19.6

Notes:

[8] - Adjusted for previous infliximab use (or prior anti-TNF use for participants randomized under original protocol), hs-CRP at Baseline (<10 mg/L, >=10 mg/L) and Crohn's disease severity at Baseline (CDAI ≤ 300, CDAI > 300).

Secondary: Percentage of Participants Who Discontinued Corticosteroid Use and Achieved Clinical Remission at Week 12 Among Participants Taking Corticosteroids at Baseline

End point title	Percentage of Participants Who Discontinued Corticosteroid Use and Achieved Clinical Remission at Week 12 Among Participants Taking Corticosteroids at Baseline

End point description:

Clinical remission was scored using the CDAI. CDAI assesses the symptoms of participants with Crohn's Disease. Scores generally range from 0 to 600, where clinical remission of Crohn's disease is defined as CDAI < 150, and very severe disease is defined as CDAI > 450.

Intent to Treat Population: all participants who were randomized. Participants taking corticosteroids at Baseline.

End point type	Secondary

End point timeframe:

Week 12

End point values	Induction: Standard Induction Dose	Induction: Higher Induction Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	153		
Units: percentage of participants				
number (not applicable)	48.0	52.9		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Risk difference = (adalimumab higher induction dose - adalimumab standard induction dose).

Comparison groups	Induction: Standard Induction Dose v Induction: Higher Induction Dose

Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.336 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.2
upper limit	18.2

Notes:

[9] - Adjusted for previous infliximab use (or prior anti-TNF use for participants randomized under original protocol), hs-CRP at Baseline (<10 mg/L, >=10 mg/L) and Crohn's disease severity at Baseline (CDAI ≤ 300, CDAI > 300).

Secondary: Percentage of Participants With Endoscopic Remission at Week 12

End point title	Percentage of Participants With Endoscopic Remission at Week 12

End point description:

Endoscopic remission was scored using the SES-CD.The SES-CD evaluates 4 endoscopic variables (ulcer size ranging from 0 [none] to 3 [very large]; ulcerated surface ranging from 0 [none] to 3 [>30%]; affected surface ranging from 0 [none] to 3 [>75%], and narrowing ranging from 0 [none] to 3 [cannot be passed]) in 5 segments assessed during ileocolonoscopy (ileum, right colon, transverse colon, sigmoid and left colon, and rectum). The total score is the sum of the 4 endoscopic variable scores and range from 0 to 56, where higher scores indicate more severe disease. Endoscopic remission was defined as SES-CD ≤ 4 and at least a 2-point reduction versus baseline and no subscore greater than 1 in any individual variable.

Intent to Treat Population: all participants who were randomized. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 12

End point values	Induction: Standard Induction Dose	Induction: Higher Induction Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	308		
Units: percentage of participants				
number (not applicable)	26.2	28.6		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Risk difference = (adalimumab higher induction dose - adalimumab standard induction dose).

Comparison groups	Induction: Standard Induction Dose v Induction: Higher Induction Dose

Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.694 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.1
upper limit	9.1

Notes:

[10] - Adjusted for previous infliximab use (or prior anti-TNF use for participants randomized under original protocol), hs-CRP at Baseline (<10 mg/L, >=10 mg/L) and Crohn's disease severity at Baseline (CDAI ≤ 300, CDAI > 300).

Secondary: Change From Baseline in Fecal Calprotectin Level at Week 4

End point title	Change From Baseline in Fecal Calprotectin Level at Week 4

End point description:

Intent to Treat Population: all participants who were randomized. Participants with a baseline and Week 4 assessment. Observed cases.

End point type	Secondary

End point timeframe:

Week 4

End point values	Induction: Standard Induction Dose	Induction: Higher Induction Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	252		
Units: µg/g				
arithmetic mean (standard deviation)	-1045.7 (± 1648.51)	-1157.0 (± 2000.69)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction: Standard Induction Dose v Induction: Higher Induction Dose
Number of subjects included in analysis	404
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.946
Method	Cochran-Mantel-Haenszel
Parameter estimate	LS mean of difference
Point estimate	6.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-192.3
upper limit	205.9

Secondary: Percentage of Participants With Hs-CRP < 5 mg/L and Fecal Calprotectin < 250 µg/g at Week 4

End point title	Percentage of Participants With Hs-CRP < 5 mg/L and Fecal Calprotectin < 250 µg/g at Week 4
End point description:	
Intent to Treat Population: all participants who were randomized. Non-responder imputation.	
End point type	Secondary
End point timeframe:	
Week 4	

End point values	Induction: Standard Induction Dose	Induction: Higher Induction Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	308		
Units: percentage of participants				
number (not applicable)	27.7	32.5		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Risk difference = (adalimumab higher induction dose - adalimumab standard induction dose).	
Comparison groups	Induction: Standard Induction Dose v Induction: Higher Induction Dose
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.293 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	11.5

Notes:

[11] - Adjusted for previous infliximab use (or prior anti-TNF use for participants randomized under original protocol), hs-CRP at Baseline (<10 mg/L, >=10 mg/L) and Crohn's disease severity at Baseline (CDAI ≤ 300, CDAI > 300).

Secondary: Percentage of Participants With Clinical Remission, Hs-CRP < 5 mg/L and Fecal Calprotectin < 250 µg/g at Week 4

End point title	Percentage of Participants With Clinical Remission, Hs-CRP < 5 mg/L and Fecal Calprotectin < 250 µg/g at Week 4

End point description:

Clinical remission was scored using the CDAI. CDAI assesses the symptoms of participants with Crohn's Disease. Scores generally range from 0 to 600, where clinical remission of Crohn's disease is defined as CDAI < 150, and very severe disease is defined as CDAI > 450.

Intent to Treat Population: all participants who were randomized. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 4

End point values	Induction: Standard Induction Dose	Induction: Higher Induction Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	308		
Units: percentage of participants				
number (not applicable)	11.2	14.3		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Risk difference = (adalimumab higher induction dose - adalimumab standard induction dose).

Comparison groups	Induction: Standard Induction Dose v Induction: Higher Induction Dose
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.304 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	8.6

Notes:

[12] - Adjusted for previous infliximab use (or prior anti-TNF use for participants randomized under original protocol), hs-CRP at Baseline (<10 mg/L, >=10 mg/L) and Crohn's disease severity at Baseline (CDAI ≤ 300, CDAI > 300).

Secondary: Percentage of Participants With Clinical Remission, Hs-CRP < 5 mg/L and Fecal Calprotectin < 250 µg/g and Endoscopic Remission at Week 12

End point title	Percentage of Participants With Clinical Remission, Hs-CRP < 5 mg/L and Fecal Calprotectin < 250 µg/g and Endoscopic Remission at Week 12

End point description:

Clinical remission was scored using the CDAI. CDAI assesses the symptoms of participants with Crohn's Disease. Scores generally range from 0 to 600, where clinical remission of Crohn's disease is defined as CDAI < 150, and very severe disease is defined as CDAI > 450.

Endoscopic remission was scored using the SES-CD.The SES-CD evaluates 4 endoscopic variables (ulcer size ranging from 0 [none] to 3 [very large]; ulcerated surface ranging from 0 [none] to 3 [>30%]; affected surface ranging from 0 [none] to 3 [>75%], and narrowing ranging from 0 [none] to 3 [cannot be passed]) in 5 segments assessed during ileocolonoscopy. The total score is the sum of the 4 endoscopic variable scores and range from 0 to 56, where higher scores indicate more severe disease. Endoscopic remission was defined as SES-CD ≤ 4 and at least a 2-point reduction versus baseline and no subscore greater than 1 in any individual variable.

End point type	Secondary

End point timeframe:

Week 12

End point values	Induction: Standard Induction Dose	Induction: Higher Induction Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206[13]	308[14]		
Units: percentage of participants				
number (not applicable)	7.3	11.7		

Notes:

[13] - Intent to Treat Population: all participants who were randomized. Non-responder imputation.

[14] - Intent to Treat Population: all participants who were randomized. Non-responder imputation.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Risk difference = (adalimumab higher induction dose - adalimumab standard induction dose).

Comparison groups	Induction: Standard Induction Dose v Induction: Higher Induction Dose
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.092 [15]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	9.1

Notes:

[15] - Adjusted for previous infliximab use (or prior anti-TNF use for participants randomized under original protocol), hs-CRP at Baseline (<10 mg/L, >=10 mg/L) and Crohn's disease severity at Baseline (CDAI ≤ 300, CDAI > 300).

Secondary: Percentage of Participants Who Achieved an SES-CD ≤ 2 at Week 12

End point title	Percentage of Participants Who Achieved an SES-CD ≤ 2 at Week 12

End point description:

The SES-CD evaluates 4 endoscopic variables (ulcer size ranging from 0 [none] to 3 [very large]; ulcerated surface ranging from 0 [none] to 3 [>30%]; affected surface ranging from 0 [none] to 3 [>75%], and narrowing ranging from 0 [none] to 3 [cannot be passed]) in 5 segments assessed during ileocolonoscopy (ileum, right colon, transverse colon, sigmoid and left colon, and rectum). The total score is the sum of the 4 endoscopic variable scores and range from 0 to 56, where higher scores indicate more severe disease.

Intent to Treat Population: all participants who were randomized. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 12

End point values	Induction: Standard Induction Dose	Induction: Higher Induction Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	308		
Units: percentage of participants				
number (not applicable)	16.0	20.1		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Risk difference = (adalimumab higher induction dose - adalimumab standard induction dose).

Comparison groups	Induction: Standard Induction Dose v Induction: Higher Induction Dose
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.322 [16]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	10.2

Notes:

[16] - Adjusted for previous infliximab use (or prior anti-TNF use for participants randomized under original protocol), hs-CRP at Baseline (<10 mg/L, >=10 mg/L) and Crohn's disease severity at Baseline (CDAI ≤ 300, CDAI > 300).

Secondary: Percentage of Participants With Clinical Response at Week 4

End point title	Percentage of Participants With Clinical Response at Week 4

End point description:

Clinical response was scored using CDAI is used to assess the symptoms of participants with Crohn's Disease. Scores generally range from 0 to 600, where remission of Crohn's disease is defined as CDAI < 150, and very severe disease is defined as CDAI > 450. Clinical response was defined as a decrease in CDAI ≥ 70 points from baseline.

Intent to Treat Population: all participants who were randomized. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 4

End point values	Induction: Standard Induction Dose	Induction: Higher Induction Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	308		
Units: percentage of participants				
number (not applicable)	70.9	74.4		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Risk difference = (adalimumab higher induction dose - adalimumab standard induction dose).

Comparison groups	Induction: Standard Induction Dose v Induction: Higher Induction Dose
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.353 [17]
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	11.5

Notes:

[17] - Adjusted for previous infliximab use (or prior anti-TNF use for participants randomized under original protocol), hs-CRP at Baseline (<10 mg/L, >=10 mg/L) and Crohn's disease severity at Baseline (CDAI ≤ 300, CDAI > 300).

Secondary: Percentage of Participants With Clinical Response at Week 12

End point title	Percentage of Participants With Clinical Response at Week 12

End point description:

Clinical response was scored using CDAI. CDAI assesses the symptoms of participants with Crohn's Disease. Scores generally range from 0 to 600, where clinical remission of Crohn's disease is defined as CDAI < 150, and very severe disease is defined as CDAI > 450. Clinical response was defined as a decrease in CDAI ≥ 70 points from Baseline.

Intent to Treat Population: all participants who were randomized. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 12

End point values	Induction: Standard Induction Dose	Induction: Higher Induction Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	308		
Units: percentage of participants				
number (not applicable)	74.8	83.4		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Risk difference = (adalimumab higher induction dose - adalimumab standard induction dose).

Comparison groups	Induction: Standard Induction Dose v Induction: Higher Induction Dose
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	8.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.8
upper limit	16

Secondary: Percentage of Participants Achieving Response in Inflammatory Bowel Disease Questionnaire (IBDQ) Bowel Symptom Domain at Week 4

End point title	Percentage of Participants Achieving Response in Inflammatory Bowel Disease Questionnaire (IBDQ) Bowel Symptom Domain at Week 4

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 ≥ 8.

Intent to Treat Population: all participants who were randomized. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 4

End point values	Induction: Standard Induction Dose	Induction: Higher Induction Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	308		
Units: percentage of participants				
number (not applicable)	71.4	74.7		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Risk difference = (adalimumab higher induction dose - adalimumab standard induction dose).

Comparison groups	Induction: Standard Induction Dose v Induction: Higher Induction Dose
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.394 [18]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	11.1

Notes:

[18] - Adjusted for previous infliximab use (or prior anti-TNF use for participants randomized under original protocol), hs-CRP at Baseline (<10 mg/L, >=10 mg/L) and Crohn's disease severity at Baseline (CDAI ≤ 300, CDAI > 300).

Secondary: Percentage of Participants Achieving Response in IBDQ Bowel Symptom Domain at Week 12

End point title	Percentage of Participants Achieving Response in IBDQ Bowel Symptom Domain at Week 12

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 ≥ 8.

Intent to Treat Population: all participants who were randomized. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 12

End point values	Induction: Standard Induction Dose	Induction: Higher Induction Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	308		
Units: percentage of participants				
number (not applicable)	73.3	76.9		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Risk difference = (adalimumab higher induction dose - adalimumab standard induction dose)

Comparison groups	Induction: Standard Induction Dose v Induction: Higher Induction Dose
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.349 [19]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	11.2

Notes:

[19] - Adjusted for previous infliximab use (or prior anti-TNF use for participants randomized under original protocol), hs-CRP at Baseline (<10 mg/L, >=10 mg/L) and Crohn's disease severity at Baseline (CDAI ≤ 300, CDAI > 300).

Secondary: Percentage of Participants Achieving Response in IBDQ Fatigue Item at Week 12

End point title	Percentage of Participants Achieving Response in IBDQ Fatigue Item at Week 12

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.

Intent to Treat Population: all participants who were randomized. Non-responder imputation.

End point type	Secondary

End point timeframe:

Week 12

End point values	Induction: Standard Induction Dose	Induction: Higher Induction Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	308		
Units: percentage of participants				
number (not applicable)	68.4	76.0		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Risk difference = (adalimumab higher induction dose - adalimumab standard induction dose)

Comparison groups	Induction: Standard Induction Dose v Induction: Higher Induction Dose
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.054 [20]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted risk difference
Point estimate	7.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	15.3

Notes:

[20] - Adjusted for previous infliximab use (or prior anti-TNF use for participants randomized under original protocol), hs-CRP at Baseline (<10 mg/L, >=10 mg/L) and Crohn's disease severity at Baseline (CDAI ≤ 300, CDAI > 300).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until 70 days following last dose of study drug in the induction study (up to 12
weeks) or maintenance study (up to 56 weeks).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Induction: Higher Induction Dose

Reporting group description:

Participants randomized to receive blinded adalimumab 160 mg at Baseline, Week 1, Week 2, and Week 3. At Week 4, participants receive adalimumab 40 mg eow through Week 12.

Reporting group title	Induction: Standard Induction Dose

Reporting group description:

Participants randomized to receive received blinded adalimumab 160 mg at Baseline and matching placebo at Week 1, adalimumab 80 mg and matching placebo at Week 2, matching placebo at Week 3, and then adalimumab 40 mg eow starting at Week 4 through Week 12.

Reporting group title	Maintenance: Clinically Adjusted (CA) Regimen

Reporting group description:

Participants randomized to the CA regimen receive adalimumab 40 mg eow beginning at Week 12. The adalimumab dose will be escalated to ew starting as early as Week 14 and up to Week 54 based on CDAI or hs-CRP values, using results from the prior or current study visit. Once participants in the CA regimen are escalated, they remain on adalimumab 40 mg ew dosing.

Reporting group title	Maintenance: Therapeutic Drug Management (TDM) Regimen

Reporting group description:

At Weeks 14, 28 and 42, the adalimumab dose for participants randomized to the TDM are determined by protocol-established dose adjustment criteria. Doses are determined using blinded serum concentrations at the prior visit (Weeks 12, 26 and 40, respectively) as well as the CDAI or hs-CRP values from the current or prior study visit. Participants who meet criteria for dose escalation at Weeks 14, 28 or 42 receive 40 mg ew.

Serious adverse events	Induction: Higher Induction Dose	Induction: Standard Induction Dose	Maintenance: Clinically Adjusted (CA) Regimen
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 308 (4.55%)	10 / 206 (4.85%)	5 / 109 (4.59%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
PAPILLARY RENAL CELL CARCINOMA			
subjects affected / exposed	1 / 308 (0.32%)	0 / 206 (0.00%)	0 / 109 (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
Injury, poisoning and procedural			

complications			
CLAVICLE FRACTURE			
subjects affected / exposed	1 / 308 (0.32%)	0 / 206 (0.00%)	0 / 109 (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
HIP FRACTURE			
subjects affected / exposed	0 / 308 (0.00%)	0 / 206 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RADIUS FRACTURE			
subjects affected / exposed	1 / 308 (0.32%)	0 / 206 (0.00%)	0 / 109 (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
ROAD TRAFFIC ACCIDENT			
subjects affected / exposed	1 / 308 (0.32%)	0 / 206 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRAUMATIC LIVER INJURY			
subjects affected / exposed	0 / 308 (0.00%)	0 / 206 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
SELECTIVE ABORTION			
subjects affected / exposed	1 / 308 (0.32%)	0 / 206 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
AMNESIA			
subjects affected / exposed	0 / 308 (0.00%)	1 / 206 (0.49%)	0 / 109 (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
CEREBRAL INFARCTION			

subjects affected / exposed	1 / 308 (0.32%)	0 / 206 (0.00%)	0 / 109 (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
Eye disorders			
SCLERITIS			
subjects affected / exposed	0 / 308 (0.00%)	0 / 206 (0.00%)	0 / 109 (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
UVEITIS			
subjects affected / exposed	0 / 308 (0.00%)	0 / 206 (0.00%)	0 / 109 (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
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	1 / 308 (0.32%)	1 / 206 (0.49%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CROHN'S DISEASE			
subjects affected / exposed	3 / 308 (0.97%)	3 / 206 (1.46%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FAECALOMA			
subjects affected / exposed	1 / 308 (0.32%)	0 / 206 (0.00%)	0 / 109 (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
GASTROINTESTINAL INFLAMMATION			
subjects affected / exposed	0 / 308 (0.00%)	1 / 206 (0.49%)	0 / 109 (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
INTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 308 (0.00%)	0 / 206 (0.00%)	0 / 109 (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
INTESTINAL OBSTRUCTION			

subjects affected / exposed	2 / 308 (0.65%)	0 / 206 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LARGE INTESTINAL STENOSIS			
subjects affected / exposed	0 / 308 (0.00%)	1 / 206 (0.49%)	0 / 109 (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
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 308 (0.00%)	1 / 206 (0.49%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBILEUS			
subjects affected / exposed	1 / 308 (0.32%)	0 / 206 (0.00%)	0 / 109 (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
Skin and subcutaneous tissue disorders			
DRUG ERUPTION			
subjects affected / exposed	0 / 308 (0.00%)	0 / 206 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	1 / 308 (0.32%)	0 / 206 (0.00%)	0 / 109 (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
SUICIDAL IDEATION			
subjects affected / exposed	0 / 308 (0.00%)	0 / 206 (0.00%)	0 / 109 (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			
HYDRONEPHROSIS			
subjects affected / exposed	1 / 308 (0.32%)	0 / 206 (0.00%)	0 / 109 (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

NEPHROLITHIASIS			
subjects affected / exposed	1 / 308 (0.32%)	0 / 206 (0.00%)	0 / 109 (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
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 308 (0.32%)	0 / 206 (0.00%)	0 / 109 (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
BACK PAIN			
subjects affected / exposed	1 / 308 (0.32%)	0 / 206 (0.00%)	0 / 109 (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			
ABDOMINAL ABSCESS			
subjects affected / exposed	0 / 308 (0.00%)	1 / 206 (0.49%)	0 / 109 (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
ABSCESS LIMB			
subjects affected / exposed	0 / 308 (0.00%)	1 / 206 (0.49%)	0 / 109 (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
ACQUIRED IMMUNODEFICIENCY SYNDROME			
subjects affected / exposed	1 / 308 (0.32%)	0 / 206 (0.00%)	0 / 109 (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
CELLULITIS			
subjects affected / exposed	0 / 308 (0.00%)	1 / 206 (0.49%)	0 / 109 (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
INFECTIOUS MONONUCLEOSIS			

subjects affected / exposed	0 / 308 (0.00%)	0 / 206 (0.00%)	0 / 109 (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
INTESTINAL TUBERCULOSIS			
subjects affected / exposed	0 / 308 (0.00%)	1 / 206 (0.49%)	0 / 109 (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
PNEUMOCYSTIS JIROVECII PNEUMONIA			
subjects affected / exposed	1 / 308 (0.32%)	0 / 206 (0.00%)	0 / 109 (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
PYELONEPHRITIS			
subjects affected / exposed	1 / 308 (0.32%)	0 / 206 (0.00%)	0 / 109 (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
SEPSIS			
subjects affected / exposed	0 / 308 (0.00%)	0 / 206 (0.00%)	0 / 109 (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	1 / 308 (0.32%)	0 / 206 (0.00%)	0 / 109 (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
VARICELLA			
subjects affected / exposed	0 / 308 (0.00%)	0 / 206 (0.00%)	0 / 109 (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
Metabolism and nutrition disorders			
HYPOKALAEMIA			
subjects affected / exposed	0 / 308 (0.00%)	1 / 206 (0.49%)	0 / 109 (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
HYPOVOLAEMIA			

subjects affected / exposed	0 / 308 (0.00%)	1 / 206 (0.49%)	0 / 109 (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	Maintenance: Therapeutic Drug Management (TDM) Regimen		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 109 (6.42%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
PAPILLARY RENAL CELL CARCINOMA			
subjects affected / exposed	0 / 109 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
CLAVICLE FRACTURE			
subjects affected / exposed	0 / 109 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HIP FRACTURE			
subjects affected / exposed	0 / 109 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
RADIUS FRACTURE			
subjects affected / exposed	0 / 109 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ROAD TRAFFIC ACCIDENT			
subjects affected / exposed	0 / 109 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
TRAUMATIC LIVER INJURY			

subjects affected / exposed	0 / 109 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
SELECTIVE ABORTION			
subjects affected / exposed	0 / 109 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
AMNESIA			
subjects affected / exposed	0 / 109 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CEREBRAL INFARCTION			
subjects affected / exposed	0 / 109 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
SCLERITIS			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
UVEITIS			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 109 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CROHN'S DISEASE			

subjects affected / exposed	1 / 109 (0.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
FAECALOMA				
subjects affected / exposed	0 / 109 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
GASTROINTESTINAL INFLAMMATION				
subjects affected / exposed	0 / 109 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
INTESTINAL HAEMORRHAGE				
subjects affected / exposed	1 / 109 (0.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
INTESTINAL OBSTRUCTION				
subjects affected / exposed	0 / 109 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
LARGE INTESTINAL STENOSIS				
subjects affected / exposed	0 / 109 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SMALL INTESTINAL OBSTRUCTION				
subjects affected / exposed	0 / 109 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SUBILEUS				
subjects affected / exposed	0 / 109 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
DRUG ERUPTION				

subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SUICIDAL IDEATION			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
HYDRONEPHROSIS			
subjects affected / exposed	0 / 109 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
NEPHROLITHIASIS			
subjects affected / exposed	0 / 109 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 109 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
BACK PAIN			
subjects affected / exposed	0 / 109 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
ABDOMINAL ABSCESS			

subjects affected / exposed	0 / 109 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ABSCESS LIMB			
subjects affected / exposed	0 / 109 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ACQUIRED IMMUNODEFICIENCY SYNDROME			
subjects affected / exposed	0 / 109 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CELLULITIS			
subjects affected / exposed	0 / 109 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
INFECTIOUS MONONUCLEOSIS			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
INTESTINAL TUBERCULOSIS			
subjects affected / exposed	0 / 109 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PNEUMOCYSTIS JIROVECII PNEUMONIA			
subjects affected / exposed	0 / 109 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PYELONEPHRITIS			
subjects affected / exposed	0 / 109 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SEPSIS			

subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
VARICELLA			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
HYPOKALAEMIA			
subjects affected / exposed	0 / 109 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HYPOVOLAEMIA			
subjects affected / exposed	0 / 109 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Induction: Higher Induction Dose	Induction: Standard Induction Dose	Maintenance: Clinically Adjusted (CA) Regimen
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 308 (18.83%)	54 / 206 (26.21%)	41 / 109 (37.61%)
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	2 / 308 (0.65%)	11 / 206 (5.34%)	0 / 109 (0.00%)
occurrences (all)	2	13	0
HEADACHE			
subjects affected / exposed	17 / 308 (5.52%)	18 / 206 (8.74%)	9 / 109 (8.26%)
occurrences (all)	19	24	9
Gastrointestinal disorders			

CROHN'S DISEASE			
subjects affected / exposed	14 / 308 (4.55%)	12 / 206 (5.83%)	16 / 109 (14.68%)
occurrences (all)	15	14	20
DIARRHOEA			
subjects affected / exposed	2 / 308 (0.65%)	3 / 206 (1.46%)	6 / 109 (5.50%)
occurrences (all)	2	3	7
NAUSEA			
subjects affected / exposed	9 / 308 (2.92%)	15 / 206 (7.28%)	5 / 109 (4.59%)
occurrences (all)	10	17	7
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	10 / 308 (3.25%)	16 / 206 (7.77%)	8 / 109 (7.34%)
occurrences (all)	10	19	8
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	19 / 308 (6.17%)	9 / 206 (4.37%)	15 / 109 (13.76%)
occurrences (all)	21	11	15

Non-serious adverse events	Maintenance: Therapeutic Drug Management (TDM) Regimen		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 109 (30.28%)		
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	0 / 109 (0.00%)		
occurrences (all)	0		
HEADACHE			
subjects affected / exposed	8 / 109 (7.34%)		
occurrences (all)	18		
Gastrointestinal disorders			
CROHN'S DISEASE			
subjects affected / exposed	15 / 109 (13.76%)		
occurrences (all)	17		
DIARRHOEA			
subjects affected / exposed	4 / 109 (3.67%)		
occurrences (all)	4		
NAUSEA			

subjects affected / exposed occurrences (all)	3 / 109 (2.75%) 3		
Musculoskeletal and connective tissue disorders ARTHRALGIA subjects affected / exposed occurrences (all)	 4 / 109 (3.67%) 5		
Infections and infestations NASOPHARYNGITIS subjects affected / exposed occurrences (all)	 10 / 109 (9.17%) 12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 May 2014	Major changes included: Clarification as to when corticosteroid therapy dose adjustment may occur. Updated inclusion criterion 2 to clarify that biopsy results consistent with diagnosis of CD, are to be available at the time of inclusion. Updated inclusion criterion 4 to clarify that, per the investigator, the subject had CDAI ≥ 220 and ≤ 450 despite adequate treatment. Updated inclusion criterion 7 to clarify appropriate and approved forms of contraception. Inclusion criterion 12 updated with additional biologic medications that subject cannot be exposed to previously. Updated to Secondary Variables and Additional Variables to revise the order of ranked secondary endpoints and to add new endpoints assessing hospitalization, extra-intestinal manifestation (EIM), and achievement of both symptomatic remission and endoscopic improvement. Blinding of investigational product updated to clarify that if subject safety is of concern, contact to the Study-Designated Physician is not required. AE Collection Period updated to clarify definition of end of trial, and to clarify that all AEs collected during 70-day follow-up period will be captured in the clinical database. Analyzable population updated to clarify the definition of intent-to-treat (ITT) subjects. Primary Efficacy Variable updated with an additional analysis and the appropriateness for Cochran-Mantel-Haenszel (CMH) test was addressed. Language in Subject Information and Consent updated regarding incentives, provisions on treatment/compensating subjects harmed during study which follows new protocol template.
21 May 2015	Major changes included: Allowed video recorded endoscopies performed within 45 days of Baseline to be sent for central review for inclusion into the study as long as elements noted are met. Modified the inclusion criterion 3 for SES-CD total score and eliminated the ulceration subscore of 2 or 3 to allow broader enrollment of patients, including those with CD limited to the ileum, as these individuals with moderate to severe CD and a substantial burden of mucosal inflammation are appropriate candidates for this trial. Modified the co-primary and secondary variables as a result of the modified SES-CD entry criteria. Modified inclusion criterion 4 to clarify what 6-TGN level is considered adequate in thiopurine dosing. Correction added that cyclosporine, tacrolimus, or mycophenolate mofetil are prohibited within 60 days prior to baseline. Ensured appropriate endpoints are analyzed and in the correct order of importance based on Agency request. Implemented the collection of Product Quality Complaints. Added language to explain sensitivity analysis that may be done on a certain set of subjects. Added language on imputation methods that will be used in sensitivity analysis. Added a subgroup Region (US, ex US) to be analyzed based on Agency feedback.

14 December 2015	Major changes included: Clarification of procedures for corticosteroid taper at Week 4. Clarification regarding inclusion criterion 4 and required 6-TGN levels. Clarification that PK testing is to remain blinded and local PK testing should not be performed. Explained that adjudication will be triggered for endoscopy screening timepoints, prior to eligibility reporting, when the central reviewers do not agree on whether or not a subject meets the eligibility criteria. Updated language regarding AE reporting and the 24-hour AbbVie Medical Escalation Hotline.
28 March 2016	Major changes included: Language for the induction study and new maintenance study; added a 44-week DB maintenance study to follow with 2 study drug arms, one using TDM and the other using clinical assessment. Added a new ranked secondary endpoint following International Organization for the Study of Inflammatory Bowel Disease (IOIBD) expert recommendation, and the addition of 300 subjects. Removal of language regarding the ability to roll into extension Study M14-347. Clarified how the sample size is being calculated as a result of the increased number of subjects and the addition of the secondary endpoint. Clarified how secondary endpoint number 4 will be compared and added the endpoint regarding subject who achieve SES-CD ≤ 2 at Week 12 per IOIBD recommendation. Explained that the PK concentration levels determined for the TDM regimen were based on 2 concentration thresholds in conjunction with clinical response criteria as expected to occur in clinical setting. Identified changes in the efficacy endpoints in the induction study as well as added all new efficacy endpoints for the maintenance study.
20 March 2017	Major changes included: Clarified that low-dose aspirin for prevention of heart attacks, unstable angina, or transient ischemic attacks is acceptable to use prior to and during the study. Clarified when an endoscopy is required for subjects that prematurely discontinue.
27 November 2018	Major changes included: Sample size was updated based on adequacy of power assumed for updated endoscopic co-primary variable. Update to endoscopic co-primary variable. Updated secondary and exploratory maintenance endpoints to reflect change in primary endoscopic endpoint. Modified ranked secondary endpoint #13 and #14 to focus on evaluation of bowel symptom domain of Inflammatory Bowel Disease Questionnaire (IBDQ) that is directly related to the disease and relevant to IBD patients. Added ranked secondary endpoint #15 to include fatigue in the evaluation as it is considered relevant to IBD patients and may provide information complimentary to the primary endpoint. Added and modified non-ranked secondary endpoints to examine the effect of treatment on various aspects of patients' life as measured by IBDQ total score and domain scores, as well as the fatigue item in IBDQ. Modified non-ranked efficacy endpoint definition for symptomatic remission and response to align with current AbbVie IBD registrational trials. Added additional non-ranked efficacy endpoints at Week 56 to assess the effect of dose escalation. Added information to describe Interim Analysis which may be performed via a database cut.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported