Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study Investigating the Efficacy and Safety of Mesalamine 4 g Extended Release Granules (Sachet) for the Induction of Clinical and Endoscopic Remission in Active, Mild to Moderate Ulcerative Colitis

Summary

EudraCT number	2015-002557-35
Trial protocol	BE HU LV BG
Global end of trial date	03 April 2018

Results information

Result version number	v1 (current)
This version publication date	12 April 2019
First version publication date	12 April 2019

Trial information

Trial identification

Sponsor protocol code	000174

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02522767
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ferring International Pharmascience Center US, Inc.
Sponsor organisation address	100 Interpace Parkway, Parsippany, NJ, United States, 07054
Public contact	Global Clinical Compliance, Ferring Pharmaceuticals, DK0-Disclosure@ferring.com
Scientific contact	Global Clinical Compliance, Ferring Pharmaceuticals, DK0-Disclosure@ferring.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	03 April 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate efficacy of mesalamine 4 g extended release granules (sachet) once daily (QD) in the induction of clinical and endoscopic remission versus placebo in subjects with active, mild to moderate ulcerative colitis (UC)

Protection of trial subjects:

The trial was performed in accordance with the Declaration of Helsinki and its amendments in force at the initiation of the trial, in compliance with the approved protocol and its amendments, Good Clinical Practice and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 October 2015
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	Canada: 10
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	Russian Federation: 40
Country: Number of subjects enrolled	Serbia: 11
Country: Number of subjects enrolled	Ukraine: 114
Country: Number of subjects enrolled	United States: 27
Country: Number of subjects enrolled	Bulgaria: 8
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Latvia: 6
Worldwide total number of subjects	228
EEA total number of subjects	17

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)	212
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 71 sites in 10 countries (Bulgaria, Canada, Hungary, Latvia, Mexico, Russia, Serbia, Switzerland, Ukraine, and United States) recruited subjects to this trial between October 2015 to November 2017, the last subject completed last visit in April 2018.

Pre-assignment

Screening details:

A total of 411 subjects were screened, of which 228 subjects were randomised in a 1:1 ratio to either mesalamine or placebo group (114 subjects each), for 8 weeks double-blind treatment.
Subjects who completed 8 weeks but failed to meet the defined criteria for remission received open-label treatment with mesalamine for additional 8 weeks.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Mesalamine

Arm description:

Mesalamine 4 g extended release granules (sachet), administered orally QD

Arm type	Experimental
Investigational medicinal product name	Mesalamine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules in sachet
Routes of administration	Oral use

Dosage and administration details:

Doses (4 g extended release granules, sachet) were administered QD at least 1 hour before or at least 2 hours after a meal at approximately the same time each day. The sachet was emptied on the tongue and swallowed with at least 8 ounces (240 mL) of water.

Arm title	Placebo

Arm description:

Placebo 4 g to match mesalamine extended release granules, administered orally QD

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules in sachet
Routes of administration	Oral use

Dosage and administration details:

Doses (4 g placebo sachet matching mesalamine extended release granules, sachet) were administered QD at least 1 hour before or at least 2 hours after a meal at approximately the same time each day. The sachet was emptied on the tongue and swallowed with at least 8 ounces (240 mL) of water.

Number of subjects in period 1	Mesalamine	Placebo
Started	114	114
Completed	103	90
Not completed	11	24
Consent withdrawn by subject	8	11
Adverse event, non-fatal	1	10
Protocol violation	-	1
Protocol deviation	1	-
Lost to follow-up	1	-
Lack of efficacy	-	2

Period 2

Period 2 title	Open-Label
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Mesalamine (Open-Label)

Arm description:

Mesalamine 4 g extended release granules (sachet), administered orally QD

Arm type	Experimental
Investigational medicinal product name	Mesalamine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules in sachet
Routes of administration	Oral use

Dosage and administration details:

Doses (4 g extended release granules, sachet) were administered QD at least 1 hour before or at least 2 hours after a meal at approximately the same time each day. The sachet was emptied on the tongue and swallowed with at least 8 ounces (240 mL) of water.

Number of subjects in period 2[1]	Mesalamine (Open-Label)
Started	170
Completed	158
Not completed	12
Consent withdrawn by subject	5
Protocol violation	1
Adverse event, non-fatal	3

Lost to follow-up	1
Lack of efficacy	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: Subjects provided their consent to receive additional 8 weeks open-label treatment with mesalamine.

Baseline characteristics

Reporting groups	
Reporting group title	Mesalamine
Reporting group description:	
Mesalamine 4 g extended release granules (sachet), administered orally QD	
Reporting group title	Placebo
Reporting group description:	
Placebo 4 g to match mesalamine extended release granules, administered orally QD	

Reporting group values	Mesalamine	Placebo	Total
Number of subjects	114	114	228
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	107	105	212
From 65-84 years	7	9	16
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	41.2	43.9	
standard deviation	± 13.09	± 13.68	-
Gender categorical Units: Subjects			
Female	57	64	121
Male	57	50	107
Race Units: Subjects			
American Indian or Alaska Native	3	5	8
Asian	1	2	3
Black or African American	5	4	9
White	105	103	208
Ethnicity Units: Subjects			
Hispanic or Latino	9	9	18
Not Hispanic or Latino	105	105	210
Body Mass Index Units: kg/m^2			
arithmetic mean	24.68	24.63	
standard deviation	± 4.546	± 4.578	-
Stool frequency score Units: points			

arithmetic mean	1.6	1.8	
standard deviation	± 0.81	± 0.78	-
Rectal bleeding score Units: points			
arithmetic mean	1.2	1.2	
standard deviation	± 0.54	± 0.58	-
Endoscopic Response Score Units: points			
arithmetic mean	2.7	2.6	
standard deviation	± 0.47	± 0.48	-

Subject analysis sets

Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-to-treat (ITT) analysis set comprised all randomised subjects.

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety analysis set comprised all subjects who received at least 1 dose of investigational medicinal product (IMP), and was analysed according to actual treatment received.

Reporting group values	Intention-to-treat	Safety Analysis Set	
Number of subjects	228	228	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	212	212	
From 65-84 years	64	64	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	42.5	42.5	
standard deviation	± 13.42	± 13.42	
Gender categorical Units: Subjects			
Female	121	121	
Male	107	107	
Race Units: Subjects			
American Indian or Alaska Native	8	8	
Asian	3	3	
Black or African American	9	9	
White	208	208	

Ethnicity Units: Subjects			
Hispanic or Latino	18	18	
Not Hispanic or Latino	210	210	
Body Mass Index Units: kg/m^2			
arithmetic mean	24.66	24.66	
standard deviation	± 4.552	± 4.552	
Stool frequency score Units: points			
arithmetic mean	1.7	1.7	
standard deviation	± 0.80	± 0.80	
Rectal bleeding score Units: points			
arithmetic mean	1.2	1.2	
standard deviation	± 0.55	± 0.55	
Endoscopic Response Score Units: points			
arithmetic mean	2.7	2.7	
standard deviation	± 0.47	± 0.47	

End points

End points reporting groups

Reporting group title	Mesalamine
Reporting group description:	
Mesalamine 4 g extended release granules (sachet), administered orally QD	
Reporting group title	Placebo
Reporting group description:	
Placebo 4 g to match mesalamine extended release granules, administered orally QD	
Reporting group title	Mesalamine (Open-Label)
Reporting group description:	
Mesalamine 4 g extended release granules (sachet), administered orally QD	
Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The Intention-to-treat (ITT) analysis set comprised all randomised subjects.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set comprised all subjects who received at least 1 dose of investigational medicinal product (IMP), and was analysed according to actual treatment received.	

Primary: Proportion of Subjects With Remission

End point title	Proportion of Subjects With Remission
End point description:	
The proportion of subjects with remission was defined by the Clinical and Endoscopic Response Score: 0 for rectal bleeding; 0 or 1 with at least 1 point decrease from baseline for stool frequency; 0 or 1 for endoscopic score. The Clinical and Endoscopic Response Score ranged between 0-9, higher scores indicating greater disease severity. This score had two components: Clinical Response which assessed subject's symptoms and ranged between 0-6, and Endoscopic Response which assessed objective evidence of inflammation and ranged between 0-3. Further, the Clinical Response component included two subscales: stool frequency and rectal bleeding (each ranged between 0-3 each) obtained from subjects' daily records. The Endoscopic Response component had one subscale: flexible sigmoidoscopy/colonoscopy (ranging between 0-3).	
End point type	Primary
End point timeframe:	
At Week 8	

End point values	Mesalamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	114		
Units: Counts of subjects	19	13		

Statistical analyses

Statistical analysis title	Primary endpoint analysis

Statistical analysis description:

Proportions were compared between treatment groups, at a two-sided 0.05 significance level.

Comparison groups	Mesalamine v Placebo
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [1]
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	3.32

Notes:

[1] - The p-value was based on chi-square test without a continuity correction.

Secondary: Proportion of Subjects With Remission in the Primary Endpoint and the Physician's Global Assessment (PGA) score of ≤ 1 (Modified Mayo Score)

End point title	Proportion of Subjects With Remission in the Primary Endpoint and the Physician's Global Assessment (PGA) score of ≤ 1 (Modified Mayo Score)

End point description:

The Modified Mayo score was calculated as the sum of the Clinical and Endoscopic Response Score (Range: 0-9) and the standard PGA score (range: 0-3; normal [score=0], mild disease [score=1], moderate disease [score=2], severe disease [score=3]).
The statistical test was to be conducted only if the primary analysis was significant.

End point type	Secondary

End point timeframe:

At Week 8

End point values	Mesalamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	114		
Units: Counts of subjects	19	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Cessation of Rectal Bleeding

End point title	Time to Cessation of Rectal Bleeding

End point description:

Defined as time in days from randomization to the first day of 3 consecutive days with a rectal bleeding

score of 0, based on subject's daily diary.
The statistical test was to be conducted only if the primary analysis was significant.

End point type	Secondary

End point timeframe:

Up to Week 8

End point values	Mesalamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	114[2]		
Units: Days				
median (confidence interval 95%)	18.0 (13.0 to 30.0)	43.0 (23.0 to 99999)		

Notes:

[2] - CIs for placebo group are not valid values. System limitations do not allow NE for not estimable

Statistical analyses

No statistical analyses for this end point

Secondary: The Proportion of Subjects With Endoscopic Improvement

End point title	The Proportion of Subjects With Endoscopic Improvement

End point description:

Defined as an Endoscopic Response Score of 0 or 1, with at least a 1 point reduction from baseline in the endoscopic score at Week 8.

End point type	Secondary

End point timeframe:

At Week 8

End point values	Mesalamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	114		
Units: Number of subjects	34	22		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis

Statistical analysis description:

Proportions were compared between treatment groups at a two-sided 0.05 significance level.

Comparison groups	Mesalamine v Placebo

Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [3]
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	3.29

Notes:

[3] - The p-value was based on chi-square test without a continuity correction.

Secondary: The Proportion of Subjects in Clinical Remission at Weeks 2, 4, and 8

End point title	The Proportion of Subjects in Clinical Remission at Weeks 2, 4, and 8

End point description:

Defined as a score of 0 for rectal bleeding and 0 or 1 with at least 1 point decrease from baseline for stool frequency in the Clinical Response Score subset.

End point type	Secondary

End point timeframe:

At Week 2, 4, and 8

End point values	Mesalamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	114		
Units: Number of subjects				
Week 2	19	17		
Week 4	29	26		
Week 8	40	28		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis

Statistical analysis description:

Proportions were compared between treatment groups over 8 weeks, at a two-sided 0.05 significance level.

Comparison groups	Mesalamine v Placebo

Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Generalised estimating equation approach
Parameter estimate	Odds ratio (OR)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	2.15

Secondary: Time to Normal Stool Pattern

End point title	Time to Normal Stool Pattern

End point description:

Defined as time in days from randomization to the first day of 3 consecutive days with a stool frequency score of 0, based on subject daily diary.

End point type	Secondary

End point timeframe:

Up to Week 8

End point values	Mesalamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114[4]	114[5]		
Units: Days				
median (confidence interval 95%)	55.0 (35.0 to 99999)	99 (99 to 99999)		

Notes:

[4] - CIs for mesalamine are not valid values. System limitations do not allow NE for not estimable.

[5] - CIs and mean for placebo are not valid values. System limitations do not allow NE for not estimable

Statistical analyses

Statistical analysis title	Secondary endpoint analysis

Statistical analysis description:

Times to normal stool pattern were compared between treatment groups, at a two-sided 0.05 significance level.

Comparison groups	Mesalamine v Placebo
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	2.02

Notes:

[6] - The p-value was based on log-rank test.

Secondary: The Change From Baseline in Rectal Bleeding Score at Weeks 2, 4, and 8

End point title	The Change From Baseline in Rectal Bleeding Score at Weeks 2, 4, and 8

End point description:

Defined as change from baseline in rectal bleeding score at Weeks 2, 4, and 8 based on subject daily diary.

End point type	Secondary

End point timeframe:

From baseline to Week 2, 4, and 8

End point values	Mesalamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	114		
Units: points				
number (not applicable)				
Week 2	-0.39	-0.23		
Week 4	-0.56	-0.31		
Week 8	-0.64	-0.33		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis

Statistical analysis description:

Change from baseline scores were compared between treatment groups over 8 weeks, at a two-sided 0.05 significance level.

Comparison groups	Mesalamine v Placebo
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Repeated Measures ANCOVA
Parameter estimate	Treatment difference
Point estimate	-0.24

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	-0.08

Secondary: The Change From Baseline in Serum C-reactive Protein (CRP) Levels at Weeks 2, 4, and 8

End point title	The Change From Baseline in Serum C-reactive Protein (CRP) Levels at Weeks 2, 4, and 8

End point description:

The adjusted mean changes in serum CRP levels from baseline and the difference between treatment groups are presented for each time point.

End point type	Secondary

End point timeframe:

From baseline up to Week 2, 4, and 8

End point values	Mesalamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	114		
Units: mg/L				
number (not applicable)				
Week 2	-0.26	1.07		
Week 4	-1.62	-0.08		
Week 8	-2.41	1.90		

Statistical analyses

Statistical analysis title	Secondary endpoint Analysis

Statistical analysis description:

Change from baseline scores were compared between treatment groups over 8 weeks, at a two-sided 0.05 significance level.

Comparison groups	Mesalamine v Placebo
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Repeated-measures ANCOVA
Parameter estimate	Treatment difference
Point estimate	-2.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.46
upper limit	0.67

Secondary: The Change From Baseline in Fecal Calprotectin Levels at Week 8

End point title	The Change From Baseline in Fecal Calprotectin Levels at Week 8

End point description:

The adjusted mean change from baseline in fecal calprotectin levels at Week 8 are presented.

End point type	Secondary

End point timeframe:

From baseline to Week 8

End point values	Mesalamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	114		
Units: ug/g				
number (not applicable)	-263.95	25.74		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis

Statistical analysis description:

Changes from baseline were compared between treatment groups, at a two-sided 0.05 significance level.

Comparison groups	Mesalamine v Placebo
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-289.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-514.96
upper limit	-64.42

Secondary: The Change From Baseline in Health Related Quality of Life (QoL) score

End point title	The Change From Baseline in Health Related Quality of Life (QoL) score

End point description:

The change from baseline to Week 2, 4, and 8 in Inflammatory Bowel Disease Questionnaire (IBDQ) scores. The adjusted changes from baseline and their differences between treatment groups are

presented.
The IBDQ is an instrument used to assess quality of life in adult patients with UC.
Subjects were asked to recall symptoms and QoL from last two weeks and to rate each item on a 7-point Likert score (higher scores equate to higher QoL).

End point type	Secondary

End point timeframe:

From baseline to Week 2, 4, and 8

End point values	Mesalamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	114		
Units: point				
number (not applicable)				
Week 2	25.97	17.38		
Week 4	34.74	23.46		
Week 8	36.27	17.74		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis

Statistical analysis description:

Change from baseline scores were compared between treatment groups over 8 weeks, at a two-sided 0.05 significance level.

Comparison groups	Mesalamine v Placebo
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Repeated measures ANCOVA
Parameter estimate	Treatment difference
Point estimate	12.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.1
upper limit	20.5

Secondary: Incidence of Adverse Events

End point title	Incidence of Adverse Events

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a subject taking part in a clinical trial.
A 'treatment-emergent AE (TEAE)' is defined as an AE which occurs in the time interval from initial dosing (IMP intake) to the end of treatment visit.
Proportion of subjects with any TEAE (serious or non-serious) are presented.

End point type	Secondary

End point timeframe:

Up to Week 16

End point values	Mesalamine	Placebo	Mesalamine (Open-Label)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	114	114	170	
Units: Count of Participants				
Any TEAE	28	37	31	
Serious AE	1	0	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of Adverse Events

End point title	Severity of Adverse Events

End point description:

The proportion of subjects with intensity of AEs (classified as mild, moderate or severe) are presented.

End point type	Secondary

End point timeframe:

Up to Week 16

End point values	Mesalamine	Placebo	Mesalamine (Open-Label)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	114	114	170	
Units: Number of subjects				
Mild	23	27	21	
Moderate	6	15	11	
Severe	5	3	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subject With Abnormal Laboratory Values (Haematology)

End point title	Proportion of Subject With Abnormal Laboratory Values (Haematology)

End point description:

Proportion of subjects with markedly abnormal changes from baseline in haematology values are presented.

Laboratory value (Low/Normal/High) to abnormal: Subjects in Mesalamine; Placebo; Mesalamine (Open-Label) group:
Eosinophils/Leucocytes (Leuc) (%), Normal>=10: 108;108;165
Erythrocytes (10^6/uL), Low<=3.5: 10;11;15
Erythrocytes (10^6/uL), Normal<=3.5: 101; 98; 153
Haematocrit (%), Low<=0.32: 13;11;20
Haematocrit (%), Normal<=0.32; 98;98;147
Haematocrit (%), Normal>=0.56; 98;98;147
Haemoglobin (Hb) (g/dL), Low<=115: 35;35;53
Hb (g/dL), Normal<=115: 78;75;117
Leuc(10^3/uL), Normal <=2.8: 103; 104; 155
Leuc(10^3/uL), Normal >=16.0: 103; 104; 155
Leuc(10^3/uL), High>=16.0: 8;5;12
Lymphocytes (Lymp)/Leuc (%), Low<=10: 22;25;35
Lymp/Leuc (%), Normal<=10: 90;84;133
Lymp/Leuc (%), High>=80: 1;1;2
Neutrophils (Neut)/Leuc (%), Normal <=15: 98;93;148
Neut/Leuc (%), Normal >=90: 98;93;148
Neut/Leuc (%), High >=90: 15;17; 22
Platelets (10^3/uL), High>=700: 19; 22; 34

End point type	Secondary

End point timeframe:

Up to Week 16

End point values	Mesalamine	Placebo	Mesalamine (Open-Label)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	114	114	170	
Units: number				
number (not applicable)				
Eosinophils/Leucocytes (%), Normal>=10 to Abnormal	0	2	4	
Erythrocytes (10^6/uL), Low<=3.5 to Abnormal	2	4	4	
Erythrocytes (10^6/uL), Normal<=3.5 to Abnormal	1	0	2	
Haematocrit (%), Low<=0.32 to Abnormal	4	1	5	
Haematocrit (%), Normal<=0.32 to Abnormal	0	3	4	
Haematocrit (%), Normal>=0.56 to Abnormal	0	1	0	
Haemoglobin (g/dL), Low<=115 to Abnormal	21	23	37	
Haemoglobin (g/dL), Normal<=115 to Abnormal	12	15	29	
Leucocytes (10^3/uL), Normal <=2.8 to Abnormal	1	0	2	
Leukocytes (10^3/uL), Normal >=16.0 to Abnormal	0	2	2	
Leucocytes (10^3/uL), High >=16.0 to Abnormal	0	1	1	
Lymphocytes/Leucocytes (%), Low<=10 to Abnormal	0	3	1	
Lymphocytes/Leucocytes (%), Normal<=10 to Abnormal	4	2	6	
Lymphocytes/Leucocytes (%), High>=80 to Abnormal	1	0	1	

Neutrophils/Leucocyte (%), Normal<=15 to Abnormal	2	0	2	
Neutrophils/Leucocyte (%), Normal>=90 to Abnormal	0	1	2	
Neutrophils/Leucocyte (%), High >=90 to Abnormal	0	1	1	
Platelets (10^3/uL), High>=700 to Abnormal	2	0	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Abnormal Laboratory Values (Coagulation)

End point title	Proportion of Subjects With Abnormal Laboratory Values (Coagulation)

End point description:

Proportion of subjects with markedly abnormal changes from baseline values in coagulation laboratory values are presented.
INR= International normalised ratio.
Laboratory value (Low/Normal/High) to abnormal: Subjects in Mesalamine; Placebo; Mesalamine (Open-Label) group:
Prothrombin INR, Normal <0.8: 81; 80; 127
Prothrombin INR, Normal >1.1: 81; 80; 127
Prothrombin INR, High >1.1: 20; 22; 40

End point type	Secondary

End point timeframe:

Up to Week 16

End point values	Mesalamine	Placebo	Mesalamine (Open-Label)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	114	114	170	
Units: Counts of participants				
Prothrombin INR, Normal <0.8 to Abnormal	0	0	1	
Prothrombin INR, Normal >1.1 to Abnorma	14	14	28	
Prothrombin INR, High >1.1 to Abnormal	4	10	22	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Abnormal Laboratory Values (Serum Chemistry)

End point title	Proportion of Subjects With Abnormal Laboratory Values (Serum Chemistry)

End point description:

Proportion of subjects with markedly abnormal changes in serum chemistry laboratory values are presented.
ALT=Alanine aminotransferase; AST=Aspartate aminotransferase; BUN=Blood urea nitrogen; GGT=Gamma glutamyl transferase.
Laboratory value (Low/Normal/High) to abnormal: Subjects in Mesalamine; Placebo; Mesalamine (Open-Label) group:
ALT (U/L), Normal >3xULN: 110;108;169
AST (U/L), Normal >3xULN: 107;107;163
AST (U/L), High >3xULN: 5;5;7
Bilirubin (mg/dL), Normal >=1.5xULN: 106;100;157
Bilirubin (mg/dL), High >=1.5xULN: 7;10;13
BUN (mg/dL), Normal >=10.7: 102;92;145
Calcium (mg/dL), Normal <=1.8: 110;104;162
Chloride (mmol/L), Normal >=115: 94; 98; 146
Chloride (mmol/L), High >=115: 18; 12;23
GGT (U/L), High >3xULN: 13;10;16
Glucose (mg/dL),Normal >=10: 94; 85;134
Glucose (mg/dL),High >=10: 13; 20; 25
Potassium (mmol/L), Normal <=3.0: 107; 110; 166
Potassium (mmol/L),Normal >=5.8: 107; 110; 166
Potassium (mmol/L), High >=5.8: 5;2;3
Sodium (mmol/L), Low<=130: 1;1;1

End point type	Secondary

End point timeframe:

Up to Week 16

End point values	Mesalamine	Placebo	Mesalamine (Open-Label)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	114	114	170	
Units: Subjects				
ALT (U/L), Normal >3xULN to Abnormal	1	0	2	
AST (U/L), Normal >3xULN to Abnormal	1	0	2	
AST (U/L), High >3xULN to Abnormal	0	0	1	
Bilirubin (mg/dL), Normal >=1.5xULN to Abnormal	1	0	1	
Bilirubin (mg/dL), High >=1.5xULN to Abnormal	2	1	4	
BUN (mg/dL), Normal >=10.7 to Abnormal	0	1	1	
Calcium (mg/dL), Normal <=1.8 to Abnormal	1	0	1	
Chloride (mmol/L), Normal >=115 to Abnormal	1	0	1	
Chloride (mmol/L), High >=115 to Abnormal	1	0	1	
GGT (U/L), High >3xULN to Abnormal	2	2	4	
Glucose (mg/dL), Normal >=10 to Abnormal	1	1	1	
Glucose (mg/dL), High >=10 to Abnormal	0	2	1	
Potassium (mmol/L), Normal <=3.0 to Abnormal	1	0	1	
Potassium (mmol/L), Normal >=5.8 to Abnormal	1	0	3	

Potassium (mmol/L), High >=5.8 to Abnormal	0	0	1	
Sodium (mmol/L), Low<=130 to Abnormal	0	1	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
TEAE occurred in the time interval from initial dosing (IMP intake) to the end of trial visit.	
Adverse event reporting additional description:	
TEAEs were defined as AE which occurred in the time interval from initial dosing (IMP intake) to the end of treatment visit.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Mesalamine
Reporting group description:	
Mesalamine 4 g extended release granules (sachet), administered orally QD	
Reporting group title	Placebo
Reporting group description:	
Placebo 4 g to match mesalamine extended release granules, administered orally QD	
Reporting group title	Mesalamine (Open-Label)
Reporting group description:	
Mesalamine 4 g extended release granules (sachet), administered orally QD	

Serious adverse events	Mesalamine	Placebo	Mesalamine (Open-Label)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 114 (0.88%)	0 / 114 (0.00%)	2 / 170 (1.18%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Musculoskeletal and connective tissue disorders			
Spondylitis			
subjects affected / exposed	0 / 114 (0.00%)	0 / 114 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Tracheitis			
subjects affected / exposed	1 / 114 (0.88%)	0 / 114 (0.00%)	0 / 170 (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
Appendicitis			

subjects affected / exposed	0 / 114 (0.00%)	0 / 114 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Mesalamine	Placebo	Mesalamine (Open-Label)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 114 (16.67%)	13 / 114 (11.40%)	8 / 170 (4.71%)
Investigations			
C-reactive protein increased			
subjects affected / exposed	6 / 114 (5.26%)	1 / 114 (0.88%)	0 / 170 (0.00%)
occurrences (all)	6	1	0
Faecal calprotectin increased			
subjects affected / exposed	5 / 114 (4.39%)	2 / 114 (1.75%)	4 / 170 (2.35%)
occurrences (all)	5	2	4
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 114 (2.63%)	2 / 114 (1.75%)	0 / 170 (0.00%)
occurrences (all)	3	3	0
Leukocytosis			
subjects affected / exposed	1 / 114 (0.88%)	3 / 114 (2.63%)	0 / 170 (0.00%)
occurrences (all)	1	3	0
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	3 / 114 (2.63%)	10 / 114 (8.77%)	4 / 170 (2.35%)
occurrences (all)	3	10	4
Diarrhoea			
subjects affected / exposed	1 / 114 (0.88%)	3 / 114 (2.63%)	0 / 170 (0.00%)
occurrences (all)	1	3	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 July 2015	This was a substantial amendment, which was implemented during the conduct of the trial. This amendment included correction of language and inconsistencies in the protocol and changes made to the planned statistical analysis.
30 July 2015	This was a substantial amendment, which was implemented during the conduct of the trial. This amendment included correction of language and inconsistencies in the protocol and additional clarifications within the methodology section of the protocol.
11 January 2017	This was a substantial amendment, which was implemented during the conduct of the trial. This amendment included clarification of language and procedures related to primary and secondary endpoints, methodology, exclusion criteria, video submission of flexible sigmoidoscopy/colonoscopy and additional clarifications within the protocol. With this amendment, the definition of remission used for analysis of the primary endpoint was changed from 'rectal bleeding and stool frequency scores of 0 with an endoscopic score of 0 or 1 in the Clinical and Endoscopic Response Score', to 'rectal bleeding score of 0 and stool frequency score of 0 or 1 with at least 1 point decrease from baseline, with an endoscopic score of 0 or 1 in the Clinical and Endoscopic Response Score.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: