Statistical Analysis Plan

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: 02 Apr 2018

STATISTICAL ANALYSIS PLAN

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

Investigational Product:	Mesalamine 4 g Extended Release Granules (Sachet)
Indication:	Induction of clinical and endoscopic remission in active, mild to moderate ulcerative colitis
Phase:	3
Author:	[redacted]
Date of issue:	02-Apr-2018
Version:	3.0

Change log

Version No.	Effective Date	Reason for the Change / Revision	Supersedes
2.0	August 7, 2015	- Reflected protocol amendments 1 and 2 - Addressed FDA's comments on the initial SAP o Added modified ITT analysis set to the sensitivity analysis o Added sensitivity analyses using multiple imputation methods and pattern mixture models under missing at random and missing not at random assumptions, respectively.	Version 1.0
3.0	April 2, 2018	- Reflected protocol amendments 3 and 4, especially for changes in the primary endpoint regarding stool frequency criteria for remission - Clarified stool frequency and rectal bleeding score calculation - Updated definition of major protocol deviations, analysis visit windows, and subgroups - Clarified summaries for laboratory variables against normal ranges	Version 2.0

Signed agreement on Statistical Analysis Plan

Author:

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Review:

This statistical analysis plan was reviewed and signed electronically in the REAL system by:

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1 Introduction

This document describes the planned statistical analyses for Study 000174 based on the Consolidated Protocol Incorporating Amendments 1.0, 2.0, 3.0, and 4.0 dated January 11, 2017.

1.1 Definitions/ Abbreviations

1.1.1 Definition of Terms

Terms	Definitions
Clinical Response Score	Stool frequency and rectal bleeding subscale of Clinical and Endoscopic Response Score
Endoscopic Response Score	Flexible sigmoidoscopy findings subscale of Clinical and Endoscopic Response Score

1.1.2 Abbreviations

Abbreviations	Meaning of abbreviations in document
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BM	Bowel movement
CRP	C-reactive protein
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
GEE	Generalized estimating equations
GGT	Gamma glutamyl transferase
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
IBDQ	Inflammatory bowel disease questionnaire
IMP	Investigational medicinal product
INR	International normalized ratio
ITT	Intention-to-treat
MAR	Missing at random
MedDRA	Medical dictionary for regulatory activities
MI	Multiple imputation
mITT	Modified ITT
MNAR	Missing not at random
OL	Open label
PGA	Physician’s global assessment
PMM	Pattern mixture model
PP	Per protocol
PT	Preferred term

Abbreviations	Meaning of abbreviations in document
QD	Once daily
QTc	Corrected QT interval
SOC	System organ class
TEAE	Treatment-emergent adverse event
UC	Ulcerative colitis
US	United states
WBC	White blood cell
WHO-Drug	World health organization drug dictionary

2 Trial Objectives and Endpoints

2.1 Objectives

2.1.1 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)

2.1.2 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

2.2 Endpoints

2.2.1 Primary endpoint

The primary efficacy endpoint is the proportion of subjects with remission, defined by the Clinical and Endoscopic Response Score (Table 1) at Week 8 as a score of,

- 0 for rectal bleeding, and
- "0" or "1 with at least 1 point decrease from baseline" for stool frequency, and
- 0 or 1 for endoscopic score.

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

Table 1 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 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.

2.2.2 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

2.2.3 Secondary endpoints

- 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

- 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

- 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

- The change from baseline in rectal bleeding score at Weeks 2, 4, and 8, based on subject daily diary

- The change from baseline in serum CRP levels at Weeks 2, 4, and 8
- The change from baseline in fecal calprotectin levels at Week 8
- The change from baseline to each scheduled assessment for published and validated domain scores of the IBDQ
- Safety assessed by incidence and severity of AEs and abnormal laboratory values

3 Trial design

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 scores 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.

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. If the local site's endoscopic reading determines the subject is ineligible, the subject will be screen failed. If the local site's endoscopic reading determines that the subject is eligible, the flexible sigmoidoscopy recording will be sent to the independent central reader for final determination of eligibility. A flexible sigmoidoscopy will also be performed at Weeks 8 and 16 as applicable. These recordings will 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.

The schedule of trial procedures is presented in Appendix 2.

3.1 General Design Considerations

This trial is designed as a randomized, double-blind, placebo-controlled trial with 8 weeks of treatment. Subjects who achieve remission after the 8-week treatment will be allowed to enroll into a maintenance trial (Study 000175). To increase the number of subjects who continues to the maintenance trial from the current trial, an additional 8-week open-label mesalamine treatment period will be offered to subjects who complete Week 8 but fail to meet the defined criteria for remission.

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

3.2 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 et al. (2007)(3), Lichtenstein et al. (2007)(4), and Marteau et al. (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.

4 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.

5 Protocol Deviations

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

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

The final definition of major protocol deviations will be determined prior to breaking the blind.

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

6 Analysis sets

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

6.1 Intention-To-Treat Analysis Set

The intention-to-treat (ITT) analysis set includes all randomized subjects. Analyses for the ITT analysis set will be conducted according to the randomized treatment regardless of the actual treatment received.

6.2 Modified Intention-To-Treat Analysis Set

The modified intention-to-treat (mITT) analysis set includes all randomized subjects who receive at least one dose of IMP. Analyses for the mITT analysis set will be conducted according to the randomized treatment regardless of the actual treatment received.

6.3 Per Protocol Analysis Set

The Per-protocol (PP) analysis set includes all randomized subjects who receive at least one dose of IMP and who do not have any of the major protocol deviations defined in Section 5.

6.4 Safety Analysis Set

The safety analysis set includes all subjects who receive at least one dose of IMP. Safety analyses will be conducted according to the treatment actually received.

7 Trial population

7.1 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 unless otherwise specified.

Categorical data will be summarized using numbers and percentages. The percentages will be based on the total number of subjects with a corresponding assessment. Continuous data will be presented using the number of subjects, mean, standard deviation, median, minimum, and maximum.

7.1.1 Demographics

Baseline demographics and other baseline characteristics will be summarized by treatment group.

7.1.2 Disease Characteristics

Baseline disease characteristics (e.g., time since diagnosis of UC, extent of disease) will be summarized by treatment group.

Baseline Clinical and Endoscopic Response Scores will be summarized by treatment group.

7.1.3 Laboratory Efficacy/Pharmacodynamic Parameters at Baseline

Baseline serum CRP and fecal calprotectin levels will be summarized by treatment group.

7.2 Medical History

Medical history will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 or later and summarized by SOC (in alphabetical order), PT (in decreasing order of frequency), and treatment group for the ITT and safety analysis sets.

7.3 Prior and Concomitant Medication

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 (alphabetically), ATC classification 2nd level (in decreasing order of frequency) and treatment group for subjects in the ITT and safety analysis sets. These medications will be tabulated separately for:

1) Prior medication; i.e. medication taken exclusively prior to treatment (i.e. with stop date before date of first IMP administration);
2) Concomitant medication, i.e. medication taken during the treatment period (i.e. medication that was not stopped before date of first IMP administration or started on or after the first IMP administration

If the timing of the dose of a concomitant medication cannot be established in relation to the administration of IMP, it will be considered as concomitant medication.

Concomitant medications used during the double-blind period will be identified.

7.4 Physical Examination

Subjects with abnormalities at any screening, baseline, or post-baseline visit will be listed with all physical examination evaluations.

8 Exposure and Treatment Compliance

8.1 Extent of Exposure

The length of the treatment, calculated as (last dose date – first dose date + 1), will be summarized by treatment group for the safety analysis set. The summaries will be made for the double-blind period only, open-label period only, and combined double-blind and open-label periods. The combined summary will be made only for the exposure to mesalamine.

Following categorical summaries will be made for the double-blind period only:

- < 14 days, 14 - < 28 days, 28 - <42 days, 42 - <56 days, and 56 days or more
- At least 1 day, at least 14 days, at least 28 days, at least 42 days, and at least 56 days

8.2 Treatment Compliance

The overall compliance during the double-blind period will be calculated as number of days with IMP intake based on the daily diary data divided by the number of days that the subject is supposed to take the IMP during the treatment period. It will be summarized for the safety analysis set.

9 Efficacy

9.1 General Considerations

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

Statistical tests for the primary and key secondary endpoints will be conducted using a fixed-sequence procedure according to the pre-specified order to maintain the overall Type I error rate to a two-sided 5%. All other secondary endpoints will be tested without adjustment for multiplicity.

Stool frequency and rectal bleeding scores at each visit will be calculated as an average of the daily scores collected within 5 days prior to the visit (excluding the visit day and the day before the visit day if the bowel preparation is needed on the day before the visit). If the daily scores in this period are available for fewer than 3 days, the average score will be considered missing. The average scores will be rounded to the nearest integer for the final score determination (e.g., 0.3 will be rounded to 0, and 0.5 will be rounded to 1).

The average scores will be calculated at Visit 2 (Week 2), Visit 3 (Week 4), and Visit 4 (Week 8) for the double-blind period, and Visit 6 (Week 10) and Visit 7 (Week 16) for the open-label period. Although both Visit 4 and Visit 5 are designated as Week 8 in the double-blind period, Visit 4 corresponds to the visit for the endoscopic assessment, and therefore, the stool frequency and rectal bleeding scores will be calculated at Visit 4. Similarly, the scores will be calculated at Visit 7 for the end of the open-label period instead of at Visit 8.

However, in one section (Section 7.1.3) of Protocol Amendment 2, it was unintentionally indicated that the scores would be calculated at Visit 5 and Visit 8 instead of Visit 4 and Visit 7. As a result, some of these subjects completed the diary fewer than 3 days within 5 days prior to Visit 4 and/or Visit 7 but completed 3 or more days prior to Visit 5 and/or Visit 8. Therefore, for those subjects who consented with Protocol Amendment 2, the average scores calculated at Visit 5 and/or Visit 8, as indicated in Section 7.1.3 of Protocol Amendment 2, will be used if the average scores at Visit 4 and/or Visit 7 are missing. Handling of other missing data in the statistical analyses will be described for each endpoint.

For the endoscopic assessment, the outcomes determined by the independent central reading procedure will be used for all analyses.

For visit-based data, the data collected on the day that is closest to the scheduled trial day within a window will be assigned to the corresponding analysis visit. Table 2 and Table 3 show the scheduled trial day and window for each analysis visit during the double-blind period and open-label period, respectively.

Table 2 Scheduled trial day and window for analysis visits: double-blind period

Analysis visit	Scheduled trial day	Window
Baseline	Day 1	prior to the first dose of IMP

Week 2	Day 15	Day 1 to Day 22
Week 4	Day 29	Day 23 to Day 43
Week 8	Day 57	Day 44 or after, but before 1st dose of OL period

OL: open label

Table 3 Scheduled trial day and window for analysis visits: open-label period

Analysis visit	Scheduled trial day	Window
Week 10	Day 71	After 1st dose of OL period up to Day 92
Week 16	Day 113	Day 93 or after

OL: open label

If the closest day cannot be uniquely identified for an analysis visit, the data collected on an earlier trial day will be assigned to the analysis visit.

The efficacy data captured during the 8-week open-label period will be descriptively summarized and used for exploratory purposes only.

9.2 Primary Endpoint(s)

9.2.1 Primary Variable(s) Analysis

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 a chi-square test without a continuity correction 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 for the treatment group compared to the control group will be estimated and its 95% confidence interval will be provided using the Woolf's approximation (Woolf, 1955)(6).

9.2.2 Sensitivity Analyses

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
- Analysis using the last observed Clinical and Endoscopic Response Score
- Fisher-exact test combined with Cornfield's exact 95% CI (Cornfield, 1956)(7)

The same analysis conducted for the primary analysis will be repeated for these sensitivity analyses.

Since the definition of remission was modified during the study, an analysis based on the original definition, i.e., rectal bleeding and stool frequency scores of 0 with an endoscopic score of 0 or 1 in the Clinical and Endoscopic Response Score, will also be conducted for reporting purpose.

In addition, sensitivity analyses using multiple imputation (MI) methods and pattern mixture models (PMMs) under missing at random (MAR) and missing not at random (MNAR) assumptions, respectively, will be conducted.

Under the MAR assumption, the missing stool frequency and rectal bleeding scores (Clinical Response scores) for Weeks 2, 4, and 8 will be imputed sequentially by regression-based imputation models using treatment group, baseline characteristics, and outcomes from preceding visits as the predictors. Once the missing Week 8 Clinical Response scores have been imputed, Week 8 Endoscopic Response score will be imputed by regression-based imputation models using treatment group, baseline characteristics, and Week 8 Clinical Response scores as the predictors. Based on the imputed Clinical and Endoscopic Response scores, the remission status at Week 8 will be determined. This imputation procedure will be repeated 100 times, and the primary analysis method will be applied to each of the imputed dataset. A combined estimate of the odds ratio for the treatment group compared to the control group and its 95% confidence interval will be obtained by the methods described in Rubin (1987)(8).

Under the MNAR assumption, a similar MI method described above will be applied. However, in this analysis, only the data from the control group will be used for the regression-based imputation for Clinical Response scores at each visit and Endoscopic Response score at Week 8 by assuming that subjects from the treatment group will follow the same profile as the subjects on the control group after withdrawal from the study (Little & Yau, 1996(9); Ratitch & O'Kelly, 2011(10)).

The primary endpoint will also be analyzed for the following subgroups for the ITT analysis set. The homogeneity of odds ratios across the strata will be tested by the Breslow-Day test at a 0.05 significance level, and the odds ratios for each subgroup will be presented in forest plots.

- Baseline demographic characteristics (age, gender, and race)
- Baseline disease characteristics (previous 5-ASA treatment (yes/no), extent of UC, and severity of UC)
- Geographical region (North America including US and Canada or rest of the world)

The treatment group comparisons after controlling each factor listed above will be conducted by the Mantel-Haenszel test as sensitivity analyses.

9.3 Secondary Endpoint(s)

9.3.1 Key Secondary Endpoints

The following key secondary endpoints will be analyzed for the ITT analysis set.

1. The proportion of subjects with remission in the primary endpoint and the 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

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. Only if the analysis for the first key secondary endpoint is statistically significant at a two-sided 0.05 significance level, the second key secondary endpoint will be declared statistically significant when the log-rank test is statistically significant at a two-sided 0.05 significance level. The hazard ratio of cessation of rectal bleeding for mesalamine relative to placebo will be estimated (including the 95% CI) using the Cox proportional hazards model with treatment group as a factor.

For the first key secondary endpoint, subjects who discontinue the double blind regimen before Week 8, as well as subjects with missing assessment at Week 8, will be considered not having achieved the response criteria.

For the second key secondary endpoint, if a subject does not achieve the cessation of rectal bleeding by Day 56, the time to cessation of rectal bleeding will be censored at the earlier of the day that the last diary entry is made or Day 56.

9.3.2 Other Secondary Endpoints

The following secondary endpoints will be analyzed for the ITT analysis set.

- 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
- 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 reduction from baseline” for stool frequency in the Clinical Response Score subset
- 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
- The change from baseline in rectal bleeding score at Weeks 2, 4, and 8, based on subject daily diary
- The change from baseline in serum CRP levels at Weeks 2, 4, and 8
- The change from baseline in fecal calprotectin levels at Week 8

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 (GEE) approach as longitudinal binary outcomes. The model will include treatment, time, and treatment- by-time interaction. The clinical remission rates and odds ratio will be estimated for each time point. The overall treatment difference over 8 weeks will be estimated as the main effect for treatment in the model. The missing values will be imputed as non-remission, and an unstructured working correlation matrix will be used.

The time to normal stool patter 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. The adjusted changes from baseline and their difference between treatment groups will be estimated for each time point. The overall treatment difference over 8 weeks will be estimated as the main effect for treatment in the model. The missing values will be left as missing, and an unstructured correlation matrix will be assumed.

The change from baseline in fecal calprotectin levels at Week 8 will be analyzed by an ANCOVA model that includes treatment as a factor and the baseline value as a covariate. The adjusted changes from baseline and their difference between treatment groups will be estimated.

9.4 Other Endpoint(s)

9.4.1 Health Related Quality of Life

The change from baseline in the IBDQ will be analyzed for the ITT analysis set.

The following domain scores for the IBDQ (Guyatt et al., 1989)(11) will be calculated by adding up scores from questions included in the domain for each subject at each time point:

- Bowel symptoms: Questions 1, 5, 9, 13, 17, 20, 22, 24, 26, 29
- Emotion function: Questions 3, 7, 11, 15, 19, 21, 23, 25, 27, 30, 31, 32
- Systemic symptoms: Questions 2, 6, 10, 14, 18
- Social function: Questions 4, 8, 12, 16, 28

The total score will be calculated by adding up all scores for each subject at each time point.

The handling of missing score in the calculation of the domain and total scores will be based on McMaster University (2010)(12). If there is only one missing response within a domain, the missing response will be imputed as an average of other responses within the domain. If there are two or more missing responses within a domain, the domain score will be considered missing. For the total score, if there are up to four missing responses, the missing responses will be imputed as an average of other responses. If there are more than four missing responses, the total score will be considered missing.

The change from baseline in the IBDQ domain and total scores at Weeks 2, 4, and 8 will be analyzed by repeated-measures ANCOVA models that include treatment, time, and treatment-by-time interaction as fixed effects, and the corresponding baseline value as a covariate. The adjusted changes from baseline and their difference between treatment groups will be estimated for each time point. The missing values will be left as missing, and an unstructured correlation matrix will be assumed.

9.4.2 Efficacy Endpoints During 8-week Open-label Trial Period

The following endpoints will be descriptively summarized by the treatment received during the double-blind period for subjects who receive the 8-week open-label treatment.

- The proportion of subjects in 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 16
- The proportion of subjects with endoscopic improvement, defined as an endoscopic score of 0 or 1, with at least a 1 point reduction from baseline in the endoscopic score at Week 16
- The proportion of subjects in 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 at Weeks 10 and 16
- The change from baseline in serum CRP levels at Weeks 10 and 16
- The change from baseline in fecal calprotectin levels at Weeks 16
- The change from baseline in the IBDQ domain and total scores at Weeks 10 and 16

10 Safety

10.1 General Considerations

Safety parameters will be evaluated for the safety analysis set by treatment group.

10.2 Adverse Events

Adverse events (AEs) will be classified according to the MedDRA version 17.1 or later.

Written narratives will be issued for all serious AEs (including deaths) and AEs leading to discontinuation.

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. An AE that occurs after the first dose of the open-label period will be considered a TEAE for the open-label period.

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).

10.2.1 Overview of Treatment-Emergent Adverse Events

An AE overview summary table will be prepared including the number of subjects reporting an AE, the percentage of subjects (%) with an AE, and the number of events (E) reported, for the following categories:

- Any TEAEs
- Deaths
- Serious adverse events
- Adverse events leading to discontinuation
- Severe TEAEs
- Adverse drug reactions

A similar summary table will be provided for the AEs occurring during the open-label period for subjects who receive the open-label treatment.

10.2.2 Incidence of Adverse Events

The summaries will include the total number of subjects reporting an AE, the percentage of subjects (%) with an AE, and the number of events (E) reported. AEs will be presented by SOC sorted alphabetically and PT sorted in decreasing frequency of occurrence.

Summary tables will be prepared for:

- Any TEAEs
- Common TEAEs, defined as TEAEs with an incidence ≥ 2% of subjects in any treatment group
- Any TEAEs by causality (related/unrelated)
- Any TEAEs by intensity
- Any AEs leading to death
- Serious adverse events
- Any TEAEs leading to discontinuation

Supporting data listings will be provided for:

- All adverse events sorted by trial site and subject ID
- All adverse events sorted by MedDRA SOC and PT
- Serious adverse events
- Adverse events leading to death
- Adverse events leading to discontinuation

A listing of SOC and PT for all unique verbatim will be provided.

For the open-label period, the following summaries and listings will be provided for subjects who receive the open-label treatment:

- Any TEAEs
- Any TEAEs by causality (related/unrelated)
- Any TEAEs by intensity
- Any AEs leading to death
- Serious adverse events
- Any TEAEs leading to discontinuation

10.3 Safety Laboratory Variables

Baseline for all laboratory analyses will be the values obtained at the last assessment prior to the first dose of the IMP. Treatment-emergent laboratory data will include tests completed after the first dose of IMP. End of double-blind period will include the last post-baseline observation during the double-blind period. End of open-label period will include the last observation during the open-label period.

Laboratory variables will be grouped under “Haematology”, “Coagulation”, “Serum chemistry” or “Urinalysis”

10.3.1 Summary Statistics

Change and percentage change from baseline at end of double-blind period will be presented for each laboratory variable. In addition, descriptive statistics, i.e., the number of subjects with data,

mean (standard deviation), median, minimum, and maximum values, will be presented for observed values and change/percentage change from baseline at baseline, Weeks 2, and 8 for each laboratory variable. The Weeks 2 and 8 measurements for the analysis will be identified based on the method described in Section 9.1.

For the open-label period, similar summaries will be provided for subjects who receive the open-label treatment.

10.3.2 Laboratory Variable Changes Relative to Normal Range

A shift table regarding the laboratory value category defined below will be created for baseline and end of double-blind period for each laboratory parameter.

- Low: Values which are below the lower reference range limit;
- Normal: Values which are within the lower and upper reference range;
- High: Values which are above the upper reference range limit.
- Absent: No value for measured variable (for urinalysis only)
- Present: Any value obtained for measured variable (for urinalysis only)

For the open-label period, similar shift tables will be provided for subjects who receive the open-label treatment.

10.3.3 Markedly Abnormal Changes

Number and percentage of subjects who experienced at least one pre-specified markedly abnormal value (Appendix 1) during the double-blind period for each laboratory variable will be summarized by the baseline category defined in Section 10.3.2 (i.e., low, normal, high, absent, or present).

For the open-label period, similar summaries will be provided for subjects who receive the open-label treatment.

10.3.4 Data Listings

Data listings will be prepared by treatment group and trial site for all subjects with any abnormal laboratory values at any time-point (including screening, baseline, double-blind period, and open-label period).

10.4 Vital Signs and ECG

10.4.1 Vital Signs

Baseline for all vital signs will be the values obtained at the last assessment prior to the first dose of IMP. Treatment-emergent vital signs data will include tests completed after the first dose of IMP. End of double-blind period will include the last post-baseline observation during the double-blind period. End of open-label period will include the last observation during the open-label period.

10.4.1.1 Summary Statistics

Change and percentage change from baseline at end of double-blind period will be presented for each vital sign variable. In addition, descriptive statistics, i.e., the number of subjects with data, mean (standard deviation), median, minimum, and maximum values, will be presented for observed values and change/percentage change from baseline at baseline, Weeks 2, 4, and 8 for each vital sign variable. The Weeks 2, 4, and 8 measurements for the analysis will be identified based on the method described in Section 9.1.

For the open-label period, similar summaries will be provided for subjects who receive the open-label treatment.

10.4.1.2 Markedly Abnormal Changes

Number and percentage of subjects who experienced at least one pre-specified markedly abnormal value (Appendix 1) during the double-blind period for each vital sign variable will be summarized.

For the open-label period, similar summaries will be provided for subjects who receive the open-label treatment.

10.4.1.3 Data Listings

Data listings will be prepared by trial site for all subjects with any markedly abnormal vital sign values at any time-point (including screening, baseline, double-blind period, and open-label period).

10.4.2 ECGs

Baseline for all ECG variables will be the values obtained at the last assessment prior to the first dose of IMP. Treatment-emergent ECG data will include values measured after the first dose of IMP. End of double-blind period will include the last post-baseline observation during the double-blind period. End of open-label period will include the last observation during the open-label period.

QTc will be calculated based on Bazett's (QTcB) and Fridericia's (QTcF) corrections.

$$QTcB[ms] = \frac{QT}{\sqrt{RR}}$$

$$QTcF[ms] = \frac{QT}{\sqrt[3]{RR}}$$

$$where, RR = \frac{60}{Heart\ Rate}$$

10.4.2.1 Summary Statistics

Change from baseline at end of double-blind period will be presented for each ECG variable. In addition, descriptive statistics, i.e., the number of subjects with data, mean (standard deviation), median, minimum, and maximum values, will be presented for observed values and change from baseline at baseline and Week 8 for each ECG variable. The Week 8 measurement for the analysis will be identified based on the method described in Section 9.1.

For the open-label period, similar summaries will be provided for subjects who receive the open-label treatment.

10.4.2.2 Markedly Abnormal Changes

Number and percentage of subjects who experienced at least one pre-specified markedly abnormal value (Appendix 1) during the double-blind period for each ECG variable will be summarized.

For the open-label period, similar summaries will be provided for subjects who receive the open-label treatment.

10.4.2.3 Data Listings

Data listings will be prepared by trial site for all subjects with any abnormal ECG findings at any time-point (including screening, baseline, double-blind period, and open-label period).

11 Interim analyses

No interim analysis is planned.

12 Deviations from protocol analysis

There is no deviation from the planned analysis described in the protocol.

13 References

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14 Tables, Listings and Figures

Tables, figures and listings shells will be presented in a separate document.

Appendix 1 Markedly Abnormal Laboratory Safety Values, Vital Signs and ECGs

Table A 1. Markedly abnormal Criteria for Laboratory Tests

Variable	Units	Markedly abnormal Criteria	
		Low	**High**
Haematology			
Haemoglobin	g/L	≤ 115	Not applicable
Haematocrit	Ratio	≤ 0.32	≥ 0.56
Total WBC	10^9/L	≤ 2.8	≥ 16.0
Eosinophils	%	Not applicable	≥ 10
Neutrophils	%	≤ 15	≥ 90
Lymphocytes	%	≤ 10	≥ 80
Monocytes	%	Not applicable	≥ 20
Basophils	%	Not applicable	≥ 5
Platelets	10^9/L	≤ 75	≥ 700
Total RBC	10^{12}/L	≤ 3.5	Not applicable
Clinical Chemistry			
AST	IU/L	Not applicable	> 3xULN
ALT	IU/L	Not applicable	> 3xULN
Alkaline phosphatase	IU/L	Not applicable	> 3xULN and 25% increase from baseline
GGT	IU/L	Not applicable	> 3xULN
Total bilirubin	µmol/L	Not applicable	≥ 1.5xULN
Urea nitrogen	mmol/L	Not applicable	≥ 10.7
Creatinine	µmol/L	Not applicable	≥ 177
eGFR	mL/min	<30	Not applicable
Total protein	g/L	≤ 45	≥ 90
Albumin	g/L	≤ 25	≥ 65
Sodium	mmol/L	≤ 130	≥ 155
Potassium	mmol/L	≤ 3.0	≥ 5.8
Chloride	mmol/L	≤ 90	≥ 115
Calcium	mmol/L	≤1.8	≥ 3.9
Glucose	mmol/L	≤ 2.8	≥ 10
Coagulation			
INR		<0.8	>1.1
Activated partial thromboplastin time	Sec	Not applicable	>70

Table A 2. Markedly abnormal Criteria for Vital Signs*

Variable	Criterion Value	Change from Baseline
Systolic blood pressure	≥ 180 mmHg ≤ 90 mmHg	Increase of ≥ 20 mmHg Decrease of ≥ 20 mmHg
Diastolic blood pressure	≥ 105 mmHg ≤ 50 mmHg	Increase of ≥ 15 mmHg Decrease of ≥ 15 mmHg
Pulse rate	≥ 120 bpm ≤ 50 bpm	Increase of ≥ 15 bpm Decrease of ≥ 15 bpm
Body temperature		Increase to ≥ 39.4°C

* To be identified as markedly abnormal, a treatment value must meet the criterion value and also the specified change from baseline.

Table A 3. Abnormal Criteria for Quantitative ECG Data*

Variable	Abnormal Treatment-Emergent Value
ECG heart rate	≤ 50 bpm and decrease from baseline of ≥ 15 bpm ≥ 120 bpm and increase from baseline of ≥ 15 bpm
Duration of PR interval	> 220 msec
Duration of QRS interval	> 120 msec
Duration of QTc interval	> 450 msec
Duration of QTc interval	> 480 msec
Duration of QTc interval	> 500 msec
Duration of QTc interval	Increase from baseline of ≥ 30 msec
Duration of QTc interval	Increase from baseline of ≥ 60 msec

* QTc will be calculated using both Bazett's and Fridericia's corrections.

Appendix 2 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	

	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)**
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
Distribution of trial medication		X	X	X		X[f]			X
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.