Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study Investigating the Efficacy and Safety of Mesalamine 2 g Extended Release Granules (Sachet) for Maintenance of Clinical and Endoscopic Remission in Ulcerative Colitis

Summary

EudraCT number	2015-002558-11
Trial protocol	BE HU LV BG
Global end of trial date	19 September 2018

Results information

Result version number	v1 (current)
This version publication date	21 September 2019
First version publication date	21 September 2019

Trial information

Trial identification

Sponsor protocol code	000175

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02522780
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ferring Pharmaceuticals, 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	24 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of mesalamine 2 g extended release granules (sachet) once daily (QD) compared to placebo in the maintenance of clinical and endoscopic remission of 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	01 February 2016
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	Bulgaria: 10
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Latvia: 11
Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	Russian Federation: 71
Country: Number of subjects enrolled	Serbia: 12
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Ukraine: 145
Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	276
EEA total number of subjects	25

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)	259
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 50 sites in 10 countries randomised subjects to this trial between February 2016 to April 2018, the last subject completed last visit in September 2018. Of 403 subjects screened, 276 subjects were randomised in a 1:1 ratio to either mesalamine or placebo group (138 subjects each), for 6 months.

Pre-assignment

Screening details:

Of 276 subjects, (a) 53 were rolled-over from Trial 000174 (2015-002557-35) who achieved remission after 8-weeks double-blind treatment with placebo (Pathway 1a; 4 subjects) or mesalamine (Pathway 1b; 10 subjects), or an additional 8-weeks open-label treatment with mesalamine (Pathway 2; 39 subjects), and (b) 223 subjects were de novo (Pathway 3).

Period 1

Period 1 title	All Randomised Subjects
Is this the baseline period?	No
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 2 g extended release granules (sachet), administered orally QD for 6 months.

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 (2 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 matched to mesalamine extended release granules (sachet), administered orally QD for 6 months.

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 (placebo matched to 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	138	138
Treated	137	135
Completed	121	111
Not completed	17	27
Consent withdrawn by subject	5	7
Adverse event, non-fatal	11	16
Subject refused endoscopic procedure	-	1
Protocol deviation	1	3

Period 2

Period 2 title	Intention-to-treat (ITT) Analysis Set
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Mesalamine

Arm description:

Mesalamine 2 g extended release granules (sachet), administered orally QD for 6 months.

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 (2 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 matched to mesalamine extended release granules (sachet), administered orally QD for 6 months.

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 (placebo matched to 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.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 included all randomised subjects whereas Period 2 included all randomised subjects who were assigned to mesalamine 4 g extended release granules in the Trial 000174 (2015-002557-35) (Pathway 1b) or randomised via Pathways 2 or 3 (ITT analysis set).

Number of subjects in period 2	Mesalamine	Placebo
Started	136	136
Completed	119	109
Not completed	17	27
Consent withdrawn by subject	5	7
Adverse event, non-fatal	11	16
Subject refused endoscopic procedure	-	1
Protocol deviation	1	3

Baseline characteristics

Reporting groups[1]	
Reporting group title	Mesalamine
Reporting group description:	
Mesalamine 2 g extended release granules (sachet), administered orally QD for 6 months.	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to mesalamine extended release granules (sachet), administered orally QD for 6 months.	

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: Period 1 included all randomised subjects whereas Period 2 included all randomised subjects who were assigned to mesalamine 4 g extended release granules in the Trial 000174 (2015-002557-35) (Pathway 1b) or randomised via Pathways 2 or 3 (ITT analysis set).

Reporting group values	Mesalamine	Placebo	Total
Number of subjects	136	136	272
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)	130	126	256
From 65-84 years	6	10	16
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	41.5	45.2	
standard deviation	± 13.50	± 13.65	-
Gender categorical Units: Subjects			
Female	70	77	147
Male	66	59	125
Race Units: Subjects			
American Indian or Alaska Native	4	4	8
Black or African American	2	1	3
White	130	130	260
Multiple	0	1	1
Ethnicity Units: Subjects			
Hispanic or Latino	6	9	15
Not Hispanic or Latino	130	127	257

Body Mass Index Units: kg/m^2			
arithmetic mean	24.56	24.89	
standard deviation	± 4.812	± 4.657	-

End points

End points reporting groups

Reporting group title	Mesalamine
Reporting group description:	
Mesalamine 2 g extended release granules (sachet), administered orally QD for 6 months.	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to mesalamine extended release granules (sachet), administered orally QD for 6 months.	
Reporting group title	Mesalamine
Reporting group description:	
Mesalamine 2 g extended release granules (sachet), administered orally QD for 6 months.	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to mesalamine extended release granules (sachet), administered orally QD for 6 months.	

Primary: Proportion of Subjects with Remission at Month 6

End point title	Proportion of Subjects with Remission at Month 6
End point description:	
The proportion of subjects with remission was defined by Clinical and Endoscopic Response Score: 0 for rectal bleeding; 0 or 1 for stool frequency; 0 or 1 for endoscopic score. The Clinical and Endoscopic Response Score ranged between 0 (normal) to 9 (severe disease), higher scores indicating greater disease severity. The score included clinical response component to assess subject's symptoms and endoscopic response component to assess objective evidence of inflammation. Clinical response component had two subscales: stool frequency ranging from 0 (normal number of stools) to 3 (>=5 stools more than normal) and rectal bleeding ranging from 0 (no blood seen) to 3 (blood alone passes). The Endoscopic Response component had one subscale: flexible sigmoidoscopy/colonoscopy ranging from 0 (normal) to 3 (severe disease). The analysis was based on ITT analysis set. Data is presented cumulative for all pathways.	
End point type	Primary
End point timeframe:	
Month 6	

End point values	Mesalamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: subjects	82	67		

Statistical analyses

Statistical analysis title	Primary endpoint analysis
Statistical analysis description:	
Proportions were compared between treatment groups at Month 6.	
Comparison groups	Mesalamine v Placebo

Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	2.54

Notes:

[1] - The p-value was based on Cochran-Mantel-Haenszel test by controlling pathway of randomisation, at a 0.05 significance level.

Secondary: Proportion of Subjects in Clinical Remission at Month 2, 4, and 6

End point title	Proportion of Subjects in Clinical Remission at Month 2, 4, and 6

End point description:

The proportion of subjects in clinical remission was defined as a score of 0 for rectal bleeding and 0 or 1 for stool frequency based on clinical response score component of the Clinical and Endoscopic Response Score. Clinical response score component had two subscales to assess subject's symptoms: rectal bleeding ranging from 0 (no blood seen) to 3 (blood alone passes) and stool frequency ranging from 0 (normal number of stools) to 3 (>=5 stools more than normal). The scores of clinical response component ranged from 0 (normal) to 6 (severe disease), higher scores indicating greater disease severity. The analysis was based on ITT analysis set. Data is presented cumulative for all pathways.

End point type	Secondary

End point timeframe:

Month 2, 4, and 6

End point values	Mesalamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: subjects				
Month 2	122	116		
Month 4	113	113		
Month 6	96	89		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis

Statistical analysis description:

Proportions were compared between treatment groups over 6 months.

Comparison groups	Mesalamine v Placebo

Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [2]
Method	Generalised estimating equation approach
Parameter estimate	Odds ratio (OR)
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	2.03

Notes:

[2] - The p-value was based on Generalized estimating equations (GEE) approach with binary outcomes (clinical remission) and an unstructured working correlation matrix, at a 0.05 significance level.

Secondary: Time to Relapse

End point title	Time to Relapse

End point description:

Time to relapse was defined as the number of days from randomisation to the day of withdrawal due to escalation of therapy. The analysis was based on ITT analysis set. Here, 99999 signifies that median and 95% confidence interval (CI) was not estimable due to insufficient events to meet the threshold for 50% on the Kaplan-Meier curve. Data is presented cumulative for all pathways.

End point type	Secondary

End point timeframe:

Time from randomisation to the day of withdrawal due to escalation of therapy (up to 6 months)

End point values	Mesalamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: Days				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis

Statistical analysis description:

Times to relapse were compared between treatment groups.

Comparison groups	Mesalamine v Placebo
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	1.44

Notes:

[3] - The p-value was based on log-rank test using pathway of randomisation as the stratification factor, at a 0.05 significance level.

Secondary: Proportion of Subjects with an Increase from Baseline in the Clinical and Endoscopic Response Score by 2 or More Points in at least 1 Component or by 1 or More Points in at least 2 Components at Month 6

End point title	Proportion of Subjects with an Increase from Baseline in the Clinical and Endoscopic Response Score by 2 or More Points in at least 1 Component or by 1 or More Points in at least 2 Components at Month 6

End point description:

The proportion of subjects with an increase from baseline in the Clinical and Endoscopic Response Score by 2 or more points in at least 1 component, or by 1 or more points in at least 2 components were reported. The Clinical and Endoscopic Response Score ranged between 0 (normal) to 9 (severe disease), higher scores indicating greater disease severity. The score included clinical response component to assess subject's symptoms and endoscopic response component to assess objective evidence of inflammation. Clinical Response component had two subscales: stool frequency ranging from 0 (normal number of stools) to 3 (>=5 stools more than normal) and rectal bleeding ranging from 0 (no blood seen) to 3 (blood alone passes). The Endoscopic Response component had one subscale: flexible sigmoidoscopy/colonoscopy ranging from 0 (normal) to 3 (severe disease). The analysis was based on ITT analysis set. Data is presented cumulative for all pathways.

End point type	Secondary

End point timeframe:

Month 6

End point values	Mesalamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: subjects	14	30		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis

Statistical analysis description:

Proportions were compared between treatment groups at Month 6.

Comparison groups	Mesalamine v Placebo
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.39

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	0.79

Notes:

[4] - The p-value was based on Cochran-Mantel-Haenszel test by controlling pathway of randomisation, at a 0.05 significance level.

Secondary: Change from Baseline in Serum C-reactive Protein (CRP) Levels at Month 2, 4, and 6

End point title	Change from Baseline in Serum C-reactive Protein (CRP) Levels at Month 2, 4, and 6

End point description:

The adjusted mean change from baseline in serum CRP levels at Month 2, 4, and 6 were reported. The analysis was based on ITT analysis set. Data is presented cumulative for all pathways.

End point type	Secondary

End point timeframe:

Baseline, Month 2, 4, and 6

End point values	Mesalamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: mg/L				
number (not applicable)				
Month 2	0.8	2.4		
Month 4	1.0	1.0		
Month 6	1.0	2.6		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis

Statistical analysis description:

Adjusted mean treatment difference in CRP levels over 6 months was reported.

Comparison groups	Mesalamine v Placebo
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [5]
Method	ANCOVA
Parameter estimate	Mean difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	0.7

Notes:

[5] - The p-value was based on a repeated-measures analysis of covariance (ANCOVA) model with an unstructured correlation matrix, at a 0.05 significance level.

Secondary: Change from Baseline in Fecal Calprotectin Levels at Month 2, 4, and 6

End point title	Change from Baseline in Fecal Calprotectin Levels at Month 2, 4, and 6

End point description:

The adjusted mean change from baseline in fecal calprotectin levels at Month 2, 4, and 6 were reported. The analysis was based on ITT analysis set. Data is presented cumulative for all pathways.

End point type	Secondary

End point timeframe:

Baseline, Month 2, 4, and 6

End point values	Mesalamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: mcg/g				
number (not applicable)				
Month 2	-55.6	5.6		
Month 4	-9.6	59.8		
Month 6	-25.5	44.6		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis

Statistical analysis description:

Adjusted mean treatment difference in fecal calprotectin levels over 6 months was reported.

Comparison groups	Mesalamine v Placebo
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [6]
Method	ANCOVA
Parameter estimate	Mean difference
Point estimate	-66.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-140.2
upper limit	6.36

Notes:

[6] - The p-value was based on a repeated-measures ANCOVA model with an unstructured correlation matrix, at a 0.05 significance level.

Secondary: Change from Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) Total Scores at Months 2, 4, and 6

End point title	Change from Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) Total Scores at Months 2, 4, and 6

End point description:

The IBDQ is an instrument used to assess quality of life in adult subjects with UC. It includes 32 questions on 4 domains of Health-Related Quality-of-Life (HRQOL): Bowel Systems (10 items), Emotional Function (12 items), Social Function (5 items), and Systemic Function (5 items). Subjects were asked to recall symptoms and quality of life from the last 2 weeks and rate each item on a 7-point Likert scale (1=worst to 7=best). The total IBDQ was computed as the sum of the responses to the individual IBDQ questions. The total score can range between 32 to 224 with higher scores indicating a better HRQOL. The analysis was based on ITT analysis set. The adjusted mean change from baseline at Month 2, 4, and 6 for the IBDQ total scores were reported. Data is presented cumulative for all pathways.

End point type	Secondary

End point timeframe:

Baseline, Month 2, 4, and 6

End point values	Mesalamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: score on a scale				
number (not applicable)				
Month 2	-2.5	-2.6		
Month 4	-2.8	-1.5		
Month 6	-2.8	-3.1		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis

Statistical analysis description:

Adjusted mean treatment difference in IBDQ total scores over 6 months was reported.

Comparison groups	Mesalamine v Placebo
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [7]
Method	ANCOVA
Parameter estimate	Mean difference
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.41
upper limit	3.77

Notes:

[7] - The p-value was based on a repeated-measures ANCOVA model with an unstructured correlation matrix, at a 0.05 significance level.

Secondary: Proportion of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Proportion of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE is defined as any untoward medical occurrence in a subject participating in a clinical trial. Any AEs includes serious as well as non-serious AEs. An SAE is defined as any untoward medical occurrence that at any dose resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, resulted in a congenital anomaly/birth defect, or was an important medical event. Any AE which occurred in the time interval from initial dosing (investigational medicinal product [IMP] intake) to the end of treatment visit (Month 6) was considered treatment-emergent. The analysis was based on safety analysis set which included all subjects who received at least 1 dose of IMP. Data is presented cumulative for all pathways.

End point type	Secondary

End point timeframe:

Up to Month 6

End point values	Mesalamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	135		
Units: subjects				
Any Treatment-Emergent AEs	42	49		
Treatment-Emergent SAEs	2	3		

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 number of subjects with intensity of AEs (classified as mild, moderate or severe) were presented. The analysis was based on safety analysis set. Data is presented cumulative for all pathways.

End point type	Secondary

End point timeframe:

Upto Month 6

End point values	Mesalamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	135		
Units: subjects				
Mild	32	32		
Moderate	18	22		
Severe	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Markedly Abnormal Laboratory Values: Hematology

End point title	Proportion of Subjects With Markedly Abnormal Laboratory Values: Hematology

End point description:

Proportion of subjects with markedly abnormal changes from baseline in hematology values are presented. Criteria for markedly abnormal laboratory (Hematology): Basophils/Leukocytes: >=5%, Eosinophils/Leukocytes: >=10%, Erythrocytes: <=3.5*10^6/µL, Hematocrit: <=0.32%; >=0.56%, Hemoglobin: <=11.5 g/dL, Leukocytes: <=2.8*10^3/µL; >=16.0*10^3/µL, Lymphocytes/Leukocytes: <=10%; >=80%, Monocytes/Leukocytes: >=20%, Neutrophils/Leukocytes: <=15%; >=90%, Platelets: <=75*10^3/µL; >=700*10^3/µL. The analysis was based on safety analysis set. Here, 'n' signifies number of subjects with available data at specified category for each arm, respectively. Data is presented cumulative for all pathways.

End point type	Secondary

End point timeframe:

Baseline to Month 6

End point values	Mesalamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	135		
Units: subjects				
Basophils/Leukocytes: >=5% (n= 135, 135)	0	1		
Eosinophils/Leukocytes: >=10% (n= 135, 135)	3	7		
Erythrocytes: <=3.5*10^6/µL (n= 135, 135)	2	1		
Hematocrit: <=0.32% (n= 135, 135)	1	0		
Hematocrit: >=0.56% (n= 135, 135)	8	12		
Hemoglobin: <=11.5 g/dL (n= 135, 135)	29	23		
Leukocytes: <=2.8*10^3/µL (n= 135, 135)	4	4		
Leukocytes: >=16.0*10^3/µL (n= 135, 135)	2	0		
Lymphocytes/Leukocytes: <=10% (n= 135, 135)	3	4		
Lymphocytes/Leukocytes: >=80% (n= 135, 135)	0	0		
Monocytes/Leukocytes: >=20% (n= 135, 135)	0	1		
Neutrophils/Leukocytes: <=15% (n= 135, 135)	0	0		
Neutrophils/Leukocytes: >=90% (n= 135, 135)	0	0		
Platelets: <=75*10^3/µL (n= 135, 134)	0	0		
Platelets: >=700*10^3/µL (n= 135, 134)	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Markedly Abnormal Laboratory Values: Coagulation

End point title	Proportion of Subjects With Markedly Abnormal Laboratory Values: Coagulation

End point description:

Proportion of subjects with markedly abnormal changes from baseline in coagulation values are presented. Criteria for markedly abnormal laboratory (coagulation): Activated Partial Thromboplastin Time (aPTT): >70 seconds (sec), Prothrombin International Normalized Ratio (INR): <0.8; >1.1. The analysis was based on safety analysis set. Here, 'n' signifies number of subjects with available data at specified category for each arm, respectively. Data is presented cumulative for all pathways.

End point type	Secondary

End point timeframe:

Baseline to Month 6

End point values	Mesalamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	135		
Units: subjects				
aPTT: >70 sec(n=133,131)	0	0		
Prothrombin INR: <0.8 (n= 133, 130)	0	2		
Prothrombin INR: >1.1 (n= 133, 130)	46	54		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Markedly Abnormal Laboratory Values: Serum Chemistry

End point title	Proportion of Subjects With Markedly Abnormal Laboratory Values: Serum Chemistry

End point description:

Proportion of subjects with markedly abnormal changes from baseline in serum chemistry values are presented. Criteria for markedly abnormal laboratory (serum chemistry): Alanine Aminotransferase (ALT): >3*upper limit of normal (ULN), Alkaline Phosphatase (ALP): >3*ULN and 25% increase (inc) from baseline (BL), Aspartate Aminotransferase (AST): >3* ULN, Bilirubin: >=1.5* ULN, Blood Urea Nitrogen: >=10.7 mg/dL, Calcium: <=1.8 mg/dL; >=3.9 mg/dL, Chloride: <=90 mmol/L; >=115 mmol/L, Creatinine: >=177 mg/dL, Gamma Glutamyl Transferase: >3*ULN, Glomerular Filtration Rate (GFR): <30 mL/min, Glucose: <=2.8 mg/dL; >=10 mg/dL, Potassium: <=3.0 mmol/L; >=5.8 mmol/L, Sodium: <=130 mmol/L; >=155 mmol/L. The analysis was based on safety analysis set. Here, 'n' signifies number of subjects with available data at specified category for each arm, respectively. Data is

presented cumulative for all pathways.

End point type	Secondary

End point timeframe:

Baseline to Month 6

End point values	Mesalamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	135		
Units: subjects				
ALT: >3*ULN (n= 135, 135)	1	1		
ALP: >3*ULN & 25% inc from BL(n= 135, 135)	0	0		
AST: >3*ULN (n= 135, 135)	2	2		
Bilirubin: >=1.5*ULN (n= 135, 135)	8	5		
Blood Urea Nitrogen: >=10.7 mg/dL (n= 135, 135)	8	11		
Calcium: <=1.8 mg/dL (n= 135, 135)	0	0		
Calcium: >=3.9 mg/dL (n= 135, 135)	9	12		
Chloride: <=90 mmol/L (n= 135, 135)	0	0		
Chloride: >=115 mmol/L (n= 135, 135)	0	0		
Creatinine: >=177 mg/dL (n= 135, 135)	0	0		
Gamma Glutamyl Transferase: >3*ULN (n= 135, 135)	6	4		
GFR: <30 mL/min (n= 111, 109)	0	0		
Glucose: <=2.8 mg/dL (n= 135, 135)	0	0		
Glucose: >=10 mg/dL (n= 135, 135)	11	14		
Potassium: <=3.0 mmol/L (n= 135, 135)	0	0		
Potassium: >=5.8 mmol/L (n=135, 135)	0	2		
Sodium: <=130 mmol/L (n=135, 135)	0	0		
Sodium: >=155 mmol/L (n=135, 135)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Month 6

Adverse event reporting additional description:

Treatment-Emergent AEs were defined as AEs 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 2 g extended release granules (sachet), administered orally QD for 6 months.

Reporting group title	Placebo

Reporting group description:

Placebo matched to mesalamine extended release granules (sachet), administered orally QD for 6 months.

Serious adverse events	Mesalamine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 137 (1.46%)	3 / 135 (2.22%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 137 (0.73%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 137 (0.73%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis ulcerative			

subjects affected / exposed	0 / 137 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Ecthyma			
subjects affected / exposed	0 / 137 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 137 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 137 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Mesalamine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 137 (16.79%)	28 / 135 (20.74%)	
Investigations			
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 137 (0.73%)	5 / 135 (3.70%)	
occurrences (all)	1	6	
Alanine aminotransferase increased			
subjects affected / exposed	4 / 137 (2.92%)	1 / 135 (0.74%)	
occurrences (all)	4	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 137 (2.92%)	1 / 135 (0.74%)	
occurrences (all)	4	1	
Faecal calprotectin increased			

subjects affected / exposed occurrences (all)	3 / 137 (2.19%) 3	1 / 135 (0.74%) 1	
Gastrointestinal disorders Colitis ulcerative subjects affected / exposed occurrences (all)	 14 / 137 (10.22%) 14	 20 / 135 (14.81%) 21	
Infections and infestations Respiratory tract infection viral subjects affected / exposed occurrences (all)	 3 / 137 (2.19%) 3	 1 / 135 (0.74%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 July 2015	This amendment included correction of language and inconsistencies in the protocol, an update of the 'Statistical Methods and Sample Size' section, and an increase of the total number of subjects required for the trial.
30 July 2015	This amendment included correction of language and inconsistencies in the protocol and an update of the overall trial design.
16 June 2016	This amendment included clarifications within the methodology sections of the protocol and modifications of the eligibility criteria.
17 January 2017	This amendment included change in the definition of remission used for analysis of the primary endpoint and definition of clinical remission used for analysis of the secondary endpoint based on draft Food and Drug Administration (FDA) guidance on clinical trial endpoints in UC, issued during the trial. In addition, changed the clinical and endoscopic evaluation criteria used to assess remission for inclusion of de novo subjects (Pathway 3).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported