FERRING
PHARMACEUTICALS

Protocol

Title of trial: 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
NCT number: NCT02522767
Sponsor trial code: 000174
Date: 11 Jan 2017

CLINICAL TRIAL PROTOCOL

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

000174
Consolidated Protocol Incorporating Amendments 1.0, 2.0, 3.0 and 4.0

EudraCT Number:	2015-002557-35
IND Number:	122553
Investigational Medicinal Product:	Mesalamine 4 g Extended Release Granules (Sachet)
Indication:	Induction of Clinical and Endoscopic Remission in active, mild to moderate ulcerative colitis
Phase:	3
Name and Address of Sponsor:	Ferring International PharmaScience Center U.S., Inc. 100 Interpace Parkway Parsippany, NJ 07054 Office: 973-796-1600 Fax: 973-796-1699
GCP Statement:	This trial will be performed in compliance with Good Clinical Practice (GCP).

SYNOPSIS

TITLE OF TRIAL

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

SIGNATORY INVESTIGATOR(S)

[redacted] University of Pennsylvania Division of Gastroenterology; Perleman Center for Advanced Medicine, Philadelphia, PA, USA

TRIAL SITES

Approximately 110 sites in North America and Europe

PLANNED TRIAL PERIOD	CLINICAL PHASE
First subject first visit: Q3 2015 Last subject last visit: Q3 2017	3

OBJECTIVES

Primary objective:

- 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)

Secondary objectives:

- To evaluate the efficacy of mesalamine 4 g extended release granules (sachet) using the Clinical and Endoscopic Response Score and the Clinical Response Score subset
- To assess C-reactive protein (CRP) levels and fecal calprotectin levels
- To assess health-related quality of life (HRQoL) using the Inflammatory Bowel Disease Questionnaire (IBDQ)
- To assess the incidence and severity of adverse events (AEs) and abnormal laboratory values

ENDPOINTS

Primary endpoint:

The primary efficacy endpoint is the proportion of subjects with remission, defined by the Clinical and Endoscopic Response Score at Week 8 (see table below) as a score of:

- 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 endoscopic score will be determined by an independent central reader.

ENDPOINTS

Key secondary endpoints:

1. The proportion of subjects with remission in the primary endpoint and the Physician's Global Assessment (PGA) score of ≤1 (Modified Mayo) at Week 8
2. Time to cessation of rectal bleeding, 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 daily diary

Secondary endpoints:

1. The proportion of subjects with endoscopic improvement, 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
2. The proportion of subjects in clinical remission at Weeks 2, 4, and 8, 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
3. Time to normal stool pattern, 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
4. The change from baseline in rectal bleeding score at Weeks 2, 4, and 8, based on subject daily diary
5. The change from baseline in serum CRP levels at Weeks 2, 4, and 8
6. The change from baseline in fecal calprotectin levels at Week 8
7. The change from baseline to each scheduled assessment for published and validated domain scores of the IBDQ
8. Safety assessed by incidence and severity of AEs and abnormal laboratory values

Clinical and Endoscopic Response Score (0 – 9)

Components	Subscale	Severity	Score
CLINICAL RESPONSE (Subject's Symptoms)	**Stool Frequency[a] (daily)**	Normal number of stools for subject	0
		1 to 2 stools more than normal	1
		3 to 4 stools more than normal	2
		≥5 stools more than normal	3
	Rectal Bleeding[b] (daily)	No blood seen	0
		Streaks of blood with stool	1
		Obvious blood with stool	2
		Blood alone passes	3
ENDOSCOPIC RESPONSE (Objective Evidence of Inflammation)	**Flexible Sigmoidoscopy /colonoscopy Findings**	Normal or inactive disease	0
		Mild disease (erythema, decreased vascular pattern, granularity)	1
		Moderate disease (marked erythema, absent vascular pattern, any friability, erosions)	2
		Severe disease (spontaneous bleeding, ulceration)	3

Adapted from: Schroeder et al., 1987(1); Sninsky et al., 1991(2); Modified by Ferring Group, 2014

a. Each subject serves as his or her own control to establish the degree of abnormality of the stool frequency.
b. The daily bleeding score represents the most severe bleeding of the day.

METHODOLOGY

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, international, phase 3 trial to investigate the safety and efficacy of mesalamine 4 g extended release granules (sachet) for the induction of clinical and endoscopic remission in subjects with active, mild to moderate active UC. Following completion of Visit 0/screening, the subjects will be randomized to a treatment group during Visit 1/baseline. Each subject will receive a total of 8 weeks of double-blind treatment with either:

- one mesalamine 4 g extended release granules (sachet) QD (4 g/day) OR
- one 4 g placebo sachet to match mesalamine extended release granules (sachet)

Dose will be administered QD at least 1 hour before or at least 2 hours after a meal at approximately the same time each day. The sachet will be emptied on the tongue and swallowed with at least 8 ounces (240 mL) of water. Following randomization, the first dose of investigational medicinal product (IMP) will be administered at the site during Visit 1.

Subjects will visit the trial site 4 times during the double-blind part of trial for safety and efficacy evaluations: baseline and Weeks 2, 4, and 8. On a daily basis, subjects will record clinical symptoms (stool frequency and rectal bleeding) in an electronic diary. The Clinical and Endoscopic Response Score assessments and PGA will be performed at screening/baseline and Week 8. After 8 weeks of treatment, subjects will be evaluated for remission, defined as a Clinical and Endoscopic Response Score of 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. Whereas, subjects will have only a Clinical Response Score assessment at Weeks 2 and 4.

Subjects who discontinue during the double-blind treatment before Week 8 will complete the double-blind end-of-treatment assessments and will be treated via investigator's decision with local standard of care, see Section 6.2.4.

Subjects who are found to be worse defined by an increased number of bowel movements [BM], blood in the stool, abdominal pain and distention, or clinically relevant changes in laboratory chemistry and/or hematology on or after Week 2 will be offered early escape during the trial before Week 8 and will be treated by local standard of care. Subjects who complete Week 8 but fail to meet the defined criteria for remission will be given an option to receive open-label treatment with mesalamine 4 g extended release granules (sachet) for 8 additional weeks in the current trial. If subjects do not opt to receive the 8-week open-label mesalamine treatment, they will be treated by local standard of care. If subjects opt to receive the additional 8-week open-label mesalamine treatment, they will continue with daily diary entries and visit the trial site at 10 and 16 weeks, with only a Clinical Response Score assessment at Week 10, and a Clinical and Endoscopic Response Score assessment performed at Week 16 in order to determine the subject's eligibility for entry into the maintenance trial.

Flexible sigmoidoscopy/colonoscopy will be video recorded and transferred to the independent central reader. The details of the tools, recording, data transfer, and assessment will be documented in an Imaging Charter. The flexible sigmoidoscopy/colonoscopy recording during screening will be sent to the independent central reader for final determination of eligibility, regardless of the local site's score. A flexible sigmoidoscopy/colonoscopy will also be performed at Weeks 8 and 16 as applicable. These recordings will also be sent to the independent central reader for endoscopic endpoint scoring.

Subjects from either treatment group who meet the defined remission criteria after the 8-week double-blind treatment period will be allowed to enroll into a double-blind trial investigating maintenance therapy of mesalamine 2 g extended release granules (Study 000175). Those subjects who do not achieve remission after the 8 additional weeks of open-label treatment will not be enrolled into Study 000175 and will be treated with the local standard of care.

NUMBER OF SUBJECTS

Approximately 220 subjects with active, mild to moderate UC will be randomized (110/treatment regimen).

CRITERIA FOR INCLUSION / EXCLUSION

Inclusion Criteria:

1. Male or nonpregnant female subjects aged 18 to 75 years
2. Newly diagnosed or recurrent mild to moderate UC as defined by the Modified Mayo score of ≥4 but not >10 and a score of ≥2 for flexible sigmoidoscopy/colonoscopy
3. Extent of colonic involvement as confirmed by flexible sigmoidoscopy; colonoscopy to be performed if flexible sigmoidoscopy cannot establish the upper border of UC involvement, or at the discretion of the Investigator
4. Negative stool test at screening to rule out parasites, bacterial pathogens, and *Clostridium difficile*. Subjects who test positive for *Clostridium difficile* can be rescreened if treated and *Clostridium difficile* negative for 2 consecutive months
5. Estimated creatinine clearance ≥60 mL/min
6. Females of childbearing potential must agree to use an adequate contraception during the course of the trial. Accepted forms of contraception are: i.e., implants, injectables, hormonal intrauterine device, combined hormonal contraceptives, sexual abstinence, and vasectomized sexual partner. Sterilized or postmenopausal women may also participate. Women must have a negative serum pregnancy test result at screening and negative urine pregnancy test result at Visit 1 (baseline/randomization)
7. Signed informed consent obtained before any trial-related procedures

CRITERIA FOR INCLUSION / EXCLUSION (Continued)

Exclusion Criteria:

1. Use of oral 5-aminosalicylic acid (5-ASA) products at a dose >2.5 g/day or topical rectal 5-ASA within 7 days prior to Visit 1 *(use of any 5-ASA during the course of the trial is prohibited)*
2. Disease limited to proctitis <15 cm
3. Short bowel syndrome
4. Prior colon resection surgery
5. History of severe/fulminant UC
6. Evidence of other forms of inflammatory bowel disease
7. Infectious disease (including human immunodeficiency virus [HIV], hepatitis B virus [HBV], or hepatitis C virus [HCV])
8. Intolerant or allergic to aspirin or salicylate derivatives
9. Taking the following treatments:
   a. Aspirin within 7 days prior to Visit 1 (except for cardioprotective reasons - maximum dose 325 mg/day)
   b. Loperamide and other antidiarrheal agents, mucilages, antibiotics (metronidazole and ciprofloxacin), nonsteroidal anti-inflammatory drugs (NSAIDs), nicotine patch within 1 week
   c. Corticosteroids (oral, intravenous, or intramuscular) within the previous month
   d. Immunomodulating/suppressing drugs within the previous 6 weeks
   e. Use of rectal formulations (5-ASA, steroids) within 7 days prior to Visit 1
   f. History of biologics (e.g., Remicade)
10. Alanine transaminase; aspartate transaminase (ALT; AST) ≥3 x upper limit of normal (ULN) or severe liver impairment
11. Clinically significant hematological function abnormalities
12. Known alcohol or drug abuse
13. Women who are pregnant or nursing
14. History of or known malignancy (Note: Adequately treated (i.e. cured) basal cell carcinoma and cervical intraepithelial neoplasia (CIN) or carcinoma in situ of the cervix with no evidence of recurrence within the previous 5 years can be included)
15. History of bleeding disorders, active gastric or active duodenal ulcers, autoimmune diseases, or mental/emotional disorders, that would interfere with their participation in the trial
16. Participation in a clinical trial with administration of another investigational medicinal product within the previous 30 days
17. Unable to comply with the requirements of the protocol
18. Unable to complete the subject daily diary or follow data-capturing procedures

MEDICINAL PRODUCTS

The IMP for the trial will be mesalamine 4 g extended release granules (sachet) and placebo, which will be identical in appearance.

DURATION OF TREATMENT

The duration of treatment for each subject will be 8 weeks. Subjects who complete Week 8 but fail to meet the defined criteria for remission will be given the option of an additional 8 weeks of treatment with open-label mesalamine (4 g/day).

STATISTICAL METHODS

Sample size: The true remission rates at Week 8 for mesalamine 4 g extended release granules (sachet) and placebo regimens were assumed as 36% and 18%, respectively, based on Kamm (2007),(3) Lichtenstein (2007),(4) and Marteau (2005).(5) Under these assumptions, a sample size of 110 randomized subjects per group will provide at least 85% power to detect a statistically significant treatment group difference in the remission rate at a two-sided 0.05 significance level using the chi-square test.

Efficacy: The primary efficacy analysis will be based on all randomized subjects (ITT; intent-to-treat). The primary efficacy endpoint will be the proportion of subjects who achieved remission, defined as 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 Clinical and Endoscopic Response Score at Week 8.

The treatment group difference in the proportion of subjects with remission at Week 8 will be assessed by the chi-square test at a two-sided 0.05 significance level. Subjects who discontinue the double-blind regimen before Week 8, as well as subjects with missing remission assessment at Week 8, will be considered not having achieved remission. The odds ratio will be estimated and its 95% confidence interval will be provided.

The key secondary endpoints will be analyzed by a fixed-sequence procedure according to the pre-specified order to maintain the overall Type 1 error rate to a two-sided 5%.

If the primary efficacy analysis demonstrates a statistically significant difference between the treatment groups, the proportion of subjects with remission in the primary endpoint and the PGA score of $\leq$1 (Modified Mayo) will be compared using the same statistical method used for the primary efficacy analysis. If the analysis for the first key secondary endpoint is statistically significant, time to cessation of rectal bleeding, defined as time in days from randomization to the first day of 3 consecutive days with a rectal bleeding score of 0 (i.e., the second key secondary endpoint), will be compared by the log-rank test at a two-sided 0.05 significance level.

Other secondary endpoints will be analyzed individually at a two-sided 0.05 significance level.

The efficacy data captured during the 8-week open-label mesalamine 4 g/day treatment will be used for exploratory purposes only.

STATISTICAL METHODS (Continued)

Safety: The safety analyses will be based on all subjects who receive at least 1 dose of IMP. All adverse events will be coded by system organ class and preferred term using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). A treatment-emergent adverse event will be defined as any adverse event occurring after the start of IMP or pre-existing medical condition that worsens in intensity after the start of IMP.

Clinical laboratory variables will be presented in 2 ways. First, mean change from baseline to the end of the double-blind treatment visit will be summarized. Baseline will be defined as the last assessment before the first dose of IMP. Second, the number and percentage of subjects with treatment-emergent potentially clinically significant laboratory values on or before the end of the double-blind treatment visit will be tabulated.

Other safety assessments will also be summarized descriptively.

Similar safety data summaries will be made for the open-label treatment period data.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

List of Abbreviations

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ASA	Aminosalicylic acid
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
BM	Bowel movement
CRO	Contract research organization
CRP	C-reactive protein
D	Day
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EudraCT	European Union Clinical Trial Database
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat

IVRS	Interactive Voice Response system
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NIMP	Non-investigational medicinal product
NSAID	Nonsteroidal anti-inflammatory drug
OL	Open-label
PGA	Physician's Global Assessment
PP	Per protocol
PT	Preferred term
QD	Once daily
SAE	Serious adverse event
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
UC	Ulcerative colitis
ULN	Upper limit of normal
US	United States
V	Visit
WHO-Drug	World Health Organization Drug Dictionary
Wk	Week

Definition of Terms

Clinical remission	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
Endoscopic improvement	an endoscopic score of 0 or 1, with at least a 1 point reduction from baseline in the endoscopic score
Modified Mayo score	sum of the Clinical and Endoscopic Response Scores (any friability will be scored a 2) and the standard PGA score as in the original Mayo Score
Remission	defined by the Clinical and Endoscopic Response Score as a score of 0 for rectal bleeding and 0 or 1 with at least 1 point decrease from baseline for stool frequency, with an endoscopic score of 0 or 1
Time to cessation of rectal bleeding	time in days from randomization to the first day of 3 consecutive days with a rectal bleeding score of 0, based on the subject daily diary
Time to normal stool pattern	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
Disease Worsening	increased number of bowel movements [BM], increased blood in the stool, increased abdominal pain and distention, or clinically relevant changes in laboratory chemistry and/or hematology

1 INTRODUCTION

1.1 Background

Ulcerative colitis (UC), an inflammatory bowel disease, is a chronic condition of unknown origin. Ulcerative colitis is a relapsing and remitting disease characterized by acute non-infectious inflammation of the colorectal mucosa.(6) In the United States (US), about 1 million people are affected with UC.(7,8) The annual incidence of UC per 100,000 people is 10.4 to 12 cases in the US and 8 cases in Europe. The prevalence rate per 100,000 people is 35 to 100 cases in the US and 21 to 243 in Europe. UC is slightly more common in women than in men. Although the disease can occur at any age, the age of onset follows a bimodal pattern, with a peak at 15 to 25 years and a smaller peak at 55 to 65 years.(9)

Active episodes of UC are marked by passing of blood and mucus, diarrhea, and abdominal pain, frequently accompanied by urgency and tenesmus. (10) In the most severe forms, systemic signs comprising fever, anorexia, and weight loss may occur. Approximately 60% of patients have a mild form, 25% a moderate form, and 15% a severe disease. Despite treatment, it is estimated that approximately 1 of every 2 patients with UC will experience a relapse within 1 year; the cumulative probability of relapse is 80% within 2 years and 95% within 10 years. (11)

Involvement of the rectal mucosa is a constant feature while the inflammation spreads to higher levels in continuous and retrograde fashion, with no sparing of mucosa from the anorectal junction. Hence, UC may be divided in proctitis, proctosigmoiditis, left-sided colitis (the proximal limit being below the splenic flexure), extensive colitis (involving the transverse colon), and pancolitis (involving the entire colon).

The aim of the treatment of active mild-to-moderate UC is the induction of remission and maintenance of remission, and the prevention of complication of long-term UC.

Several therapeutic drug classes are used in UC: 5-aminosalicylic acid (5-ASA) derivatives, corticosteroids, immunosuppressants, and anti-tumor necrosis factor-α agents. At present, aminosalicylate derivatives are the main and first-line therapy for mild to moderate episodes of UC and for maintenance treatment.(12) Rectal administration of salicylate-type drugs constitutes the treatment of choice in proctitis, proctosigmoiditis, and left-sided UC.(13,14,15) The extended release mesalamine granules are purposed to treat all forms of active mild-to-moderate UC in all segments of the colon.

Ferring recently developed a prolonged release granule formulation with a high drug load (95% load) to provide a better alternative for patients that have difficulty swallowing the tablet or capsule forms, and thereby may help increase treatment compliance. The safety and tolerability of various mesalamine dosing regimens have been demonstrated. (5,16) The optimum dose of oral mesalamine for induction therapy in order to achieve remission is between 2 and 4 g/day. (17)

1.2 Scientific Justification for Conducting the Trial

The mesalamine 4 g extended release granules (sachet) is approved in 19 countries worldwide for treatment of active mild to moderate ulcerative colitis. The granules are packaged in a foil laminate pouch (sachet). The 4 g once-daily (QD) dosing regimen was first approved in The Netherlands in 2012.

This dosage form was developed as a true QD regimen to provide an alternative for patients who have difficulty swallowing the tablets or large capsules forms. There are no sachet granular forms available for both induction and maintenance of remission. The availability of this easier-to-take formulation might potentially help increase compliance, and would be an overall useful tool in the care of these suffering patients.

1.3 Benefit / Risk Aspects

The 95% granules allow for a true once a day convenient dosing with the highest unit dosage form available for induction and maintenance of UC. In addition the granules are easier to swallow than the tablets and capsules currently available in the US.

The most common adverse events (AEs) considered related to treatment with mesalamine formulations up to 4 g per day have been diarrhea, nausea, abdominal pain, headache, vomiting, and rash. Hypersensitivity reactions and drug fever may occasionally occur.

To mitigate risk, all subjects, including those in the placebo arm, will be offered early escape to local standard of care. Notably, all previous 5-ASA registration trials leading to an approval in the US utilized a placebo-controlled design.

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary Objective

The primary objective of this trial is to demonstrate efficacy of mesalamine 4 g extended release granules (sachet) QD in the induction of clinical and endoscopic remission versus placebo in subjects with active, mild to moderate UC.

Secondary Objectives

The secondary objectives of this trial are to:

- evaluate the efficacy of mesalamine 4 g extended release granules (sachet) using the Clinical and Endoscopic Response Score subsets
- assess C-reactive protein (CRP) levels and fecal calprotectin levels
- assess health-related quality of life (HRQoL) using the Inflammatory Bowel Disease Questionnaire (IBDQ)
- assess the incidence and severity of AEs and abnormal laboratory values

2.2 Endpoints

Primary Endpoint

The primary efficacy endpoint is the proportion of subjects in remission at Week 8, defined by the Clinical and Endoscopic Response Score (Table 2) as a score of:

- 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 endoscopic score will be determined by the independent central reader.

Key Secondary Endpoints

Secondary endpoints are the following:

1. The proportion of subjects with remission in the primary endpoint and the Physician's Global Assessment (PGA) score of $\leq$1 (Modified Mayo) at Week 8
2. Time to cessation of rectal bleeding, 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 daily diary

Secondary Endpoints

1. The proportion of subjects with endoscopic improvement, 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

2. The proportion of subjects in clinical remission at Weeks 2, 4, and 8, 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
3. Time to normal stool pattern, 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
4. The change from baseline in rectal bleeding score at Weeks 2, 4, and 8, based on subject daily diary
5. The change from baseline in serum CRP levels at Weeks 2, 4, and 8
6. The change from baseline in fecal calprotectin levels at Week 8
7. The change from baseline to each scheduled assessment for published and validated domain scores of the IBDQ
8. Safety, assessed by incidence and severity of AEs and abnormal laboratory values

3 INVESTIGATIONAL PLAN

3.1 Overall Trial Design

3.1.1 Overall Design and Control Methods

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, international, phase 3 trial to investigate the safety and efficacy of mesalamine 4 g extended release granules (sachet) for the induction of clinical and endoscopic remission in subjects with active, mild to moderate UC. Following completion of Visit 0/screening, the subjects will be randomized to 1 of 2 treatment groups during Visit 1/baseline. Each subject will receive a total of 8 weeks of double-blind treatment with either:

- one mesalamine 4 g extended release granules (sachet) QD (4 g/day) *OR*
- one 4 g placebo sachet to match mesalamine extended release granules (sachet)

Doses will be administered QD at least 1 hour before or at least 2 hours after a meal at approximately the same time each day. The sachet will be emptied on the tongue and swallowed with at least 8 ounces (240 mL) of water. Following randomization, the first dose of investigational medicinal product (IMP) will be administered at the site during Visit 1.

Subjects will visit the trial site 4 times during the double-blind part of trial for safety and efficacy evaluations: baseline and Weeks 2, 4, and 8. On a daily basis, subjects will record clinical symptoms (stool frequency and rectal bleeding) in an electronic diary. The Clinical and Endoscopic Response Score assessments and PGA will be performed at screening/baseline and Week 8. After 8 weeks of treatment, subjects will be evaluated for remission, defined as a Clinical and Endoscopic Response Score of 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. Whereas, subjects will have only a Clinical Response Score assessment at Weeks 2 and 4.

If subjects discontinue the double-blind treatment before Week 8, the subjects will complete the double-blind end-of-treatment assessments and will be treated via investigator's decision with local standard of care.

Subjects who are found to be worse, defined by an increased number of bowel movements (BM), blood in the stool, abdominal pain and distention, or clinically relevant changes in laboratory chemistry and/or hematology on or after Week 2 will be offered early escape during the trial before Week 8 and will be treated by local standard of care. Subjects who complete Week 8 but fail to meet the defined criteria for remission will be given an option to receive open-label treatment with mesalamine 4 g extended release granules (sachet) for 8 additional weeks in the current trial. If subjects do not opt to receive the 8-week open-label mesalamine treatment, they will be treated by local standard of care. If subjects opt to receive the additional 8-week open-label mesalamine treatment, they will continue with daily diary entries and visit the trial site at 10 and 16 weeks, with only a Clinical Response Score assessment at Week 10, and a Clinical and Endoscopic Response

Score assessment performed at Week 16 in order to determine the subject's eligibility for entry into the maintenance trial (Study 000175).

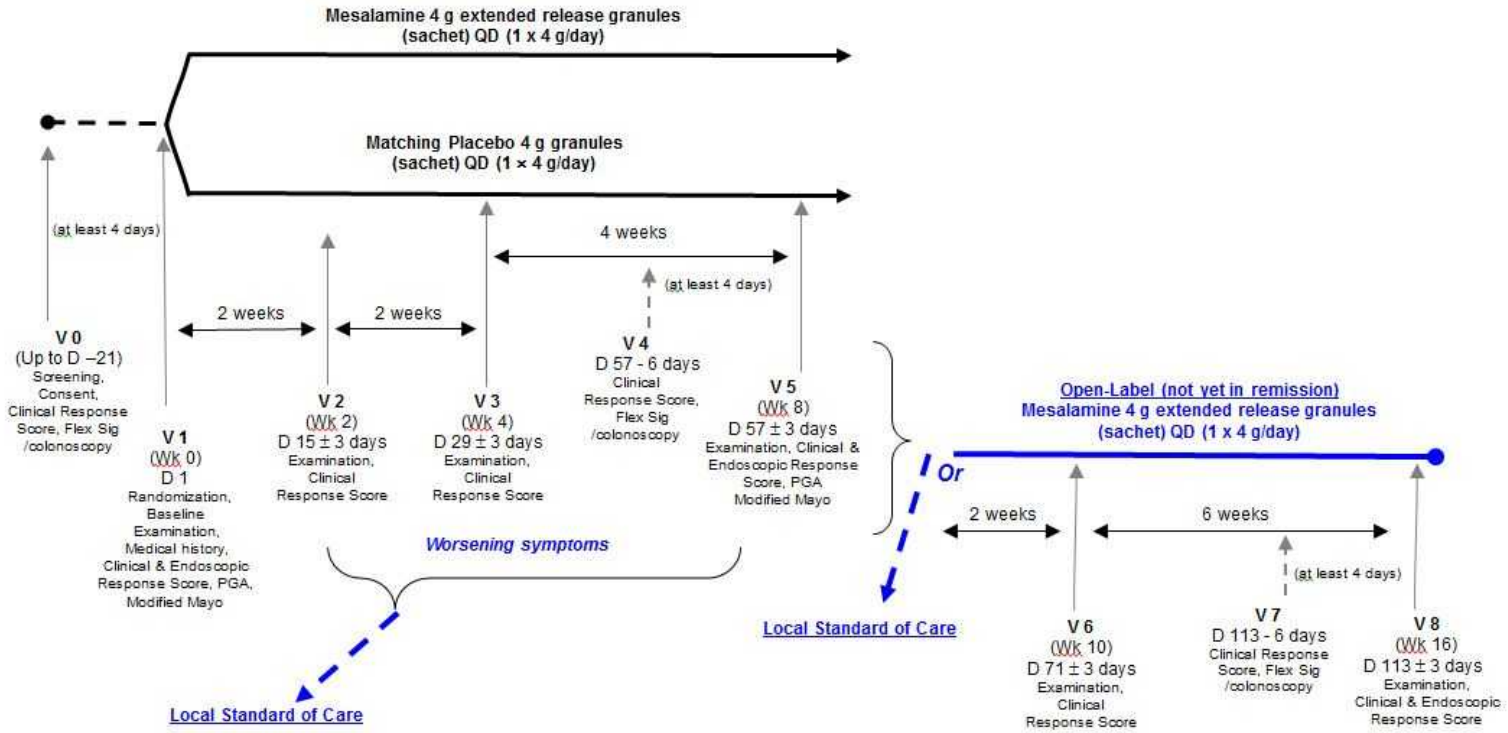
Flexible sigmoidoscopy/colonoscopy will be video recorded and transferred to the independent central reader. The details of the tools, recording, data transfer, and assessment will be documented in an Imaging Charter. The flexible sigmoidoscopy/colonoscopy recording during screening will be sent to the independent central reader for final determination of eligibility, regardless of the local site's score. A flexible sigmoidoscopy/colonoscopy will also be performed at Weeks 8 and 16 as applicable. These recordings will also be sent to the independent central reader for endoscopic endpoint scoring.

Subjects from either treatment group who meet the defined remission criteria after the 8-week double-blind treatment period will be allowed to enroll into a double-blind trial investigating maintenance therapy of mesalamine 2 g extended release granules (Study 000175). Those subjects who do not achieve remission after the 8 additional weeks of open-label treatment will not be enrolled into Study 000175 and will be treated with the local standard of care.

3.1.2 Trial Design Diagram

The trial design is displayed in Figure 1.

Figure 1: Trial Design Diagram



D = Day, V = Visit; Wk = Week

3.1.3 Trial Schedule

First subject first visit is expected to occur in the third quarter of 2015 and last subject last visit is expected in the third quarter of 2017. For each subject, the total time in trial from screening (within 21 days before dosing) will be approximately 71 days. For subjects opting to participate in the 8-week open-label period, the total time in the trial will be approximately 126 days.

3.2 Planned Number of Trial Sites and Subjects

This trial will be conducted at approximately 110 sites in North America and Europe. Approximately 220 subjects with active, mild to moderate UC will be randomized to receive mesalamine 4 g extended release granules (sachet) or matching placebo in a 1:1 ratio (110/treatment regimen).

3.3 Interim Analysis

No interim analysis is planned for this trial.

3.4 Data Monitoring Committee

No data monitoring committee will be established for this trial.

3.5 Discussion of Overall Trial Design and Choice of Control Groups

3.5.1 Trial Design

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, international phase 3 trial. Following completion of Visit 0/screening, subjects will be randomized in a 1:1 ratio during Visit 1/baseline to receive either mesalamine 4 g extended release granules (sachet) or matching placebo.

3.5.2 Selection of Endpoints

The endpoints selected are similar to those used in other clinical studies of mesalamine oral formulation in UC.

3.5.3 Blinding

This is a randomized, double-blind, placebo-controlled trial. For more information on blinding, see Section 5.5.

3.5.4 Selection of Doses in the Trial

The well accepted oral dosage for mesalamine induction of remission ranges from 2.4 g to 4.8 g/day. In this trial, the sponsor will utilize the 4 g/day dose of mesalamine 4 g extended release granules (sachet), which is consistent with the approved dose of the marketed mesalamine product for the induction of remission and the treatment of mild to moderate active UC.

3.5.5 Selection and Timing of Dose for Each Subject

Each subject will be randomized to receive either mesalamine 4 g extended release granules (sachet) QD or matching placebo QD. Doses will be administered at least 1 hour before or at least 2 hours after a meal at approximately the same time each day. The sachet will be emptied on the tongue and swallowed with at least 8 ounces (240 mL) of water. Following randomization, the first dose of IMP will be administered at the site during Visit 1.

Subjects who do not meet the defined criteria for remission at Week 8 will be given an option to receive open-label treatment with mesalamine 4 g extended release granules (sachet) for 8 additional weeks in the current trial. The first dose of IMP will be administered the day following the end of double-blind treatment. If subjects do not opt to receive the 8-week open-label mesalamine treatment, they will be treated by local standard of care.

3.5.6 Selection of Trial Population

Subjects with active, newly diagnosed or recurrent, mild to moderate, UC are eligible for enrolment in this trial. For more information on eligibility criteria, see Section 4.

3.5.7 Withdrawal Criteria

No trial-specific criteria for withdrawal are defined with the exception of worsening of UC with a need for an escalation of the therapy (i.e., surgical therapy, use of steroids, immunosuppressive or immunomodulating drugs, biologics, increase dose of 5-ASA in any form).

3.5.8 Follow-up Procedures

Subjects whose condition worsens in intensity will be given the option of early escape (on or after Week 2 and before Week 8) and will be treated by local standard of care.

If subjects discontinue the double-blind treatment before Week 8, they will complete the end-of-treatment assessments and will be treated via investigator's decision with local standard of care.

Subjects who complete Week 8 but fail to meet the defined criteria for remission will be given an option to receive open-label treatment with mesalamine 4 g extended release granules (sachet) for 8 additional weeks in the current trial.

Subjects in protocol defined remission at the end of this 8-week open-label period will be given an option to be randomized into the long-term maintenance trial (Study 000175). Those subjects who do not achieve the defined criteria for remission after the 8 additional weeks will not be enrolled into Study 000175 and will be treated with the local standard of care.

If subjects who do not meet the defined criteria for remission at Week 8 and do not opt to receive the 8-week open-label mesalamine sachet treatment, they will be treated by local standard of care. If subjects opt to receive the additional 8-week open-label mesalamine treatment, they will continue

with daily diary entries and visit the trial site at 10 and 16 weeks, with a Clinical and Endoscopic Response Score assessment performed at Week 16 in order to determine the subject's eligibility for entry into the maintenance trial.

4 SELECTION OF TRIAL POPULATION

4.1 Trial Population

4.1.1 Inclusion Criteria

1. Male or nonpregnant female subjects aged 18 to 75 years
2. Newly diagnosed or recurrent mild to moderate UC as defined by Modified Mayo score of ≥4 but not >10 and a score of ≥2 for flexible sigmoidoscopy/colonoscopy
3. Extent of colonic involvement as confirmed by flexible sigmoidoscopy; colonoscopy to be performed if flexible sigmoidoscopy cannot establish the upper border of UC involvement, or at the discretion of the Investigator
4. Negative stool test at screening to rule out parasites, bacterial pathogens, and *Clostridium difficile*. Subjects who test positive for *Clostridium difficile* can be rescreened if treated and *Clostridium difficile* negative for 2 consecutive months.
5. Estimated creatinine clearance ≥60 mL/min
6. Females of childbearing potential must agree to use an adequate contraception during the course of the trial. Accepted forms of contraception are: i.e., implants, injectables, hormonal intrauterine device, combined hormonal contraceptives, sexual abstinence, and vasectomized sexual partner. Sterilized or postmenopausal women may also participate. Women must have a negative serum pregnancy test result at screening and negative urine pregnancy test result at Visit 1 (baseline/randomization)
7. Signed informed consent obtained before any trial-related procedures

4.1.2 Exclusion Criteria

1. Use of oral 5-ASA products at a dose >2.5 g/day or topical rectal 5-ASA within 7 days prior to Visit 1 *(use of any 5-ASA during the course of the trial is prohibited)*
2. Disease limited to proctitis <15 cm
3. Short bowel syndrome
4. Prior colon resection surgery
5. History of severe/fulminant UC
6. Evidence of other forms of inflammatory bowel disease
7. Infectious disease (including human immunodeficiency virus [HIV], hepatitis B virus [HBV], or hepatitis C virus [HCV])
8. Intolerant or allergic to aspirin or salicylate derivatives
9. Taking the following treatments:
   a. Aspirin within 7 days prior to Visit 1 (except for cardioprotective reasons - maximum dose 325 mg/day)

b. Loperamide and other antidiarrheal agents, mucilages, antibiotics (metronidazole and ciprofloxacin), nonsteroidal anti-inflammatory drugs (NSAIDs), nicotine patch within 1 week

c. Corticosteroids (oral, intravenous, or intramuscular) within the previous month

d. Immunomodulating/suppressing drugs within the previous 6 weeks

e. Use of rectal formulations (5-ASA, steroids) within 7 days prior to Visit 1

f. History of biologics (e.g., Remicade)

10. ALT; AST ≥3 x upper limit of normal (ULN) or severe liver impairment
11. Clinically significant hematological function abnormalities
12. Known alcohol or drug abuse
13. Women who are pregnant or nursing
14. History of or known malignancy (Note: Adequately treated (i.e. cured) basal cell carcinoma and cervical intraepithelial neoplasia (CIN) or carcinoma in situ of the cervix with no evidence of recurrence within the previous 5 years can be included)
15. History of bleeding disorders, active gastric or active duodenal ulcers, autoimmune diseases, or mental/emotional disorders, that would interfere with their participation in the trial
16. Participation in a clinical trial with administration of another investigational medicinal product within the previous 30 days
17. Unable to comply with the requirements of the protocol
18. Unable to complete the subject daily diary or follow data-capturing procedures

4.2 Method of Assigning Subjects to Treatment Groups

At Visit 1/baseline, subjects will be randomly assigned in a 1:1 ratio, to 1 of 2 treatment groups based on a centralized computer-generated randomization schedule via an interactive response technology (IRT). Re-enrollment of subjects is prohibited under any circumstances.

4.3 Restrictions

4.3.1 Prior and Concomitant Therapies

Subjects may not be taking or have used the following treatments and a washout period will be required prior to trial medication administration:

- aspirin within 7 days prior to Visit 1 or during the trial (except for cardioprotective reasons - maximum dose 325 mg/day)
- oral 5-ASA products at a dose > 2.5 g/day or topical rectal 5-ASA at any dose within 7 days prior to Visit 1 *(use of any 5-ASA during the course of the trial is prohibited)*
- rectal formulations (5-ASA, steroids) within 7 days prior to Visit 1 or during the trial

- loperamide and other antidiarrheal agents, mucilages, antibiotics (metronidazole and ciprofloxacin), NSAIDs, nicotine patch within the past week or during the trial
- corticosteroids (oral, intravenous, intramuscular) within the previous month or during the trial
- immunomodulating/suppressing drugs within the previous 6 weeks or during the trial

Subjects must also not have a history of taking biologics (e.g., Remicade).

4.3.2 Prohibited Therapy

The following medications are prohibited during the trial: 5-ASA products (oral or topical rectal), loperamide and other antidiarrheal agents, mucilages, antibiotics (metronidazole and ciprofloxacin), NSAIDs, nicotine patch, corticosteroids (oral, intravenous, intramuscular, or rectal), immunomodulating/suppressing drugs and biologics. Aspirin (except for cardioprotective reasons - maximum dose 325 mg/day) is prohibited during the trial.

4.3.3 Other Restrictions

Subjects will be asked to not change their habits (e.g., continue previous cigarette consumption, exercise regimen). Subjects are not to abuse alcohol, caffeine, or illegal drugs during the trial.

4.4 Withdrawal Criteria

Subjects have the right to withdraw from the trial at any time for any reason, without the need to justify their decision. However, the investigator should record the reason for the subject's withdrawal. The investigator also has the right to withdraw subjects.

Subjects will be withdrawn in the following cases:

- pregnancy at any time during the trial will be a reason for withdrawal
- withdrawal of consent
- worsening of UC with a need for an escalation of the therapy (i.e., surgical therapy, use of steroids, immunosuppressive or immunomodulating drugs, biologics, increase dose of 5-ASA in any form)
- request for termination of the trial by regulatory authorities or sponsor
- the subject develops any AE that, in the opinion of the investigator, warrants the subject's withdrawal from treatment. An AE form will be completed as appropriate, and the subject will be followed until the event is clinically stable.

For subjects who discontinue due to an AE, all efforts will be made to follow the outcome of the AE and to assess the efficacy criteria.

For any discontinuation, the investigator will obtain all the required details and document the date of the premature termination and the main reason in the electronic case report form (eCRF). Since an excessive rate of withdrawals can render the trial devoid of meaning, the unnecessary withdrawal of subjects should be avoided.

Subjects who withdrew from the trial will not be replaced.

5 TREATMENTS

5.1 Treatments Administered

5.1.1 Investigational Medicinal Product (IMP)

IMPs used in the trial are sachets of either:

- mesalamine 4 g extended release granules or
- placebo 4 g to match mesalamine extended release granules

5.1.2 Non-Investigational Medicinal Product (NIMP)

No NIMPs will be supplied to subjects participating in the trial.

5.2 Characteristics and Source of Supply

All IMPs are provided by Ferring Pharmaceuticals/Ferring Entity and will be handled according to the principles of Good Manufacturing Practice (GMP).

5.3 Packaging and Labelling

Packaging and labelling of the IMPs will be performed under the responsibility of the IMP department at Ferring Pharmaceuticals A/S in accordance with GMP and national regulatory requirements.

The IMP will be supplied to the subjects in boxes containing at least 17 sachets, enough for 2 weeks' treatment, including visit windows and will be packaged according the randomization list.

All IMP will be labelled with trial-specific labels and will contain a unique IMP number.

The label of the IMP will also contain 1 self-adhesive tear-off portion to be affixed to the drug accountability log.

5.4 Conditions for Storage and Use

The investigator will ensure that the IMPs will be stored in appropriate conditions, as stated on the labels, in a secure location with controlled access. The storage compartment must be monitored regularly and the temperature must be documented. Deviations in storage temperature must be reported without delay, and the IMP must not be used until further instructions from the sponsor are received.

5.5 Blinding / Unblinding

5.5.1 Blinding

The IMPs will be packaged according to a centralized computer-generated randomization list. The randomization list will not be available to any person involved in the conduct and evaluation of the trial until the trial database is declared clean and released to the statistician.

All IMP will be identical in appearance to protect the blinded nature of the trial.

5.5.2 Unblinding of Individual Subject Treatment

Emergency unblinding will be available to the investigator and designated persons at Ferring via the IRT system. Breaking of the blind for individual subjects in emergency situations is only permitted in case of a suspected unexpected serious adverse reaction (SUSAR) or in case of an important AE where the knowledge of the IMP in question is required for therapeutic decisions for the management of the subject. The expectedness of events will be assessed by Ferring according to the Investigator's Brochure.

As the emergency permits, the need to break the blind will be agreed upon by the investigator and Ferring. It should be recorded in the eCRF that the code is broken and why, when, and by whom. The investigator must record the event of unblinding in the subject's medical record, including the reason for unblinding, but not the treatment allocation, if this can be avoided.

In case of accidental unblinding, the same documentation as for emergency unblinding must be obtained, and the event must also be recorded in the subject's medical record.

It may be necessary to unblind an individual subject's treatment for the purposes of expedited reporting to the authorities and/or Independent Ethics Committee(s) (IEC) (s)/Institutional Review Board(s) (IRB) (s). In that situation, every effort will be made to maintain blinding of sponsor personnel involved in data analysis and interpretation. Other personnel may be unblinded for SUSARs, including trial site staff and staff acting on behalf of Ferring.

Information on whether the blind has been broken for any subjects must be collected before the database is declared clean and released to the statistician.

5.6 Treatment Compliance

5.6.1 Dispensing and Accountability

The IMP will only be dispensed to subjects who meet the eligibility criteria and are randomized to a treatment group in the trial. The investigator or coordinator will maintain a drug-dispensing log detailing the dates and quantities of IMPs dispensed to each subject. The monitor will verify the drug accountability during the course of the trial.

5.6.2 Assessment of Compliance

At Weeks 2, 4, and 8 (or at early withdrawal) during the double-blind treatment period, and at Week 16 during the open-label period, subjects will bring their unused IMP back to the trial site. Subject compliance will be assessed with a medication count by the investigator or coordinator at the end of the visit and will be documented.

5.7 Return and Destruction of Medicinal Products

All assigned, unused IMPs should be returned to the trial site and can be destroyed in accordance with the site's local requirements, after the drug accountability has been finalized, verified by the monitor, and signed off by the investigator.

All unassigned, unused IMPs will be returned as instructed by the IMP Department at Ferring Pharmaceuticals A/S after completion of drug accountability at the trial site.

6 TRIAL PROCEDURES

6.1 Trial Flow Chart

The schedule of trial procedures is presented in Table 1.

Table 1: Schedule of Trial Procedures

	Double-blind Treatment						Open-label Treatment (OL)		
	Screening	Baseline/ Randomization	Intermediate	Intermediate	End of Double-blind Treatment/ Early Withdrawal		OL Week 2	End of OL Treatment/ Early Withdrawal	
Visit	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Week	**Week -3**	**Week 0**	**Week 2**	**Week 4**	**Week 8**		**Week 10**	**Week 16**	
Trial Day (visit window)	**Up to Day -21**	**Day 1**	**Day 15 (±3 days)**	**Day 29 (±3 days)**	**Day 57 (-6 days)**	**Day 57 (±3 days)**	**Day 71 (±3 days)**	**Day 113 (-6 days)**	**Day 113 (±3 days)**
Written informed consent	X								
Inclusion/exclusion criteria review	X	X							
Medical history	X	X							
Physical examination, including weight	X	X	X	X		X	X		X
Height	X								
Vital signs	X	X	X	X		X	X		X
12-lead electrocardiogram	X					X			X
Demographic data	X								
Serum/urine pregnancy test[a]	X	X				X			X
Drug and alcohol history	X								
Immunological testing for HBV, HCV, and HIV	X								
Estimated creatinine clearance	X[b]		X		X		X	X	
Safety hematology, coagulation, and chemistry	X[b]		X[j]		X[i]	X	X[j]	X[i]	X
Standard urinalysis[c]	X[b]		X			X	X		X
Stool sample	X[b]								
Randomization		X							
Prior and concomitant medications	X	X	X	X		X	X		X
Serum CRP		X	X	X		X	X		X
Fecal calprotectin stool sample		X				X			X
Clinical Response Score (stool frequency and rectal bleeding scores)	X		X	X	X		X	X	
Flexible Sigmoidoscopy /colonoscopy -Central reading	X[d]				X			X	
Calculation of Clinical and Endoscopic Response Score		X				X			X
Calculation of Modified Mayo score		X				X			
Physician's Global Assessment		X				X			
HRQoL questionnaire: IBDQ		X	X	X		X	X		X
Adverse event recording[e]	X	X	X	X		X	X		X

	Double-blind Treatment						Open-label Treatment (OL)		
	Screening	Baseline/ Randomization	Intermediate	Intermediate	End of Double-blind Treatment/ Early Withdrawal		OL Week 2	End of OL Treatment/ Early Withdrawal	
Visit	0	1	2	3	4	5	6	7	8
Week	Week -3	Week 0	Week 2	Week 4	Week 8		Week 10	Week 16	
Trial Day (visit window)	Up to Day -21	Day 1	Day 15 (±3 days)	Day 29 (±3 days)	Day 57 (-6 days)	Day 57 (±3 days)	Day 71 (±3 days)	Day 113 (-6 days)	Day 113 (±3 days)
Distribution of trial medication		X	X	X		X[f]			
First administration of trial medication[g]		X				X			
Trial medication collection/accountability			X	X		X			X
Trial medication compliance			X	X		X			X
Subject diary activation		X							
Subject diary data review[h]			X	X		X	X		X

Note: All subjects who discontinue treatment (double-blind or open-label) will complete end-of-treatment assessments.

a For females of childbearing age or <1 year postmenopausal; if positive, the subject will not be enrolled in the trial. At screening, perform serum pregnancy test and at baseline and end of treatment (double-blind or open-label), perform urine pregnancy test. If the urine pregnancy test is positive at the end of double-blind treatment, the subject will not be enrolled in the open-label treatment period.

b Results must be available at randomization, Visit 1.

c If positive for blood, leucocytes, or nitrite microscopic urinalysis will be performed.

d Baseline flexible sigmoidoscopy/colonoscopy will be scheduled during screening and must be completed after Clinical Response Score (Visit 0). It should be scheduled to occur no more than 10 days but at least 4 days prior to randomization (Visit 1) to allow sufficient time for the central reading. A colonoscopy will be required to establish the extent of disease if the flexible sigmoidoscopy is not conclusive in establishing the upper border of UC involvement.

e Adverse events are collected from the signing of informed consent.

f Open-label trial medication will be distributed for subjects entering the open-label treatment period only.

g Double-blind trial medication first dose to be taken on Visit 1 Day 1; open-label trial medication first dose to be taken the day following the end of double-blind treatment visit.

h Subject daily diary data will be collected electronically and daily diary compliance will be assessed.

i Only liver function tests and hematology.

j No coagulation panel.

6.2 Trial Procedures

6.2.1 Screening Visit: Visit 0 (up to Day -21)

Screening procedures are to be performed within 21 days prior to the first dose of trial drug. The subject will be informed about the trial and will give written informed consent before any trial-related procedures are performed. The following will be performed/collected at Visit 0:

- written informed consent
- review of inclusion/exclusion criteria
- medical history
- Clinical Response Score (based on recall data of stool frequency and rectal bleeding in the last 3 days)
- physical examination, including height and weight
- vital signs (blood pressure and pulse rate)
- 12-lead electrocardiogram (ECG)
- demographic data
- serum pregnancy testing for females of childbearing age or <1 year postmenopausal
- history of drug and alcohol use
- HBV, HCV, and HIV testing
- estimated creatinine clearance
- clinical safety laboratory assessment: chemistry, hematology, coagulation, standard urinalysis
- stool sample to test for parasites, bacterial pathogens, and *Clostridium difficile*
- prior and concomitant medications - subjects may not be taking or have used the following treatments, and a washout period will be required prior to trial medication administration:
    - aspirin within 7 days prior to Visit 1 or during the trial (except for cardioprotective reasons - maximum dose 325 mg/day)
    - oral 5-ASA products at a dose >2.5 g/day or topical rectal 5-ASA within 7 days prior to Visit 1 *(use of any 5-ASA during the course of the trial is prohibited)*
    - rectal formulations (5-ASA, steroids) within 7 days prior to Visit 1 or during the trial
    - loperamide and other antidiarrheal agents, mucilages, antibiotics (metronidazole and ciprofloxacin), NSAIDs, nicotine patch within the past week or during the trial
    - corticosteroids (oral, intravenous, intramuscular) within the previous month or during the trial
    - immunomodulating/suppressing drugs within the previous 6 weeks or during the trial
    - subjects must also not have a history of taking biologics (e.g., Remicade)
- assessment of any AEs occurring after informed consent is signed

- flexible sigmoidoscopy/colonoscopy will be scheduled during screening and completed after Clinical Response Score. It should be scheduled to occur no more than ten (10) days but at least four (4) days prior to randomization to allow sufficient time for the central reading
- colonoscopy will be required to establish the extent of disease if the flexible sigmoidoscopy is not conclusive in establishing the upper border of UC involvement
- flexible sigmoidoscopy/colonoscopy recording will be sent to the independent central reader for assessment and qualifying scoring, regardless of the local site's score

6.2.2 Baseline/Randomization Visit: Visit 1 (Day 1)

The following will be performed/collected at Visit 1:

- review of inclusion/exclusion criteria
- review/update medical history, including history and frequency of rectal bleeding
- physical examination, including weight
- vital signs (blood pressure and pulse rate)
- urine pregnancy testing (test strip) for females of childbearing age or <1 year postmenopausal
- prior and concomitant medication review since Visit 0
- calculation of Clinical and Endoscopic Response Score (Table 2). The score for stool frequency and rectal bleeding will be calculated based on scores collected from 3 day subject recall at Visit 0
- PGA
- calculation of Modified Mayo score by the investigator to determine eligibility for entering the trial. The score for stool frequency and rectal bleeding will be calculated based on scores collected from 3 day subject recall at Visit 0
- assessment of any AEs since Visit 0

If all inclusion/exclusion criteria are met, the subject will be randomized and the following procedures performed (prior to IMP administration):

- activation of subject daily diary
- IBDQ
- serum CRP and fecal calprotectin levels
- randomized, blinded trial medication distribution

The subject administers first dose of IMP at the site, with instructions to administer the IMP at least 1 hour before or at least 2 hours after a meal at approximately the same time each day.

6.2.3 Intermediate Visits: Visit 2 (Day 15±3) and Visit 3 (Day 29±3)

The following will be performed/collected at Visits 2 and 3:

- physical examination, including weight
- vital signs (blood pressure and pulse rate)
- concomitant medication review
- estimated creatinine clearance (Visit 2 only)
- clinical safety laboratory assessment: chemistry, hematology, standard urinalysis only (Visit 2 only)
- serum CRP level
- Clinical Response Score (Table 2), based on subject recording of stool frequency and rectal bleeding in the daily diary
- IBDQ
- assessment of any AEs since the previous visit
- collection and distribution of trial medication
- review of subject daily diary data including compliance
- trial medication compliance assessment

6.2.4 Double-blind End-of-Treatment Visits: Visit 4 (Day 57 -6) and Visit 5 (Day 57 ±3)

The following will be performed/collected at Visit 4 (Day 57 – 6) or early withdrawal:

- estimated creatinine clearance
- clinical safety laboratory assessment: liver function tests (LFTs) and hematology
- Clinical Response Score (Table 2), based on subject recording of stool frequency and rectal bleeding in the daily diary
- flexible sigmoidoscopy/colonoscopy (at least 4 days prior to Visit 5 to allow sufficient time for the central reading)
- submit flexible sigmoidoscopy/colonoscopy recording to the independent central reader

The following will be performed/collected at Visit 5 (Day 57 ±3) or early withdrawal:

- physical examination, including weight
- vital signs (blood pressure and pulse rate)
- 12-lead ECG
- urine pregnancy testing (test strip) for females of childbearing age or <1 year postmenopausal; if positive, the subject will not be able to continue into the open-label period or Study 000175
- clinical safety laboratory assessment: chemistry, hematology, coagulation, standard urinalysis
- serum CRP and fecal calprotectin levels
- concomitant medication review
- calculation of Clinical and Endoscopic Response Score (Table 2).
- PGA
- calculation of Modified Mayo score
- IBDQ
- assessment of any AEs since the previous visit
- collection of trial medication
- review of subject daily diary data including compliance, and deactivation of subject daily diary for subjects not entering open-label period
- trial medication compliance assessment

At the end of Week 8, all subjects who do not meet the defined criteria for remission at Week 8 will be given an option to receive open-label treatment with mesalamine 4 g extended release granules (sachet) for 8 additional weeks in the current trial. IMP will be distributed and subjects will receive instructions on the administration of the trial medication. The first dose of IMP will be administered the day following the end of double-blind treatment visit. The IMP will be taken at least 1 hour before or at least 2 hours after a meal at approximately the same time each day during the open-label period.

6.2.5 Open-Label Visit: Visit 6 (Day 71 ±3)

The following will be performed/collected at Visit 6:

- physical examination, including weight
- vital signs (blood pressure and pulse rate)
- clinical safety laboratory assessment: chemistry, hematology, standard urinalysis only
- concomitant medication review

- serum CRP
- Clinical Response Score (Table 2), based on subject recording of stool frequency and rectal bleeding in the daily diary
- IBDQ
- assessment of any AEs since the previous visit
- review of subject daily diary data including compliance

6.2.6 Open-Label End-of-Treatment Visits: Visit 7 (Day 113 -6) and Visit 8 (Day 113 ±3)

The following will be performed/collected at Visit 7 (Day 113 – 6) or early withdrawal:

- estimated creatinine clearance
- clinical safety laboratory assessment: liver function tests (LFTs) and hematology
- Clinical Response Score (Table 2), based on subject recording of stool frequency and rectal bleeding in the daily diary
- flexible sigmoidoscopy/colonoscopy (at least 4 days prior to Visit 8 to allow sufficient time for the central reading)
- submit flexible sigmoidoscopy/colonoscopy recording to the independent central reader

The following will be performed/collected at Visit 8 (Day 113 ±3) or early withdrawal:

- physical examination, including weight
- vital signs (blood pressure and pulse rate)
- 12-lead ECG
- urine pregnancy testing (test strip) for females of childbearing age or <1 year postmenopausal (if positive, the subject will not be enrolled in Study 000175)
- clinical safety laboratory assessment: chemistry, hematology, coagulation, standard urinalysis
- concomitant medication review
- serum CRP and fecal calprotectin levels
- calculation of Clinical and Endoscopic Response Score (Table 2).
- IBDQ
- assessment of any AEs since the previous visit
- collection of trial medication

- review of subject daily diary data including compliance, and deactivation of subject daily diary
- trial medication compliance assessment

7 TRIAL ASSESSMENTS

7.1 Assessments Related to Endpoints

7.1.1 Clinical and Endoscopic Response Score and Physician's Global Assessment

The Clinical and Endoscopic Response Score will be determined, as shown in Table 2.

The Modified Mayo score will be calculated as the sum of the Clinical and Endoscopic Response Scores (Table 2) and the PGA score (Table 3).

The Endoscopic Response Score will be determined by flexible sigmoidoscopy/colonoscopy as scored by the independent central reader (Section 7.1.2).

The scores on stool frequency and rectal bleeding will be obtained from the subject electronic daily diary, with the exception of screening which will be based on subject recall (Section 7.1.3).

The Modified Mayo score will be calculated by the investigator at baseline/randomization, and at the end of double-blind treatment (Week 8 or early withdrawal).

Table 2: Clinical and Endoscopic Response Score (0 – 9)

Components	Subscale	Severity	Score
CLINICAL RESPONSE (Subject's Symptoms)	**Stool Frequency[a] (daily)**	Normal number of stools for subject	0
		1 to 2 stools more than normal	1
		3 to 4 stools more than normal	2
		≥5 stools more than normal	3
	Rectal Bleeding[b] (daily)	No blood seen	0
		Streaks of blood with stool	1
		Obvious blood with stool	2
		Blood alone passes	3
ENDOSCOPIC RESPONSE (Objective Evidence of Inflammation)	**Flexible Sigmoidoscopy /colonoscopy Findings**	Normal or inactive disease	0
		Mild disease (erythema, decreased vascular pattern, granularity)	1
		Moderate disease (marked erythema, absent vascular pattern, any friability, erosions)	2
		Severe disease (spontaneous bleeding, ulceration)	3

Adapted from: Schroeder et al., 1987 (1); Sninsky et al., 1991 (2); Modified by Ferring Group, 2014

a. Each subject serves as his or her own control to establish the degree of abnormality of the stool frequency.

b. The daily bleeding score represents the most severe bleeding of the day.

Table 3: Physician's Global Assessment

Severity	Score
Normal	0
Mild disease	1
Moderate disease	2
Severe disease	3

7.1.2 Flexible Sigmoidoscopy/colonoscopy

In order to obtain the endoscopic response score (Table 2), the objective evidence of inflammation in this trial, flexible sigmoidoscopy/colonoscopy will be performed according to a standardized manner during screening (no more than 10 days but at least 4 days prior to randomization to allow sufficient time for the central reading), the end of double-blind treatment (Week 8 or early withdrawal), and at the end of open-label treatment. Flexible sigmoidoscopy/colonoscopy will be video recorded and transferred to the independent central reader. The details of the tools, recording, data transfer, and assessment will be documented in an imaging charter. Findings will be graded on a 4-point scale (Table 2), with 0 = normal or inactive disease, 1 = mild disease (erythema, decreased vascular pattern, granularity), 2 = moderate disease (marked erythema, absent vascular pattern, any friability, erosions), and 3 = severe disease (spontaneous bleeding, ulceration). The flexible sigmoidoscopy/colonoscopy recording during screening will be sent to the independent central reader for final determination of eligibility, regardless of the local site's score. A flexible sigmoidoscopy/colonoscopy will also be performed at Weeks 8 and 16 as applicable. These recordings will also be sent to the independent central reader for endoscopic endpoint scoring. A colonoscopy will be required to establish the extent of disease if the flexible sigmoidoscopy is not conclusive in establishing the upper border of UC involvement. Extent of colitis will be documented as proctosigmoiditis, left-sided colitis, or extended colitis.

7.1.2.1 Independent Central Endoscopy Laboratory

All flexible sigmoidoscopies and colonoscopies (if required), will be performed in a standardized manner. The endoscopy completed during screening (no more than 10 days but at least 4 days prior to randomization to allow sufficient time for the central reading), at Week 8 (end of double-blind treatment/early withdrawal), and Week 16 (end of open-label treatment/early withdrawal) will be sent to the independent central reader selected by the sponsor. The screening result will be used to qualify the image for use in randomization. Image handling and instructions will be provided to all sites directly from the independent central laboratory.

The endoscopic qualifying score will be automatically uploaded to the eCRF.

Trial sites will be provided with endoscopic laboratory recording equipment, supplies, and manuals.

7.1.3 Subject Daily Diary

The subject daily diary will be completed by the subject every evening starting the day of randomization (Visit 1/Day 1). Subject diary will consist of questions regarding IMP daily intake, stool frequency, and presence of blood content. The score for stool frequency and rectal bleeding will be calculated as an average based on scores collected from 3 day subject recall at Visit 0 or from subject diary data 5 days prior to Visits 2, 3, 4, 6 and 7 (see Appendix 2). If a subject recorded fewer than 3 days of scores during this 5-day period, the average score will be considered missing.

The subject daily diary and questionnaire will be completed via a validated Interactive Voice Response system (IVRS). Instructions on the use of the subject daily diary and questionnaire will be provided to each trial center.

7.1.4 Serum CRP and Fecal Calprotectin

Serum CRP levels will be determined at baseline and Visits 2 (Week 2), 3 (Week 4), 5 (Week 8) during the double-blind treatment period, and at Visits 6 (Week 10) and 8 (Week 16) during the open-label treatment period. Fecal calprotectin levels will be determined at baseline and at Visit 5 (Week 8) of the double-blind treatment period and at Visit 8 (Week 16) of the open-label treatment period.

7.1.5 Health-Related Quality of Life/Collection Pad

The IBDQ is an instrument used to assess quality of life in adult patients with inflammatory bowel disease, UC, or Crohn's disease and has demonstrated reliability and validity in discriminating between patients in clinical remission or relapse. (18) Subjects will be asked to recall symptoms and quality of life from the last 2 weeks and to rate each item on a 7-point Likert scale (higher scores equate to higher quality of life). Subjects will complete the IBDQ questionnaire (see Appendix 1) via a validated collection pad, prior to all other trial-related procedures at the site at Visit 2 (Week 2), Visit 3 (Week 4), and Visit 5 (Week 8) (or early withdrawal) during the double-blind treatment period, and at Visits 6 (Week 10) and 8 (Week 16) during the open-label treatment period (after randomization but before IMP administration). At Visit 1, subjects must first be randomized before completion of the IBDQ.

7.1.6 Adverse Events

Adverse events will be collected as described in Section 8 of this protocol.

Laboratory abnormalities may be reported as AEs based on the discretion of the investigator, i.e., laboratory abnormalities that the investigator assesses as a clinically significant.

Physical examination and vital sign abnormalities will be reported as AEs if the investigator considers any abnormality clinically significant.

7.1.7 Clinical Laboratory Variables

Hematology, Serum Chemistry, and Urinalysis

Safety hematology, coagulation, and serum chemistry tests will be performed at Visit 0 (screening), Visits 4 and 5 (Week 8) or at early withdrawal during the double-blind treatment period, Visit 6 (Week 10) and Visits 7 and 8 (Week 16) during the open-label treatment period.

Hematology: hematocrit, hemoglobin, platelet count, red blood cell count, white blood cell count, and differential count

Coagulation: prothrombin time (measured as international normalized ratio), activated partial thromboplastin time

Serum chemistry: glucose, blood urea nitrogen, creatinine, creatinine clearance (via estimated glomerular filtration rate [eGFR]), potassium, sodium, chloride, calcium, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase

Urinalysis: leukocyte, blood, pH, specific gravity, nitrite, protein, glucose, urobilinogen, and microscopic if positive for blood, leucocytes, and nitrite

The investigator will review the laboratory results and evaluate and document whether the results are normal or abnormal and whether abnormal results are clinically significant. The laboratory report will be signed and dated by the investigator.

7.2 Other Assessments

7.2.1 Medical History and Demographic Data

Demographic data and a complete medical history will be obtained at Visit 0 (screening), with a review of medical history at Visit 1 (baseline/Day 1). Disease specific and general medical history will be recorded in the eCRF.

7.2.2 Immunological Testing

Serological testing for HBV, HCV, and HIV will be performed at Visit 0 (screening). Negative results are required for trial admission.

7.2.3 Drug and Alcohol History

At Visit 0 (screening), a drug and alcohol history evaluation will be performed by the investigator.

7.2.4 Serum/Urine Pregnancy Test

A serum pregnancy test will be performed at Visit 0 (screening). A urine pregnancy test will be performed at Visit 1 (baseline/Day 1) and Visit 5 (Week 8) or early withdrawal during the double-blind treatment period and at Visit 8 (Week 16) of the open-label treatment period (Table 1). Negative results are required for admission to each period.

7.2.5 Screening Stool Sample

A stool sample will be obtained at screening to rule out parasites, bacterial pathogens, and *Clostridium difficile*. Subjects who test positive for *Clostridium difficile* can be rescreened if treated and *Clostridium difficile* negative for 2 consecutive months.

7.2.6 Concomitant Medications

Concomitant medication information will be collected at every trial visit during the double-blind and open-label treatment periods (Table 1).

7.2.7 Physical Examinations

At the screening visit (Visit 0), physical examination with height and weight will be performed. Height will be measured at the screening visit only. Physical examination with weight will be performed at Visit 1 (baseline/Day 1), Visit 2 (Week 2), Visit 3 (Week 4), and at the end of double-blind treatment Visit 5 (Week 8 [or at early withdrawal]), as well as during open-label treatment period Visits 6 and 8 (Weeks 10 and 16 [or at early withdrawal]) (Table 1). Any clinically significant deterioration from baseline will be recorded as an AE.

7.2.8 Vital Signs

Vital signs will be measured at each trial visit except Visits 4 and 7 (Table 1). Vital signs will include blood pressure and heart rate measured under resting conditions while the subject is seated. All blood pressure measurements should be made using the same arm and prior to any scheduled blood draws.

7.2.9 12-Lead Electrocardiogram

A 12-lead ECG will be obtained at Visit 0 (screening) and Visit 5 (Week 8) or at early withdrawal during the double-blind treatment period and at Week 16 (or at early withdrawal) of the open-label treatment period (Table 1). The 12-lead ECG will be obtained after at least a 5-minute rest in a supine position.

7.2.10 Compliance

Trial medication and subject daily diary compliance will be assessed at Visit 2 (Week 2), Visit 3 (Week 4), and Visit 5 (Week 8) or at early withdrawal during the double-blind treatment period and at Visit 8 (Week 16 [or at early withdrawal]) during the open-label treatment period (Table 1). Subject

daily diary compliance will also be assessed at Visit 6 (Week 10) during the open-label treatment period.

7.3 Drug Concentration Measurements

Drug concentration measurements will not be performed for this trial.

7.4 Handling of Biological Samples

A central laboratory will be used in this trial. Sampling tubes, material for shipment of the samples, and a laboratory manual detailing all sample collection, handling and shipment procedures will be provided and distributed to the trial sites by the central laboratory.

8 ADVERSE EVENTS

8.1 Adverse Event Definition

An AE is any untoward medical occurrence in a subject participating in a clinical trial. It includes:

- any unfavorable and unintended sign, symptom or disease temporally associated with the use of the IMP, whether or not considered to be caused by the IMP
- AEs commonly observed and AEs anticipated based on the pharmacological effect of the IMP
- any laboratory abnormality, vital sign, or finding from physical (or gynecological) examination assessed as clinically significant by the investigator (note: findings from assessments and examinations done during screening are not AEs, but are recorded as medical history)
- accidental injuries, reasons for any change in medication (drug and/or dose), reasons for any medical, nursing or pharmacy consultation, or reasons for admission to hospital or surgical procedures
- overdoses and medication errors with and without clinical consequences

8.2 Collection and Recording of Adverse Events

8.2.1 Collection of Adverse Events

The investigator must monitor the condition of the subject throughout the trial from the time of obtaining informed consent until the last visit.

The sources of AEs cover:

- the subject's response to questions about his/her health (a standard non-leading question such as "How have you been feeling since your last visit?" is asked at each visit)
- symptoms spontaneously reported by the subject
- investigations and examinations where the findings are assessed by the investigator to be clinically significant changes or abnormalities
- other information relating to the subject's health becoming known to the investigator (e.g. hospitalization)

8.2.2 Recording of Adverse Events

The investigator must record all AEs in the AE log provided in each subject's eCRF with information about:

- AE

- date and time of onset (time can be omitted, if applicable)
- intensity
- causal relationship to IMP
- action taken to IMP
- other action taken
- date and time of outcome (time can be omitted, if applicable)
- outcome
- seriousness

Each of the items in the AE log is described in detail in the following sections.

Adverse Events

Adverse events should be recorded as diagnoses, if available. If not, separate signs and symptoms should be recorded. One diagnosis/symptom should be entered per record.

If a subject suffers from the same AE more than once and the subject recovers between the events, the AEs should be recorded separately. If an AE changes in intensity, a worst-case approach should be used when recording the event, i.e. the highest intensity and the longest duration of the event.[a]

A procedure is not an AE; the reason for conducting the procedure is. Hospitalization is not an AE; the reason for hospitalization is. Death is not an AE, but the cause of death is (an exception is sudden death of unknown cause, which is an AE).

Date and Time of Onset

The date of onset is the date when the first sign(s) or symptom(s) were first noted. If the AE is an abnormal clinically significant laboratory test or outcome of an examination, the onset date is the date the sample was taken or the examination was performed.

[a] Exception: if an AE with onset before the first IMP administration (i.e., a pre-treatment AE) changes in intensity, this must be recorded as 2 separate events. The initial AE should be recorded with outcome "not yet recovered" and the date and time of outcome are when the intensity changed. The second AE should be recorded with date and time of onset when the intensity changed.

Intensity

The intensity of an AE must be classified using the following 3-point scale:

Mild: awareness of signs or symptoms, but no disruption of usual activity

Moderate: event sufficient to affect usual activity (disturbing)

Severe: inability to work or perform usual activities (unacceptable)

Causal Relationship to IMP

The possibility of whether the IMP caused the AE must be classified as 1 of the following:

Reasonable possibility: There is evidence or argument to suggest a causal relationship between the IMP and the AE. The AE may occur as part of the pharmacological action of the IMP or may be unpredictable in its occurrence.

Examples:

- AEs that are uncommon but are known to be strongly associated with IMP exposure
- AEs that are not commonly associated with IMP exposure, but the event occurs in association with other factors strongly suggesting causation, such as a strong temporal association or the event recurs on rechallenge

No reasonable possibility: There is no reasonable evidence or argument to suggest a causal relationship between the IMP and the AE.

Examples:

- known consequences of the underlying disease or condition under investigation
- AEs common in the trial population, which are also anticipated to occur with some frequency during the course of the trial, regardless of IMP exposure

Action Taken with IMP

The action taken with the IMP in response to an AE must be classified as 1 of the following:

- no change (medication schedule maintained or no action taken)
- withdrawn

- interrupted

Other Action Taken

Adverse events requiring therapy must be treated with recognized standards of medical care to protect the health and well-being of the subject. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation.

If medication is administered to treat the AE, this medication should be entered in the concomitant medication log.

Date of Outcome

The date and time (time can be deleted/omitted, if applicable) the subject recovered or died will be recorded.

Outcome

The outcome of an AE must be classified as 1 of the following:

- recovered (fully recovered or the condition has returned to the level observed at initiation of trial treatment)
- recovered with sequelae (resulted in persistent or significant disability/incapacity)
- recovering
- not recovered
- fatal

8.3 Pregnancy and Pregnancy Outcome

Every effort must be made to avoid pregnancy during the trial. If a pregnancy occurs, the IMP should be immediately stopped and Global Pharmacovigilance at Ferring Pharmaceuticals must be informed using the Pregnancy Report Form within 3 calendar days. Note that pregnancy itself is not a serious adverse event (SAE). The mother and the fetus must be followed at least until the birth of the infant and 1 month after the birth of the infant. In general, the follow-up will include the course, duration, and the outcome of the pregnancy as well as neonatal health. If a pregnancy results in an abnormal outcome (birth defect/congenital anomaly), this must be reported as an SAE to Global Pharmacovigilance at Ferring Pharmaceuticals, as described in Section 8.4.2. Any abnormal pregnancy outcome that the investigator and/or sponsor consider to be related to the IMP will be treated as an expedited report.

8.4 Serious Adverse Events

8.4.1 Serious Adverse Event Definition

Serious AEs are defined as follows:

An event is defined a serious adverse event if it:	Guidance
results in **death**	Any event resulting in a fatal outcome must be fully documented and reported, including deaths occurring within 4 weeks after the treatment ends and irrespective of the causal relationship to the IMP. The death of a subject enrolled in a trial is *per se* not an event, but an outcome.
is **life-threatening**	The term life-threatening refers to an AE in which the subject was at immediate risk of death at the time of the event. It does not refer to an event, which may have caused death if it were more severe.
requires in-patient **hospitalization** or prolongation of existing hospitalization	The term hospitalization means that the subject was admitted to hospital or that existing hospitalization was extended as a result of an event. Hospitalization describes a period of at least 24 hours. Overnight stay for observation, stay at emergency room, or treatment on an outpatient basis do not constitute a hospitalization. However, medical judgment must always be exercised and, when in doubt the case should be considered serious (i.e., if case fulfils the criterion for a medically important event). Hospitalizations for administrative or social purposes do not constitute SAEs. Hospital admissions and/or surgical operations planned before trial inclusion are not considered AEs, if the illness or disease existed before the subject was enrolled in the trial, provided that the condition did not deteriorate during the trial.
results in persistent or significant **disability/incapacity**	Disability/incapacity means a substantial disruption of a person's ability to conduct normal life functions. In doubt, the decision should be left to medical judgment by the investigator.
is a **congenital anomaly/birth defect**	Congenital anomaly/birth defect observed in any offspring of the subject conceived during treatment with the IMP.
is an **important medical event**	Important medical events are events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples of important medical events include AEs that suggest a significant hazard, contraindication or precaution, occurrence of malignancy, or development of drug dependency or drug abuse. Medical and scientific judgment should be exercised in deciding whether events qualify as medically important. Important medical events include any suspected transmission of an infectious agent via a medicinal product. Any organism virus or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings indicating an infection in a subject exposed to a medicinal product.

8.4.2 Collection, Recording and Reporting of Serious Adverse Events

SAE Reporting by the Investigator

All SAEs must be reported **immediately** to Global Pharmacovigilance at Ferring Pharmaceuticals as soon as it becomes known to the investigator and not later than within 24 hours of his/her knowledge of the occurrence of an SAE. The investigator is responsible for submitting the completed paper SAE report form with the fullest possible details **within 3 calendar days** of his/her knowledge of the SAE.

The SAE must be included in the eCRF system. In addition, a paper SAE report must be completed and submitted according to the instructions provided on the form and sent to Global Pharmacovigilance at Ferring Pharmaceuticals using the contact details below.

Global Pharmacovigilance, Ferring Pharmaceuticals A/S
E-mail: [redacted]
Fax: [redacted]

eCRF information regarding demographics, AEs, medical history, and concomitant medication is **mandatory** for initial reports and for follow-up reports if any changes have been made since the initial report.

Additional information relevant to the SAE, such as hospital records, results from investigations (e.g., laboratory parameters that are not already uploaded in the eCRF, invasive procedures, scans, x-rays, and autopsy results) can be faxed or scanned and e-mailed to Ferring Global Pharmacovigilance using the contact details in the section above. In any case this information must be supplied by the investigator upon request from Ferring. On any copies provided, such details such as subject's name, address, and hospital ID number should be concealed, and subject number should be provided instead.

The investigator will supply Ferring and the IEC/IRB with any additional requested information, such as results of post-mortem examinations and hospital records.

Expedited Reporting by Ferring

Ferring will report all AEs that are **serious, unexpected, and with a reasonable possible causality to the IMP** as judged by either the investigator or Ferring to the relevant parties within the stipulated timelines. The expectedness of events will be assessed by Ferring according to the Investigator's Brochure.

SAEs will be considered reportable regardless of whether the IMP was used in accordance with the provisions in the protocol, Investigator's Brochure, and labelling.

8.5 Follow-up of Adverse Events and Serious Adverse Events

8.5.1 Follow-up of Adverse Events with Onset during the Trial

During the trial, the investigator must follow each AE until it is resolved or until the medical condition of the subject is stable.

After the subject's last visit, the investigator must follow-up on any AE classified as serious or considered to have a reasonable possible causality to the IMP until it is resolved or until the medical condition of the subject is stable. All such relevant follow-up information must be reported to Ferring. If the event is a chronic condition, the investigator and Ferring may agree that further follow-up is not required.

8.5.2 Collection of Serious Adverse Events with Onset after Last Trial Visit

If an investigator becomes aware of an SAE after the subject's last visit, and he/she assesses the SAE to have a reasonable possible causality to the IMP, the case will have to be reported to Ferring, regardless how long after the end of the trial this takes place.

9 STATISTICAL METHODS

All analyses will be detailed in a subsequent statistical analysis plan.

9.1 Determination of Sample Size

The true remission rates at Week 8 for mesalamine 4 g extended release granules (sachet) and placebo regimens were assumed as 36% and 18%, respectively, based on Kamm (2007) (3), Lichtenstein (2007) (4), and Marteau (2005).(5) Under these assumptions, a sample size of 110 randomized subjects per group will provide at least 85% power to detect a statistically significant treatment group difference in the remission rate at a two-sided 0.05 significance level using the chi-square test.

9.2 Subject Disposition

The number of screened subjects will be summarized, and for subjects not randomized, the primary reason for exclusion from randomization will be summarized.

The number and percentage of subjects who are randomized, are treated with IMP, prematurely discontinued, and completed the double-blind period of the trial will be summarized with the reason of premature discontinuations. Similar summaries will be made for subjects who are enrolled to the 8-week open-label period.

The time to discontinuation will be summarized by the Kaplan-Meier estimates, and the treatment group difference will be tested by the log-rank test. In addition, reason-specific discontinuation will be summarized by the cumulative incidence estimates.

9.3 Protocol Deviations

The following protocol deviations will be identified as major protocol deviations:

- Overall IMP compliance of less than 80%
- Not taking the randomized IMP
- Taking prohibited medications

The final definition of major and minor protocol violations will be determined prior to breaking the trial blind.

The number and percentage of subjects with major protocol deviations will be summarized.

9.4 Analysis Sets

Three analysis sets will be defined:

- Intent-to-Treat (ITT) analysis set: Includes all randomized subjects

- Modified ITT (mITT) analysis set: Includes all randomized subjects who receive at least 1 dose of IMP
- Per protocol (PP) analysis set: Includes all randomized subjects who receive at least 1 dose of IMP and who do not have any of the major protocol deviations
- Safety analysis set: Includes all subjects who receive at least 1 dose of IMP

The assignment of subjects to each analysis set will be finalized prior to breaking the trial blind.

Analyses for the ITT and mITT will be conducted according to the randomized treatment. Safety analyses will be conducted according to the treatment actually received rather than according to the treatment assigned.

For each analysis set, the number and percentage of subjects excluded from it will be summarized by the reason of the exclusion.

9.5 Trial Population

9.5.1 Demographics and other Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all subjects in the ITT, PP, and safety analysis sets by treatment group.

9.5.2 Medical History, Concomitant Medication and Other Safety Evaluations

Medical history will be coded by system organ class (SOC) and preferred term (PT) using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) available at study initiation and summarized by SOC, PT, and treatment group for the ITT and Safety analysis sets. Prior and concomitant medications will be coded by the Anatomical Therapeutic Chemical (ATC) classification system and preferred drug name using the World Health Organization Drug Dictionary (WHO-Drug). Prior and concomitant drug usage will be summarized by ATC classification 1st level, ATC classification 2nd level and treatment group for subjects in the ITT and Safety analysis sets.

9.6 Endpoint Assessments

9.6.1 General Considerations

All statistical tests will be conducted at a two-sided 0.05 significance level.

Quantitative variables will be described with the number of non-missing values, mean, standard deviation, median, and minimum/maximum values. Qualitative variables will be described with the number and percentage of subjects with each qualitative characteristic. Missing values will not be included in the calculation of percentages.

All data will be listed by individual subject and trial visit.

The efficacy data captured during the 8-week open-label mesalamine 4g/day treatment will be descriptively summarized and used for exploratory purposes only.

9.6.2 Primary Endpoint

The primary efficacy analysis will be based on all randomized subjects (ITT analysis set). The proportion of subjects with remission, defined as 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 at Week 8, will be compared between treatment groups using the chi-square test at a two-sided 0.05 significance level. Subjects who discontinue the double-blind regimen before Week 8, as well as subjects with missing remission assessment at Week 8, will be considered not having achieved remission. The odds ratio will be estimated and its 95% confidence interval will be provided.

The following sensitivity analyses will be conducted to assess the robustness of the primary analysis:

- As-treated analysis based on actually received treatment
- Analysis on the mITT analysis set
- Analysis on the PP analysis set
- Assessment of the homogeneity of odds ratios across geographical regions, baseline demographic characteristics, and baseline disease characteristics
- Analysis on the last observed Clinical and Endoscopic Response Score
- Analysis using multiple imputation methods for missing remission assessment at Week 8
- Analysis using pattern mixture models for missing remission assessment at Week 8

9.6.3 Secondary Endpoints

Key secondary endpoints are the following:

1. The proportion of subjects with remission in the primary endpoint and the PGA score of $\leq$1 (Modified Mayo) at Week 8
2. Time to cessation of rectal bleeding, 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 daily diary

Secondary endpoints are the following:

1. The proportion of subjects with endoscopic improvement, 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
2. The proportion of subjects in clinical remission at Weeks 2, 4, and 8, 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
3. Time to normal stool pattern, 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
4. The change from baseline in rectal bleeding score at Weeks 2, 4, and 8, based on subject daily diary
5. The change from baseline in serum CRP levels at Weeks 2, 4, and 8
6. The change from baseline in fecal calprotectin level at Week 8
7. The change from baseline to each scheduled assessment for published and validated domain scores of the IBDQ
8. Safety, assessed by incidence and severity of AEs and abnormal laboratory values

The key secondary endpoints will be analyzed by a fixed-sequence procedure according to the pre-specified order to maintain the overall Type 1 error rate to a two-sided 5%.

If the primary efficacy analysis demonstrates a statistically significant difference between the treatment groups, the first key secondary endpoint will be compared using the same statistical method used for the primary efficacy analysis at a two-sided 0.05 significance level. If the analysis for the first key secondary endpoint is statistically significant, the second key secondary endpoint will be compared by the log-rank test at a two-sided 0.05 significance level.

Other secondary endpoints will be analyzed individually at a two-sided 0.05 significance level.

The proportion of subjects with endoscopic improvement will be analyzed using the same statistical method used for the primary efficacy analysis.

The proportion of subjects in clinical remission at Weeks 2, 4, and 8 will be analyzed by the generalized estimating equations approach as longitudinal binary outcomes. The model will include treatment, time, and treatment- by-time interaction. The clinical remission rates and odds ratios will be estimated for each time point.

The time to normal stool pattern will be analyzed using the same statistical method used for the analysis of the time to cessation of rectal bleeding.

The change from baseline in rectal bleeding score and serum CRP levels at Weeks 2, 4 and 8 will be analyzed by repeated-measures analysis of covariance (ANCOVA) models that include treatment, time, and treatment-by-time interaction as fixed effects, and the corresponding baseline value as a covariate based on the observed data. The adjusted changes from baseline and their difference between treatment groups will be estimated for each time point. The change from baseline in the fecal calprotectin level at Week 8 will be analyzed by an ANCOVA model that includes treatment as a factor and baseline value at a covariate.

The efficacy data captured during the 8-week open-label mesalamine 4 g/day treatment period, will be used for exploratory purposes only.

9.6.4 Health-related Quality of Life

Change from baseline to each scheduled assessment will be summarized for published and validated domain scores of the IBDQ. The change from baseline in IBDQ scores will be assessed with a repeated-measures ANCOVA model that includes treatment, time, and treatment-by-time interaction as fixed effects, and baseline value as a covariate based on the observed data.

9.7 Extent of Exposure and Treatment Compliance

The length of the treatment, calculated as (last dose date – first dose date + 1 day), will be summarized by treatment group for the safety analysis set.

The overall compliance during the double-blind period will be summarized for the safety analysis set.

9.8 Safety

9.8.1 General Considerations

Safety parameters will be evaluated for the safety analysis set. Similar safety data summaries will be made for the open-label treatment period data.

9.8.2 Adverse Events

A ‘pre-treatment’ AE will be defined as an AE that occurs between screening and the first dose of the IMP. A ‘treatment-emergent AE (TEAE)’ will be an AE which occurs in the time interval from initial dosing (IMP intake) to the end of treatment visit. If an AE on Day 1 occurs before IMP intake, it will be recorded as a pre-treatment AE.

Written narratives will be issued for all SAEs and AEs leading to withdrawal. If causality is missing, the AE will be regarded as being reasonably possibly related to IMP. Related AEs (judged as being reasonably possibly related to IMP) will be termed adverse drug reactions (ADR).

An AE overview summary table will be prepared for the safety analysis population. It will display the number and percentage of subjects reporting an AE and the number of events reported for each treatment group. The following categories will be displayed:

- Any TEAEs
- Deaths
- SAEs
- AEs leading to discontinuation
- Severe AEs
- ADRs

Number and percentage of subjects reporting the following types of TEAEs will be summarized by MedDRA SOC (alphabetically) and PT (in decreasing frequency of occurrence):

- Any TEAEs
- Common TEAEs
- Causal relationship to IMP with reasonable possibility or no reasonable possibility
- Intensity with mild, moderate, or severe
- AEs leading to death
- SAEs
- AEs leading to discontinuation

Supporting data listings will be provided for:

- All AEs sorted by trial site and subject ID
- All AEs sorted by MedDRA SOC and PT
- SAEs
- AEs leading to death
- AEs leading to discontinuation

9.8.3 Safety Laboratory Variables

Clinical laboratory variables will be presented in 2 ways. First, mean change from baseline to the end of the double-blind treatment visit will be summarized. Baseline will be defined as the last assessment before the first dose of IMP. Second, the number and percentage of subjects with treatment-emergent

potentially clinically significant laboratory values on or before the end of the double-blind treatment visit will be tabulated.

9.8.4 Other Safety Variables

Other safety assessments will be summarized descriptively.

9.9 Interim Analyses

No interim analysis is planned.

10 DATA HANDLING

10.1 Source Data and Source Documents

Source Data – International Conference on Harmonization (ICH) Definition

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents - ICH Definition

Source documents are defined as original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Trial-specific Source Data Requirements – Ferring

The investigator must maintain subject records, including as a minimum: medical history; data on the condition of the subject at the time the subject is enrolled into the trial in order to document (and enable verification of) subject eligibility; diagnosis; subject's participation in trial; subject's trial identification; date of informed consent and time, if applicable, for the trial; visit dates and results of examinations and tests performed, especially results of examinations related to primary endpoints; details of IMP administration; details of AEs, concomitant medication, and of any follow-up and analysis/tests/examinations done; and reason for subject withdrawal from the trial.

10.2 eCRF

An eCRF system provided by an independent, third-party contract research organization (CRO) will be used for data capture. The system is validated and access at all levels to the system is granted/revoked following Ferring and vendor procedures, in accordance with regulatory and system requirements.

The eCRF system and the database will be hosted at the independent, third-party CRO. After the trial database is declared clean and released to the statistician, a final copy of the database will be stored at Ferring Pharmaceuticals A/S located in DK-2300 Copenhagen S, Denmark, within the SAS Drug Development system. The investigator will also receive a copy of the trial site's final and locked data (including audit trail, electronic signature and queries) as write-protected PDF files produced by the independent, third-party CRO. The PDF files will be stored on a CD and will be provided to the investigator before access to the eCRF is revoked. The Investigator will approve/authorise the eCRF

entries for each subject with an electronic signature which equals a handwritten signature. Trial data will be entered into the system in a timely manner.

Errors occurring in the eCRF will be corrected electronically. Such corrections/modifications will be automatically tracked by an audit trail detailing the date and time of the correction and the name of the person making the correction.

10.3 Data Management

All data management activities will be specified in a Data Management Plan prepared under the responsibility of Global Biometrics, Ferring Pharmaceuticals A/S. All data management activities will be performed by independent, third-party CRO, under the responsibility of Global Biometrics, Ferring Pharmaceuticals A/S. A study database will be created according to the Data Management standard operating procedures and data validation programmes will be developed to check for data completion and validity.

Laboratory data will be transferred electronically to independent, third-party CRO for inclusion in the study data base according to laboratory data transfer specifications to be agreed between the individual laboratories and independent, third-party CRO. For medical coding of AEs, medical history and concomitant medication the most recent versions of MedDRA and WHO-Drug will be used. The coding will be performed by the third-party CRO and will be reviewed and approved by Ferring. When all data have been processed, queries resolved, medical coding completed and any issues from review of protocol violations and data listings resolved, the database will be locked and any further update will be denied. A final quality assurance audit of the locked database will take place prior to transfer of the final database structured according to Ferring's data transfer specifications.

10.4 Provision of Additional Information

On request, the investigator will provide Ferring with additional data relating to the trial, duly anonymized and protected in accordance with applicable requirements.

11 MONITORING PROCEDURES

11.1 Periodic Monitoring

The monitor will contact and visit the investigator periodically to ensure adherence to the protocol, ICH-Good Clinical Practice (ICH-GCP), standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy and verifiability of eCRF entries compared to source data, verification of drug accountability, and compliance with safety reporting instructions.

The investigator will permit the monitor direct access to all source data, including electronic medical records, and/or documents in order to facilitate data verification. The investigator will cooperate with the monitor to ensure that any discrepancies that may be identified are resolved. The investigator is expected to meet the monitor during these visits.

When the first subject is randomized at the trial site, a monitoring visit will take place shortly thereafter. For this trial, the frequency of the interim monitoring visits will be determined by the enrollment rate and will be detailed in the monitoring plan.

11.2 Audit and Inspection

The investigator will make all the trial-related source data and records available at any time to quality assurance auditor(s) mandated by Ferring or to domestic/foreign regulatory inspectors or representatives from IEC(s)/IRB(s) who may audit/inspect the trial. The main purposes of an audit or inspection are to assess compliance with the trial protocol and the principles of ICH-GCP, including the Declaration of Helsinki and all other relevant regulations.

The subjects must be informed by the investigator and in the informed consent documents that authorized Ferring representatives and representatives from regulatory authorities and IEC(s)/IRB(s) may wish to inspect their medical records. During audits/inspections, the auditors/inspectors may copy relevant parts of the medical records. No personal identification other than the screening/randomization number will appear on these copies.

The investigator should notify Ferring without any delay of any inspection by a regulatory authority or IEC/IRB.

11.3 Confidentiality of Subject Data

The investigator will ensure that the confidentiality of the subjects' data will be preserved. In the eCRF or any other documents submitted to Ferring, the subjects will not be identified by their names, but by an identification system that consists of an assigned number in the trial. Documents that are not for

submission to Ferring, e.g., the confidential subject identification code and the signed informed consent documents will be maintained by the investigator in strict confidence.

12 CHANGES IN THE CONDUCT OF THE TRIAL

12.1 Protocol Amendments

Any change to this protocol will be documented in a protocol amendment, issued by Ferring, and agreed upon by the investigator and Ferring prior to its implementation. Substantial amendments will be submitted for consideration to the approving IRB/IEC and regulatory authorities, in accordance with local regulations. An approval is required for a substantial amendment, e.g., one that could affect the safety of the subjects or that entails a significant change of the scope/design of the trial.

12.2 Deviations from the Protocol

If deviations from the protocol occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed. Any deviation must be documented on the protocol violation page in the source document and eCRF with the visit number and type of violation. A log of protocol deviation reports will be maintained by Ferring. Protocol deviation reports and supporting paper documentation must be kept in the investigator's file and in the trial master file.

12.3 Premature Trial Termination

Both the investigator (with regard to his/her participation) and Ferring reserve the right to terminate the trial at any time. Should this become necessary, the procedures will be agreed upon after consultation between the 2 parties. In terminating the trial, Ferring and the investigator will ensure that adequate consideration is given to the protection of the best interests of the subjects. The regulatory authorities and IEC(s)/IRB(s) will be informed.

In addition, Ferring reserves the right to terminate the participation of individual trial sites. Conditions that may warrant termination include, but are not limited to, insufficient adherence to protocol requirements and failure to enter subjects at an acceptable rate.

13 REPORTING AND PUBLICATION

13.1 Clinical Trial Report

The data and information collected during this trial will be reported in a clinical trial report prepared by Ferring and submitted for comments and signature to the signatory investigator.

13.2 Confidentiality and Ownership of Trial Data

Any confidential information relating to the IMP or the trial, including any data and results from the trial, will be the exclusive property of Ferring. The investigator and any other persons involved in the trial will protect the confidentiality of this proprietary information belonging to Ferring.

13.3 Publications and Public Disclosure

13.3.1 Publication Policy

At the end of the trial, 1 or more manuscripts for joint publication may be prepared in collaboration between the investigator(s) offered authorship and Ferring. In a multi-site trial based on the collaboration of many sites, any publication of results must acknowledge all sites. Results from multi-site trials must be reported in entirety in a responsible and coherent manner and results from subsets should not be published in advance or without clear reference to the primary publication of the entire trial.

Authorship is granted based on the International Committee of Medical Journal Editors (ICMJE) criteria (see current official version: http/www.ICMJE.org). The total number of authors is based on the guideline from the relevant journal or congress. In the event of any disagreement in the content of a publication, both the investigator's and Ferring's opinion will be fairly and sufficiently represented in the publication.

Any external CRO or laboratory involved in the conduct of this trial has no publication rights regarding this trial.

If the investigator wishes to independently publish/present any results from the trial, the draft manuscript/presentation must be submitted in writing to Ferring for comment prior to submission. Comments will be given within 4 weeks from receipt of the draft manuscript. This statement does not give Ferring any editorial rights over the content of a publication, other than to restrict the disclosure of Ferring's intellectual property. If the matter considered for publication is deemed patentable by Ferring, scientific publication will not be allowed until after a filed patent application is published. Under such conditions the publication will be modified or delayed at the investigator's discretion, to allow sufficient time for Ferring to seek patent protection of the invention.

13.3.2 Public Disclosure Policy

ICMJE member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public, clinical trials registry. Thus, it is the responsibility of Ferring to register the trial in an appropriate public registry, i.e., www.ClinicalTrials.gov which is a website maintained by the National Library of Medicine at the US National Institutes of Health.

14 ETHICAL AND REGULATORY ASPECTS

14.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

An IEC/IRB will review the protocol and any amendments and advertisements used for recruitment. The IEC/IRB will review the subject information sheet and the informed consent form, their updates (if any), and any written materials given to the subjects. A list of all IECs/IRBs to which the protocol has been submitted and the name of the committee chairmen will be included in the clinical trial report.

14.2 Regulatory Authorities Authorization / Approval / Notification

The regulatory permission to perform the trial will be obtained in accordance with applicable regulatory requirements. All ethical and regulatory approvals must be available before a subject is exposed to any trial-related procedure, including screening tests for eligibility.

14.3 End-of-Trial and End-of-Trial Notification

At the end of the trial (last subjects completes the last visit), the appropriate regulatory authorities and the IRB(s)/IEC(s) will be notified in writing.

14.4 Ethical Conduct of the Trial

This trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki (2008 version), in compliance with the approved protocol, ICH-GCP, and applicable regulatory requirements.

14.5 Subject Information and Consent

The investigator (or the person designated by the investigator) will obtain a freely given written consent from each subject after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspects of the trial that are relevant to the subject's decision to participate. The trial subject must be given ample time to consider participation in the trial, before the consent is obtained. The informed consent documents must be signed and dated by the subject and the investigator who has provided information to the subject regarding the trial before the subject is exposed to any trial-related procedure, including screening tests for eligibility.

The investigator (or the person designated by the investigator) will explain that the subject is completely free to refuse to enter the trial or to withdraw from it at any time, without any consequences for his/her further care and without the need to justify his/her decision.

The subject will receive a copy of the subject information and his/her signed informed consent form.

If new information becomes available that may be relevant to the trial subject's willingness to continue participation in the trial, a new subject information and informed consent form will be forwarded to the

IEC(s)/IRB(s) (and regulatory authorities, if required). The trial subjects will be informed about this new information and re-consent will be obtained.

Each subject will be informed that the monitor(s), quality assurance auditor(s) mandated by Ferring, IRB/IEC representatives or regulatory authority inspector(s), in accordance with applicable regulatory requirements, may review his/her source records and data. Data protection will be handled in compliance with national/local regulations.

14.6 Compliance Reference Documents

The Helsinki Declaration, the consolidated ICH-GCP, the European Union Clinical Trials Directive, and other national laws in the countries where the trial takes place shall constitute the main reference guidelines for ethical and regulatory conduct.

15 LIABILITIES AND INSURANCE

15.1 ICH-GCP Responsibilities

The responsibilities of Ferring, the monitor, and the investigator are defined in the ICH-GCP consolidated guideline and applicable regulatory requirements in the country where the trial takes place. The investigator is responsible for adhering to the ICH-GCP responsibilities of investigators, for dispensing the IMP in accordance with the approved protocol or an approved amendment, and for its secure storage and safe handling throughout the trial.

15.2 Liabilities and Insurance

In case of any damage or injury occurring to a subject in association with the IMP or the participation in the trial, Ferring has contracted an insurance that covers the liability of Ferring, the investigator, and other persons involved in the trial, in compliance with the laws in the countries involved.

16 ARCHIVING

16.1 Investigator File

The investigator is responsible for maintaining all the records that enable the conduct of the trial at the site to be fully understood, in compliance with ICH-GCP. The trial documentation, including all the relevant correspondence, should be kept by the investigator for at least 15 years (or longer if required by local law) after the completion or discontinuation of the trial, if no further instructions are given by Ferring.

The investigator is responsible for the completion and maintenance of the confidential subject identification code, which provides the sole link between named subject source records and anonymous eCRF data for Ferring. The investigator must arrange for the retention of this subject identification log and signed informed consent documents for at least 15 years (or longer if required by local law) after the completion or discontinuation of the trial.

No trial site document may be destroyed without prior written agreement between the investigator and Ferring. Should the investigator elect to assign the trial documents to another party or move them to another location, Ferring must be notified. If the investigator retires and the documents can no longer be archived by the site, Ferring can arrange to have the investigator file archived at an external archive.

16.2 Trial Master File

Ferring will archive the trial master file in accordance with ICH-GCP and applicable regulatory requirements.

17 REFERENCES

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APPENDICES

Appendix 1 Inflammatory Bowel Disease Questionnaire (IBDQ)

For Review Purposes Only

QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from

1 BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
2 EXTREMELY FREQUENT
3 VERY FREQUENT
4 MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
5 SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
6 SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
7 NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

For Review Purposes Only

4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

6. How much energy have you had during the last 2 weeks? Please choose an option from

1 NO ENERGY AT ALL
2 VERY LITTLE ENERGY
3 A LITTLE ENERGY
4 SOME ENERGY
5 A MODERATE AMOUNT OF ENERGY
6 A LOT OF ENERGY
7 FULL OF ENERGY

For Review Purposes Only

7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem. Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

For Review Purposes Only

10. How often during the last 2 weeks have you felt generally Unwell? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from

1 A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
2 A LOT OF DIFFICULTY
3 A FAIR BIT OF DIFFICULTY
4 SOME DIFFICULTY
5 A LITTLE DIFFICULTY
6 HARDLY ANY DIFFICULTY
7 NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

For Review Purposes Only

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom close at hand? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

18. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to, the weight you would like to be at. Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

For Review Purposes Only

19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from

1 NONE OF THE TIME
2 A LITTLE OF THE TIME
3 SOME OF THE TIME
4 A GOOD BIT OF THE TIME
5 MOST OF THE TIME
6 ALMOST ALL OF THE TIME
7 ALL OF THE TIME

22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

For Review Purposes Only

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from

1 NO SEX AS A RESULT OF BOWEL DISEASE
2 MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
3 MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
4 SOME LIMITATION AS A RESULT OF BOWEL DISEASE
5 A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
6 HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
7 NO LIMITATION AS A RESULT OF BOWEL DISEASE

29. How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach? Please choose an option. from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

For Review Purposes Only

31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? Please choose one of the following options from

1 VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
2 GENERALLY DISSATISFIED, UNHAPPY
3 SOMEWHAT DISSATISFIED, UNHAPPY
4 GENERALLY SATISFIED, PLEASED
5 SATISFIED MOST OF THE TIME, HAPPY
6 VERY SATISFIED MOST OF THE TIME, HAPPY
7 EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED

Appendix 2 Subject Diary Script

Subject Diary Script

Subject Daily Diary Questions

1. Did you take your study medication today?
   a) ☐ Yes ☐ No
   If Yes;
   b) Did you take the study medication at least 1 hour before or at least 2 hours after a meal? ☐ Yes ☐ No
2. Evaluate today's bowel movement frequency.
   a) ☐ Number of bowel movements today _____

3. Have you noticed any blood in your bowel movement?
   a) ☐ Normal = (*No blood*)
   b) ☐ Streaks of blood
   c) ☐ Obvious blood
   d) ☐ Mostly blood

Note: That a bowel movement may consist of one or multiple stools; what one experiences in one visit to the toilet is classified as a bowel movement. For the rectal bleeding score, the worst score during the day is the one which will be recorded.

Bowel Movement (BM) Frequency (daily)

To determine the effect of medical therapy on your bowel movement frequency, we need you to define your "usual" non-ill state of health.

- What is your normal bowel movement frequency?

Each day during the trial you will assess your bowel movement frequency. This will be entered into your daily diary.

- What is your bowel movement frequency today?

Rectal Bleeding Occurrence (daily)

Each day during the trial you will assess your rectal bleeding. This assessment should be based on your worst episode of bleeding that day. One of the four (4) choices below will be entered into your daily diary:

Have you noticed any blood in your bowel movement? For example:

- If you see NO blood on the bowel movement or in the toilet water or visible anywhere in the toilet, enter a bleeding score of 0.

- If you see only red streaks of blood on the surface of the bowel movement, enter a bleeding score of 1.

- If you see red streaks of blood on the surface of the bowel movement and/or in the toilet water and/or visible anywhere in the toilet, enter a bleeding score of 2.

- If your bowel movement is mostly or totally blood, enter a bleeding score of 3.