Clinical trial results:
A Phase 3, Multicenter, Randomized, Double-blind Study to Determine the Safety and Efficacy of MMX Mesalamine/Mesalazine in Pediatric Subjects with Mild to Moderate Ulcerative Colitis, in Both Acute and Maintenance Phases

Summary

EudraCT number	2013-001744-65
Trial protocol	GB HU SK NL PL DE BE
Global end of trial date	28 November 2018

Results information

Result version number	v1 (current)
This version publication date	09 June 2019
First version publication date	09 June 2019

Trial information

Trial identification

Sponsor protocol code	SPD476-319

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02093663
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire
Sponsor organisation address	300 Shire Way, Lexington, United States, MA 02421
Public contact	Study Director, Shire, 1 866-842-5335, ClinicalTransparency@shire.com
Scientific contact	Study Director, Shire, 1 866-842-5335, ClinicalTransparency@shire.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001406-PIP01-12
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	12 April 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective was to assess clinical response in double-blind acute (DBA) phase and maintenance of clinical response in double-blind maintenance (DBM) phase of the study to Multi Matrix System (MMX®) mesalamine/mesalazine between a low and high dose in children and adolescents aged 5 to 17 years who were in remission with mild to moderate ulcerative colitis (UC).

Protection of trial subjects:

Study was conducted in accordance with International Council for Harmonisation of Good Clinical Practice, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 December 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	United States: 10
Country: Number of subjects enrolled	Hungary: 19
Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	Poland: 58
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	United Kingdom: 9
Worldwide total number of subjects	107
EEA total number of subjects	89

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)	10
Adolescents (12-17 years)	97
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 50 study centers and 33 sites consented at least 1 subject between 12 December 2014 (first subject first visit) and 28 November 2018 (last subject last visit).

Pre-assignment

Screening details:

Study conducted in three phases as double blind acute (DBA), open label acute (OLA), and double blind maintenance (DBM) phase. Overall, 107 subjects enrolled and entered into DBA or DBM directly and eligible subjects entered into DBM phase after DBA or OLA through DBA. Total, 105 subjects received treatment and 65 completed.

Period 1

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

Blinding implementation details:

Study included double-blind treatment in the DBA phase and DBM phase.

Arms

Arm title	Overall Study

Arm description:

Subjects with partial ulcerative colitis disease activity index (UC-DAI) greater than equal to (>=) 2 and mucosal appearance = 2 or 3 entered the DBA phase; with UC-DAI between 1 and 2 entered the OLA phase, after completing DBA phase; with UC-DAI less than equal to (<=) 1 and mucosal appearance = 0 or 1 entered the DBM phase directly. Also, subjects who had a clinical response (partial UC-DAI <= 1) after completion of DBA phase or OLA phase entered into the DBM phase. During the DBA and DBM phase, subjects received 900 to 2400 milligram per day (mg/day) (low dose) and 1800 to 4800 mg/day (high dose) of MMX mesalamine / mesalazine tablet orally once daily for 8 and 26 weeks respectively. During OLA phase, subjects received the high dose for 8 weeks.

Arm type	Experimental
Investigational medicinal product name	MMX mesalamine/mesalazine
Investigational medicinal product code	SPD476
Other name	MMX mesalamine/mesalazine,
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the DBA and DBM phase, subjects received 900 to 2400 mg/day (low dose) and 1800 to 4800 mg/day (high dose) of MMX mesalamine / mesalazine tablet orally once daily for 8 and 26 weeks respectively. During OLA phase, subjects received the high dose for 8 weeks.

Number of subjects in period 1	Overall Study
Started	105
Subjects entered directly to DBM	52 [1]
Subjects entered DBM via DBA	27 [2]
Subjects entered DBM via OLA	8 [3]

Completed	65
Not completed	40
Adverse event, non-fatal	7
Not enrolled to DBM	4
Lost to follow-up	1
Missing	1
Other (Unspecified)	4
Lack of efficacy	23

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: This milestone was added to provide more detailed input.

[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: This milestone was added to provide more detailed input.

[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: This milestone was added to provide more detailed input.

Baseline characteristics

Reporting groups[1]	
Reporting group title	Overall Study

Reporting group description:

Subjects with partial ulcerative colitis disease activity index (UC-DAI) greater than equal to (>=) 2 and mucosal appearance = 2 or 3 entered the DBA phase; with UC-DAI between 1 and 2 entered the OLA phase, after completing DBA phase; with UC-DAI less than equal to (<=) 1 and mucosal appearance = 0 or 1 entered the DBM phase directly. Also, subjects who had a clinical response (partial UC-DAI <= 1) after completion of DBA phase or OLA phase entered into the DBM phase. During the DBA and DBM phase, subjects received 900 to 2400 milligram per day (mg/day) (low dose) and 1800 to 4800 mg/day (high dose) of MMX mesalamine / mesalazine tablet orally once daily for 8 and 26 weeks respectively. During OLA phase, subjects received the high dose for 8 weeks.

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: Not all the enrolled subjects were treated, 107 subjects were enrolled and 105 subjects were treated.

Reporting group values	Overall Study	Total	
Number of subjects	105	105	
Age categorical Units: Subjects			
Age continuous			
Safety analysis set consisted of randomized subjects who had taken at least 1 dose of investigational product.			
Units: years			
arithmetic mean	14.1		
standard deviation	± 2.55	-	
Gender categorical			
Safety analysis set consisted of randomized subjects who had taken at least 1 dose of investigational product.			
Units: Subjects			
Female	53	53	
Male	52	52	
Race (NIH/OMB)			
Safety analysis set consisted of randomized subjects who had taken at least 1 dose of investigational product.			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	3	3	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	1	
White	101	101	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	104	104	
Unknown or Not Reported	0	0	

End points reporting groups

Reporting group title	Overall Study

Reporting group description:

Subjects with partial ulcerative colitis disease activity index (UC-DAI) greater than equal to (>=) 2 and mucosal appearance = 2 or 3 entered the DBA phase; with UC-DAI between 1 and 2 entered the OLA phase, after completing DBA phase; with UC-DAI less than equal to (<=) 1 and mucosal appearance = 0 or 1 entered the DBM phase directly. Also, subjects who had a clinical response (partial UC-DAI <= 1) after completion of DBA phase or OLA phase entered into the DBM phase. During the DBA and DBM phase, subjects received 900 to 2400 milligram per day (mg/day) (low dose) and 1800 to 4800 mg/day (high dose) of MMX mesalamine / mesalazine tablet orally once daily for 8 and 26 weeks respectively. During OLA phase, subjects received the high dose for 8 weeks.

Subject analysis set title	Double-Blind Acute (DBA) phase: low dose
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects with partial UC-DAI >= 2 and mucosal appearance = 2 or 3 entered the DBA phase. During the DBA low dose phase subjects weighing 18 to <= 23 kg, >23 to <=35 kg, >35 to <= 50 kg, >50 to <= 90 kg received 900, 1200, 1800, 2400 mg/day of MMX mesalamine / mesalazine tablet orally once daily for 8 weeks respectively.

Subject analysis set title	Double-Blind Acute (DBA) phase: high dose
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects with partial UC-DAI >= 2 and mucosal appearance = 2 or 3 entered the DBA phase. During the DBA high dose phase subjects weighing 18 to <= 23 kg, >23 to <=35 kg, >35 to <= 50 kg, >50 to <= 90 kg received 1800, 2400, 3600, 4800 mg/day of MMX mesalamine / mesalazine tablet orally once daily for 8 weeks respectively.

Subject analysis set title	Double-Blind Maintenance (DBM) phase: low dose
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects with partial UC-DAI <= 1 and mucosal appearance = 0 or 1 entered the DBM phase directly. Also, subjects with a clinical response (partial UC-DAI <= 1) after completion of DBA phase or OLA phase entered into the DBM phase. During the DBM low dose phase subjects weighing 18 to <= 23 kg, >23 to <=35 kg, >35 to <= 50 kg, >50 to <= 90 kg received 900, 1200, 1800, 2400 mg/day of MMX mesalamine / mesalazine tablet orally once daily for 26 weeks respectively.

Subject analysis set title	Double-Blind Maintenance (DBM) phase: high dose
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects with partial UC-DAI <= 1 and mucosal appearance = 0 or 1 entered the DBM phase directly. Also, subjects with a clinical response (partial UC-DAI <= 1) after completion of DBA phase or OLA phase entered into the DBM phase. During the DBM high dose phase subjects weighing 18 to <= 23 kg, >23 to <=35 kg, >35 to <= 50 kg, >50 to <= 90 kg received 1800, 2400, 3600, 4800 mg/day of MMX mesalamine / mesalazine tablet orally once daily for 26 weeks respectively.

Primary: Number of Subjects With Clinical Response During Double-blind Acute Phase at Week 8

End point title	Number of Subjects With Clinical Response During Double-blind Acute Phase at Week 8

End point description:

Clinical response was defined as partial ulcerative colitis disease activity index (UC-DAI) lesser then or equal to (<=) 1 with rectal bleeding equal to =0, stool frequency lesser then or equal to (<=) 1 and physician’s global assessment (PGA=0). Number of subjects with clinical response during double-blind acute phase was reported. Double-blind acute phase safety analysis set consisted of randomized subjects who had taken at least 1 dose of investigational product during the double-blind acute phase.

End point type	Primary

End point timeframe:

Week 8

End point values	Double-Blind Acute (DBA) phase: low dose	Double-Blind Acute (DBA) phase: high dose		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	26		
Units: Subjects	10	17		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Study was not powered to detect differences between treatment groups and other sensitivity analysis (last observation carried forward [LOCF] and complete case) intended to examine the robustness of the treatment estimate. This was an estimation study, and p-values were presented as descriptive statistics.

Comparison groups	Double-Blind Acute (DBA) phase: low dose v Double-Blind Acute (DBA) phase: high dose
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.074 [2]
Method	Chi-squared corrected
Parameter estimate	Odds ratio (OR)
Point estimate	3.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.22
upper limit	11.98

Notes:

[1] - Due to the difference in conclusions between the 95% CIs and the continuity corrected chi-square test, a post-hoc analysis was conducted to re-analyze the clinical response at week 8 using the uncorrected chi-squared test. The p-value based on the uncorrected chi-square test was 0.038, which is consistent with there being a difference between treatment arms.

[2] - P-value was based on continuity corrected chi-squared test. This inconsistency between the 95% CI and the p-value is likely due to the relatively small sample size, and different statistical methods give different results.

Primary: Number of Subjects With Clinical Response During Double-blind Maintenance Phase at Week 26

End point title	Number of Subjects With Clinical Response During Double-blind Maintenance Phase at Week 26

End point description:

Clinical response was defined as partial UC DAI <= 1 with rectal bleeding=0, stool frequency <= 1, and PGA=0. Number of subjects with clinical response during double-blind maintenance phase was reported. Double-blind maintenance phase safety analysis set consisted of randomized subjects who had taken at least 1 dose of
investigational product during the double-blind maintenance phase.

End point type	Primary

End point timeframe:

Week 26

End point values	Double-Blind Maintenance (DBM) phase: low dose	Double-Blind Maintenance (DBM) phase: high dose		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	45		
Units: Subjects	23	24		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Study was not powered to detect differences between treatment groups and other sensitivity analysis (LOCF and complete case) intended to examine the robustness of the treatment estimate. This was an estimation study, and p-values were presented as descriptive statistics.

Comparison groups	Double-Blind Maintenance (DBM) phase: low dose v Double-Blind Maintenance (DBM) phase: high dose
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.981 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	2.34

Notes:

[3] - P-value was based on a Cochran-Mantel-Haenszel test stratified by prior response status.

Secondary: Number of Subjects With Clinical and Endoscopic Response During Double Blind Acute Phase at Week 8 Using Central Reading

End point title	Number of Subjects With Clinical and Endoscopic Response During Double Blind Acute Phase at Week 8 Using Central Reading

End point description:

Clinical and endoscopic response was defined as UC-DAI <=2 with rectal bleeding=0 and stool frequency <=1 and PGA=0, and with mucosal healing (endoscopy score <=1) at least a 1-point reduction in endoscopy score from baseline based on central reading. Number of subjects with clinical and endoscopic response was reported. Double-blind acute phase safety analysis set consisted of randomized subjects who had taken at least 1 dose of investigational product during the double-blind acute phase. Subjects with missing data at week 8 were assumed not to have had a clinical response. Subjects who completed week 8 but did not have central reading endoscopies at both baseline and week 8 were excluded.

End point type	Secondary

End point timeframe:

Week 8

End point values	Double-Blind Acute (DBA) phase: low dose	Double-Blind Acute (DBA) phase: high dose		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	26		
Units: Subjects	1	3		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Study was not powered to detect differences between treatment groups and other sensitivity analysis (LOCF and complete case) intended to examine the robustness of the treatment estimate. This was an estimation study, and p-values were presented as descriptive statistics.

Comparison groups	Double-Blind Acute (DBA) phase: low dose v Double-Blind Acute (DBA) phase: high dose
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4 [4]
Method	Fisher exact
Parameter estimate	Difference in proportions
Point estimate	50
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.3
upper limit	100

Notes:

[4] - P-value was calculated based on Fisher's exact test

Secondary: Number of Subjects With Clinical and Endoscopic Response During Double Blind Acute Phase at Week 8 Using Local Reading

End point title	Number of Subjects With Clinical and Endoscopic Response During Double Blind Acute Phase at Week 8 Using Local Reading

End point description:

Clinical and endoscopic response was defined as UC-DAI <=2 with rectal bleeding=0 and stool frequency <=1 and PGA=0, and with mucosal healing (endoscopy score <=1) at least a 1-point reduction in endoscopy score from baseline based on local reading. Number of subjects with clinical and endoscopic response was reported. Double-blind acute phase safety analysis set consisted of randomized subjects who had taken at least 1 dose of investigational product during the double-blind acute phase. Subjects with missing data at week 8 were assumed not to have had a clinical response. Subjects who completed week 8 but did not have central reading endoscopies at both baseline and week 8 were excluded.

End point type	Secondary

End point timeframe:

Week 8

End point values	Double-Blind Acute (DBA) phase: low dose	Double-Blind Acute (DBA) phase: high dose		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	26		
Units: Subjects	1	4		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Study was not powered to detect differences between treatment groups and other sensitivity analysis (LOCF and complete case) intended to examine the robustness of the treatment estimate. This was an estimation study, and p-values were presented as descriptive statistics.

Comparison groups	Double-Blind Acute (DBA) phase: low dose v Double-Blind Acute (DBA) phase: high dose
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.333 [5]
Method	Fisher exact
Parameter estimate	Difference in proportions
Point estimate	50
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.3
upper limit	100

Notes:

[5] - P-value was based on a Fisher's exact test.

Secondary: Change from Baseline in Daily Ulcerative Colitis Scale (DUCS) Score During Double-Blind Acute Phase

End point title	Change from Baseline in Daily Ulcerative Colitis Scale (DUCS) Score During Double-Blind Acute Phase

End point description:

Change in the DUCS score from baseline to Week 8 during DBA phase was reported. DUCS score was to measure 7 specific signs or symptom and one impact (abdominal pain, nocturnal stool, daytime stool, blood in stool, diarrhea, urgency, tiredness) of UC with each item score ranged from 0 (worst) to 10 (best) with the overall score ranged from 0 (worst) to 70 (best) based on the responses. DBA phase safety analysis set consisted of randomized subjects who has taken at least 1 dose of investigational product during the DBA phase. Here n = number of subjects evaluable for this outcome at the specified time point for the respective reporting group.

End point type	Secondary

End point timeframe:

Baseline to Week 8

End point values	Double-Blind Acute (DBA) phase: low dose	Double-Blind Acute (DBA) phase: high dose		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	26		
Units: score on the scale				
arithmetic mean (standard error)				
Baseline (n = 27, 26)	32.2 (± 2.86)	31.6 (± 2.88)		
Week 2 (n = 24, 23)	-14.1 (± 3.80)	-13.2 (± 3.50)		
Week 4 (n = 20, 22)	-15.6 (± 3.96)	-16.7 (± 4.01)		
Week 8 (n = 18, 22)	-18.2 (± 4.40)	-23.1 (± 3.59)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Study was not powered to detect differences between treatment groups and other sensitivity analysis (LOCF and complete case) intended to examine the robustness of the treatment estimate. This was an estimation study, and p-values were presented as descriptive statistics.

Comparison groups	Double-Blind Acute (DBA) phase: low dose v Double-Blind Acute (DBA) phase: high dose
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.168 [6]
Method	ANCOVA
Parameter estimate	Difference in Least squares Mean
Point estimate	-5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.1
upper limit	2.4

Notes:

[6] - P-value was based on an analysis of covariance (ANCOVA) including treatment arm as a factor and baseline DUCS score as a covariate.

Secondary: Number of Subjects With Improvement in Pediatric Ulcerative Colitis Activity Index (PUCAI) Score During Double-blind Acute Phase at Week 8

End point title	Number of Subjects With Improvement in Pediatric Ulcerative Colitis Activity Index (PUCAI) Score During Double-blind Acute Phase at Week 8

End point description:

PUCAI is a physician-administered measure that focuses on 6 key signs and symptoms of UC and activity limitations producing a total score ranging from 0-85 with higher scores being worse. Recommended cut-off scores to differentiate disease activity are <10 (remission); 11-30 (mild); 31-64 (moderate) and >65 (severe). Subjects with an improvement (change of greater than or equal to (>=)20 points) in pediatric ulcerative colitis activity index (PUCAI) score. Double-blind acute phase safety analysis set consisted of randomized subjects who had taken at least 1 dose of investigational

during the double-blind acute phase.

End point type	Secondary

End point timeframe:

Week 8

End point values	Double-Blind Acute (DBA) phase: low dose	Double-Blind Acute (DBA) phase: high dose		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	26		
Units: Subjects	10	16		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Study was not powered to detect differences between treatment groups and other sensitivity analysis (LOCF and complete case) intended to examine the robustness of the treatment estimate. This was an estimation study, and p-values were presented as descriptive statistics.

Comparison groups	Double-Blind Acute (DBA) phase: low dose v Double-Blind Acute (DBA) phase: high dose
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.131 [7]
Method	Chi-squared corrected
Parameter estimate	Difference in proportions
Point estimate	24.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	50.6

Notes:

[7] - P-value was based on a continuity-corrected chi-squared test. PUCAI Score was compared between treatment arms using a continuity corrected chi-squared test. Expected cell counts are very low (< 5), then Fisher's Exact Test is alternative method.

Secondary: Number of Subjects With Clinical and Endoscopic Response During Double-Blind Maintenance Phase at Week 26 Using Central Reading

End point title	Number of Subjects With Clinical and Endoscopic Response During Double-Blind Maintenance Phase at Week 26 Using Central Reading

End point description:

Clinical and endoscopic response was defined as UC-DAI <=2 with rectal bleeding=0, stool frequency <=1, PGA=0, and with mucosal healing (endoscopy score <=1) based on central reading at Week 26. Number of subjects with clinical and endoscopic response during double-blind maintenance phase at Week 26 using central reading was reported. Double-blind maintenance phase safety analysis set consisted of randomized subjects who had taken at least 1 dose of investigational product during the double-blind maintenance phase.

End point type	Secondary

End point timeframe:

Week 26

End point values	Double-Blind Maintenance (DBM) phase: low dose	Double-Blind Maintenance (DBM) phase: high dose		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	45		
Units: Subjects	13	11		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Study was not powered to detect differences between treatment groups and other sensitivity analysis (LOCF and complete case) intended to examine the robustness of the treatment estimate. This was an estimation study, and p-values were presented as descriptive statistics.

Comparison groups	Double-Blind Maintenance (DBM) phase: low dose v Double-Blind Maintenance (DBM) phase: high dose
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.539 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.3
upper limit	12.3

Notes:

[8] - P-value was based on a CMH test adjusted by prior response status.

Secondary: Number of Subjects With Clinical and Endoscopic Response During Double-Blind Maintenance Phase at Week 26 Using Local Reading

End point title	Number of Subjects With Clinical and Endoscopic Response During Double-Blind Maintenance Phase at Week 26 Using Local Reading

End point description:

Clinical and endoscopic response was defined as UC-DAI <= 2 with rectal bleeding=0, stool frequency <= 1, PGA=0, and with mucosal healing (endoscopy score <= 1) based on local reading. Number of subjects who had maintained clinical and endoscopic response during double-blind maintenance phase at week 26 using Local reading was reported. Double-blind maintenance phase safety analysis set consisted of randomized subjects who had taken at least 1 dose of investigational product during the double-blind maintenance phase.

End point type	Secondary

End point timeframe:

Week 26

End point values	Double-Blind Maintenance (DBM) phase: low dose	Double-Blind Maintenance (DBM) phase: high dose		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	45		
Units: Subjects	18	12		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Study was not powered to detect differences between treatment groups and other sensitivity analysis (LOCF and complete case) intended to examine the robustness of the treatment estimate. This was an estimation study, and p-values were presented as descriptive statistics.

Comparison groups	Double-Blind Maintenance (DBM) phase: low dose v Double-Blind Maintenance (DBM) phase: high dose
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.129 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-16.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36
upper limit	3.6

Notes:

[9] - P-value was based on a Cochran-Mantel-Haenszel (CMH) test adjusted by prior response status.

Secondary: Change from Baseline in DUCS Score During Double-Blind Maintenance Phase

End point title	Change from Baseline in DUCS Score During Double-Blind Maintenance Phase

End point description:

DUCS score was to measure 7 specific signs or symptom and one impact (abdominal pain, nocturnal stool, daytime stool, blood in stool, diarrhea, urgency, tiredness) of UC with each score range from 0 (worst) to 10 (best) with the overall score ranging from 0 (worst) to 70 (best) based on the responses. Change from Baseline in DUCS score during double-blind maintenance phase at week 13 and Week 26 were reported. Double-blind maintenance phase safety analysis set consisted of randomized subjects who had taken at least 1 dose of investigational product during the double-blind maintenance phase. Here n = number of subjects evaluable for this outcome at the specified time point for the respective reporting group.

End point type	Secondary

End point timeframe:

Baseline, Week 13, and Week 26

End point values	Double-Blind Maintenance (DBM) phase: low dose	Double-Blind Maintenance (DBM) phase: high dose		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	41	45		
Units: score on the scale				
arithmetic mean (standard error)				
Baseline (n = 41, 45)	5.8 (± 1.37)	4.6 (± 0.79)		
Week 13 (n = 30, 34)	1.7 (± 1.61)	-0.1 (± 0.89)		
Week 26 (n = 26, 32)	1.3 (± 1.19)	4.4 (± 1.79)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Study was not powered to detect differences between treatment groups and other sensitivity analysis (LOCF and complete case) intended to examine the robustness of the treatment estimate. This was an estimation study, and p-values were presented as descriptive statistics.

Comparison groups	Double-Blind Maintenance (DBM) phase: low dose v Double-Blind Maintenance (DBM) phase: high dose
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.182 [10]
Method	ANCOVA
Parameter estimate	Difference in Least squares Mean
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	7.4

Notes:

[10] - P-value was based on an analysis of covariance (ANCOVA) including treatment arm and with prior response status.

Secondary: Number of Subjects With Remission at PUCAI Score During Double-Blind Maintenance Phase at Week 26

End point title	Number of Subjects With Remission at PUCAI Score During Double-Blind Maintenance Phase at Week 26

End point description:

PUCAI is a physician-administered measure that focuses on 6 key signs and symptoms of UC and activity limitations producing a total score ranging from 0-85 with higher scores being worse. Recommended cut-off scores to differentiate disease activity are <10 (remission); 11-30 (mild); 31-64 (moderate) and >65 (severe). Double-blind maintenance phase safety analysis set consisted of randomized subjects who had taken at least 1 dose of investigational product during the double-blind maintenance phase.

End point type	Secondary

End point timeframe:

Week 26

End point values	Double-Blind Maintenance (DBM) phase: low dose	Double-Blind Maintenance (DBM) phase: high dose		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	45		
Units: Subjects	29	27		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Study was not powered to detect differences between treatment groups and other sensitivity analysis (LOCF and complete case) intended to examine the robustness of the treatment estimate. This was an estimation study, and p-values were presented as descriptive statistics.

Comparison groups	Double-Blind Maintenance (DBM) phase: low dose v Double-Blind Maintenance (DBM) phase: high dose
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.194 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.1
upper limit	11

Notes:

[11] - P-value was based on a CMH test adjusted by prior response status. Subjects with remission (PUCAI <10) at double-blind maintenance phase at Week 26 was compared between treatment arms using a CMH test stratifying by Week 8 responder status.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration up to follow-up (up to Week 27)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Double-Blind Acute (DBA) Phase: Low Dose

Reporting group description:

Subjects with partial UC-DAI >= 2 and mucosal appearance = 2 or 3 entered the DBA phase. During the DBA low dose phase subjects weighing 18 to <= 23 kg, >23 to <=35 kg, >35 to <= 50 kg, >50 to <= 90 kg received 900, 1200, 1800, 2400 mg/day of MMX mesalamine / mesalazine tablet orally once daily for 8 weeks respectively.

Reporting group title	Double-Blind Acute (DBA) Phase: High Dose

Reporting group description:

Subjects with partial UC-DAI >= 2 and mucosal appearance = 2 or 3 entered the DBA phase. During the DBA high dose phase subjects weighing 18 to <= 23 kg, >23 to <=35 kg, >35 to <= 50 kg, >50 to <= 90 kg received 1800, 2400, 3600, 4800 mg/day of MMX mesalamine / mesalazine tablet orally once daily for 8 weeks respectively.

Reporting group title	Open-Label Acute (OLA) Phase: High Dose

Reporting group description:

Subjects with partial UC-DAI between 1 and 2 entered the OLA phase, after completing DBA phase. Subjects weighing 18 to <= 23 kg, >23 to <=35 kg, >35 to <= 50 kg, >50 to <= 90 kg received 1800, 2400, 3600, 4800 mg/day of MMX mesalamine / mesalazine tablet orally once daily for 8 weeks respectively during the high dose OLA phase

Reporting group title	Double-Blind Maintenance (DBM) Phase: Low Dose

Reporting group description:

Subjects with partial UC-DAI <= 1 and mucosal appearance = 0 or 1 entered the DBM phase directly. Also, subjects with a clinical response (partial UC-DAI <= 1) after completion of DBA phase or OLA phase entered into the DBM phase. During the DBM low dose phase subjects weighing 18 to <= 23 kg, >23 to <=35 kg, >35 to <= 50 kg, >50 to <= 90 kg received 900, 1200, 1800, 2400 mg/day of MMX mesalamine / mesalazine tablet orally once daily for 26 weeks respectively.

Reporting group title	Double-Blind Maintenance (DBM) Phase: High Dose

Reporting group description:

Subjects with partial UC-DAI <= 1 and mucosal appearance = 0 or 1 entered the DBM phase directly. Also, subjects with a clinical response (partial UC-DAI <= 1) after completion of DBA phase or OLA phase entered into the DBM phase. During the DBM high dose phase subjects weighing 18 to <= 23 kg, >23 to <=35 kg, >35 to <= 50 kg, >50 to <= 90 kg received 1800, 2400, 3600, 4800 mg/day of MMX mesalamine / mesalazine tablet orally once daily for 26 weeks respectively.

Serious adverse events	Double-Blind Acute (DBA) Phase: Low Dose	Double-Blind Acute (DBA) Phase: High Dose	Open-Label Acute (OLA) Phase: High Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 27 (14.81%)	0 / 26 (0.00%)	3 / 18 (16.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Injury, poisoning and procedural complications			
Injury corneal			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (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
Retinal injury			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (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
Road traffic accident			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (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
Spinal compression fracture			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (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
Colitis ulcerative			

subjects affected / exposed	2 / 27 (7.41%)	0 / 26 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (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	1 / 27 (3.70%)	0 / 26 (0.00%)	0 / 18 (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			
Pyelonephritis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	0 / 18 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Double-Blind Maintenance (DBM) Phase: Low Dose	Double-Blind Maintenance (DBM) Phase: High Dose	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 42 (7.14%)	2 / 45 (4.44%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Injury corneal			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal injury			

subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Enteritis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pyelonephritis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Double-Blind Acute (DBA) Phase: Low Dose	Double-Blind Acute (DBA) Phase: High Dose	Open-Label Acute (OLA) Phase: High Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 27 (55.56%)	15 / 26 (57.69%)	12 / 18 (66.67%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Inflammation			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	2 / 27 (7.41%)	1 / 26 (3.85%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Reproductive system and breast disorders			
Dysmenorrhoea			

subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 27 (7.41%)	0 / 26 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Epistaxis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hiccups			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	2 / 27 (7.41%)	0 / 26 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Restlessness			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Vitamin D decreased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Joint dislocation			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0

Lower limb fracture			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	2 / 27 (7.41%)	2 / 26 (7.69%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 27 (3.70%)	2 / 26 (7.69%)	1 / 18 (5.56%)
occurrences (all)	1	2	1
Abdominal pain lower			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Cheilosis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Colitis ulcerative			
subjects affected / exposed	6 / 27 (22.22%)	0 / 26 (0.00%)	1 / 18 (5.56%)
occurrences (all)	6	0	1
Constipation			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			

subjects affected / exposed	1 / 27 (3.70%)	3 / 26 (11.54%)	0 / 18 (0.00%)
occurrences (all)	1	3	0
Mouth ulceration			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Vomiting			
subjects affected / exposed	2 / 27 (7.41%)	1 / 26 (3.85%)	1 / 18 (5.56%)
occurrences (all)	2	1	1
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	2 / 18 (11.11%)
occurrences (all)	0	1	2
Back pain			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Torticollis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Infections and infestations			

Bronchitis			
subjects affected / exposed	1 / 27 (3.70%)	1 / 26 (3.85%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Ear infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis viral			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Gastrointestinal infection			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	1 / 27 (3.70%)	2 / 26 (7.69%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
Rhinitis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	2 / 18 (11.11%)
occurrences (all)	1	0	2
Urinary tract infection			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
Viral infection			
subjects affected / exposed	1 / 27 (3.70%)	2 / 26 (7.69%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

Non-serious adverse events	Double-Blind Maintenance (DBM) Phase: Low Dose	Double-Blind Maintenance (DBM) Phase: High Dose	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 42 (59.52%)	25 / 45 (55.56%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Inflammation			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	2 / 42 (4.76%)	2 / 45 (4.44%)	
occurrences (all)	4	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 42 (2.38%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Epistaxis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Hiccups			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 42 (2.38%)	3 / 45 (6.67%)	
occurrences (all)	1	3	
Rhinorrhoea			

subjects affected / exposed	0 / 42 (0.00%)	3 / 45 (6.67%)	
occurrences (all)	0	3	
Psychiatric disorders			
Restlessness			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	2	
Vitamin D decreased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Joint dislocation			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Lower limb fracture			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	2 / 42 (4.76%)	2 / 45 (4.44%)	
occurrences (all)	3	6	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 42 (2.38%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	3 / 42 (7.14%)	5 / 45 (11.11%)	
occurrences (all)	5	6	
Abdominal pain lower			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Abdominal pain upper			
subjects affected / exposed	3 / 42 (7.14%)	1 / 45 (2.22%)	
occurrences (all)	3	1	
Cheilosis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Colitis ulcerative			
subjects affected / exposed	5 / 42 (11.90%)	8 / 45 (17.78%)	
occurrences (all)	5	9	
Constipation			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	1 / 42 (2.38%)	2 / 45 (4.44%)	
occurrences (all)	1	2	
Dyspepsia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	2	
Mouth ulceration			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	2 / 42 (4.76%)	1 / 45 (2.22%)	
occurrences (all)	2	1	
Vomiting			
subjects affected / exposed	0 / 42 (0.00%)	3 / 45 (6.67%)	
occurrences (all)	0	8	
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Eczema			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Back pain			
subjects affected / exposed	1 / 42 (2.38%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Neck pain			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Torticollis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Gastroenteritis viral			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal infection			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Nasopharyngitis			

subjects affected / exposed	3 / 42 (7.14%)	6 / 45 (13.33%)	
occurrences (all)	4	6	
Pharyngitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 42 (2.38%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Urinary tract infection			
subjects affected / exposed	1 / 42 (2.38%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Viral infection			
subjects affected / exposed	2 / 42 (4.76%)	1 / 45 (2.22%)	
occurrences (all)	2	1	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2013	Amendment-1 • Added visit (weeks 2-4) to Double-blind Maintenance Phase for drug dispensing purposes; revised subsequent visit numbers. • Corrected terminology for subject disease state in the primary and secondary objectives for the Double-blind Maintenance Phase from "with mild to moderate UC" to "who are in remission." • Removed normal mucosal appearance criterion from "general" exclusion criteria; added to the individual exclusion criteria of the Double-blind Acute Phase. Created individual exclusion criterion for the Double-blind Maintenance Phase. • Specified in re-randomization criteria that subjects may be re-randomized into the Double-blind Maintenance Phase if they turned 18 during participation in either Acute Phase of the study. • Removed text regarding sensitivity analysis of the primary endpoint from "Double Blind Maintenance Phase" section of the protocol in Section 9.8. Also removed text from Synopsis regarding sensitivity analysis of the primary endpoint. Replaced with the newly created Sensitivity Analyses of the Primary Endpoint section. • Changed Double-blind Maintenance Phase primary efficacy endpoint test from chi-squared test to Mantel-Haenszel test with stratification by responder details. • Included Physician's Global Assessment at week 2 and week 4 of the Double-blind Acute Phase. • Corrected ages for questions and responses for rectal bleeding and stool frequency in e-diary for both versions: children and adolescents (ages 11- 17 years) and caregivers of children (children aged 5-10 years). Specified version of e-diary to be utilized in the case of a change in subject age during the study. Also updated age groups for Global Change in Health questionnaire. • Full Analysis sets have been changed to the Safety Analysis sets. • Removed double-blind Acute Phase Full Analysis Set and Double-blind Maintenance Phase Full Analysis Set.
14 July 2014	Amendment-2 • Corrected definition of Clinical Response by removing "Week 8". • "Continuity-corrected" chi-squared test was added to the method to test the primary/secondary endpoints. • Revised number of active study sites from 35 to 43 • Added comment to footnotes to clarify that final visit of Double-blind Acute Phase and of the Open-label Acute Phase will be used as Week 0 for the subject's next phase of participation. • Text amended to allow for data from an endoscopy performed within 7 days prior to the screening visit (visit 1) to be used in place of an endoscopy performed during the screening visit (Visit 1) or baseline visit (visit 2) for subjects entering the double-blind acute phase. • Added weight assessment to the end of the Double-blind Maintenance Phase. • Added clarification that an additional endoscopy is not required for subjects enrolling into the Double-blind Maintenance Phase from the Double-blind Acute Phase or the Open-label Acute Phase. • Clarified naming of laboratory assessments. • Detail added to clarify the baseline timepoint for each study phase.

03 February 2015	Amendment-3 • Added Shire and CRO contact information for SAE reporting. • Increased maximum duration of screening period from 10 to 14 days. • Updated approximate number of study sites from 43 to 48. • Added pharmacokinetic blood sampling. • Updated approximate number of countries participating in the study from 9 to 8. • Added exploratory endpoint for pharmacokinetic assessment. • Clarification of additional care of subjects added. • Added text to allow for a stool sample obtained per standard of care within 24 hours prior to the Screening Visit (Visit 1), to be used for screening stool assessments.
28 November 2016	Amendment-4 • Updated approximate number of subjects to be screened. • Added text indicating that enrollment in the Double-blind Maintenance Phase will be considered complete once 80 subjects have been randomized into this phase. • Increased maximum duration of screening period from 14 to 21 days. • Clarified eligibility criteria for Double-blind Acute Phase and Double-blind Maintenance Phase to indicate that all 3 components of the UC-DAI score are required as well as assessment of the mucosal appearance (endoscopy score). • Generated new study design flow chart to increase clarity on determination of eligibility for entry into each of the 3 treatment phases. • Updated Exclusion criteria. • Added a column and a row to the Schedule of Assessments to increase clarity and awareness for sites that it is recommended that site staff telephone subjects within 4 to 7 days prior to the Baseline Visit and prior to each site visit to remind subject or the subject's caregiver to enter their UC-DAI symptoms (rectal bleeding and stool frequency) into their e-diaries every night. This was previously only mentioned in Sections 7.1 and 7.2. • Added a footnote indicating that subjects may bring in a standard of care stool sample (if collected within 24 hours) for screening assessments and evaluations. • Updated assessment time points in schedule of assessments for Double-blind Acute Phase, Open-label Acute Phase, and Double-blind Maintenance Phase.
10 April 2017	Amendment-5 • Modified to indicate that "at least" 80 subjects will be enrolled in the Double-blind Maintenance Phase of the study. • After agreement with US FDA in September 2018, the sample size for the DBA phase was reduced to 53 subjects due to difficulties with recruitment. • Subgroup analyses for the primary endpoint were added to explore efficacy by weight group and Week 8 responder status. • Added text to indicate that, for the DBM phase, secondary endpoints of the proportion of subjects who had maintained a clinical and endoscopic response at Week 26 using central reading, and using local reading endoscopies, the CMH test was not performed if the number of subjects with central reading endoscopy data was insufficient. The number and percentage of subjects with clinical and endoscopic response were presented by treatment arm. • Added text to indicate that more data were required to perform the psychometric analysis of the DUCS for children and caregivers; therefore, the need to perform these analyses will be considered in the future. • Removed planned duration of enrollment period as this is not accurate for individual subject participation. • Removed text describing sample size calculations as this study is not powered to detect differences between treatment groups. • Added AE assessment during scheduled telephone calls and on Visit 5 • Expanded the window for acceptance of historical endoscopy results from 7 days to 21 days prior to the Screening Visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported