Statistical Analysis Plan

Title of trial: A randomized, double-blind, placebo-controlled, multicenter study investigating the efficacy and safety of mesalamine 2 g extended release granules (sachet) for maintenance of clinical and endoscopic remission in ulcerative colitis
NCT number: NCT02522780
Sponsor trial code: 000175
Date: 02 Apr 2018

STATISTICAL ANALYSIS PLAN

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

000175

Investigational Product:	Mesalamine 2 g Extended Release Granules (Sachet)
Indication:	Maintenance of clinical and endoscopic remission in 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 and modified related places accordingly o Changed to exclude subjects who are rolled over from the placebo group in the 000174 trial via Pathway 1 from the primary analysis, and consequently, the sample size was increased to approximately 260 subjects o Definition of the ITT analysis set was changed to exclude above subjects o Added all randomized and modified ITT analysis sets to the sensitivity analysis o Strata in each analysis set were defined accordingly 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 the 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

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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 000175 based on the Consolidated Protocol Incorporating Amendments 1.0, 2.0, 3.0, and 4.0 dated January 17, 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
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
PMM	Pattern mixture model
PP	Per protocol
PT	Preferred term
QD	Once daily
QTc	Corrected QT interval
SOC	System organ class

Abbreviations	**Meaning of abbreviations in document**
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 the efficacy of mesalamine 2 g extended release granules (sachet) once daily (QD) compared to placebo in the maintenance of clinical and endoscopic remission of ulcerative colitis (UC)

2.1.2 Secondary objective

- To evaluate the efficacy of mesalamine 2 g extended release granules (sachet) utilizing the Clinical and Endoscopic Response Score, Clinical Response Score subset, and frequency of treatment failures
- 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 in remission, defined by the Clinical and Endoscopic Response Score (Table 1) at Month 6 as a score of,

- 0 for rectal bleeding, and
- 0 or 1 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 Secondary endpoints

- The proportion of subjects in clinical remission at Months 2, 4, and 6, defined as a score of 0 for rectal bleeding and 0 or 1 for stool frequency based on Clinical Response Score subset of the Clinical and Endoscopic Response Score
- Time to relapse, defined as number of days from randomization to the day of withdrawal due to escalation of therapy (i.e., surgical therapy, use of steroids, immunosuppressive or immunomodulating drugs, biologics, increase dose of 5 aminosalicylic acid [5-ASA] in any form)
- The proportion of subjects with an increase from baseline in the Clinical and Endoscopic Response Score by 2 or more points in at least 1 component or by 1 or more points in at least 2 components at Month 6
- The change from baseline in serum CRP levels at Months 2, 4, and 6
- The change from baseline in fecal calprotectin levels at Months 2, 4, and 6
- 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 2 g extended release granules (sachet) for maintenance of clinical and endoscopic remission in subjects with UC. Subjects who are in remission can be enrolled in the current trial via 1 of 3 pathways.

- Pathway 1: Subjects who are in remission following 8 weeks of double-blind treatment in Study 000174 can be randomized into Study 000175. The clinical and endoscopic remission criteria for Study 000174 include a 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.

- Pathway 2: Subjects in remission at the end of the 8-week open-label treatment period in Study 000174 will be allowed to be randomized into Study 000175.

- Pathway 3 – de novo: Subjects who did not participate in Study 000174 can also be enrolled; these subjects will have been treated with various medications for UC (excluding biologics and long-term [≥6 months] immunosuppressants) and will have been in remission for <1 year. These de novo subjects will undergo a 72-hour mesalamine washout prior to entering the current trial and will have a Clinical and Endoscopic Response Score assessment to ensure eligibility.

All eligible subjects will be randomized during Visit 1/Day 0 (start of maintenance) to 1 of the following treatments:

- one mesalamine 2 g extended release granules (sachet) QD (2 g/day) OR

- one 2 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. For all subjects, the first dose of investigational medicinal product (IMP) will be administered the day following randomization/Visit 1.

During the 6-month trial period, all subjects will visit the trial site 5 times for safety and efficacy evaluations: baseline, Week 2, and Months 2, 4, and 6. 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 will be performed at baseline and Month 6. After 6 months 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 an endoscopic score of 0 or 1. Whereas, subjects will only have a Clinical Response Score assessment at Months 2 and 4. De novo subjects will have a complete screening visit, and if they are judged to be in clinical and endoscopic remission based on their Clinical and Endoscopic Score at

baseline/randomization, they will continue with the 6 month assessment for safety and efficacy evaluations.

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 (Pathway 3 – de novo). 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 (Pathway 3 – de novo). For subjects rolling over from the 000174 trial (Pathway 1 and 2), 000175 eligibility will be derived from the final end of treatment (EOT) independent central read. A flexible sigmoidoscopy will also be performed at Month 6, which will also be sent to the independent central reader for endoscopic endpoint scoring for all subjects.

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 6 months of treatment. Subjects will be randomized by pathway of enrollment, and Pathway 1 will be further stratified by the treatment group assigned in the 000174 trial.

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

3.2 Determination of Sample Size

The true remission rates at Month 6 for mesalamine 2 g extended release granules (sachet) and placebo regimens were assumed as 68% and 49%, respectively, based on The mesalamine Study Group (1996)(3), Hawkey et al (1997)(4), and Apriso™ package insert (2009)(5). Under these assumptions, a sample size of 120 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. To maintain the power for the primary efficacy analysis that excludes subjects who are rolled over from the placebo group in the 000174 trial via Pathway 1, approximately 260 subjects will be randomized.

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 trial will be summarized with the reason of premature discontinuations.

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%
- Not taking the randomized IMP
- Taking prohibited medications

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 All Randomized Analysis Set

The all randomized analysis set includes all randomized subjects. Analyses for the all randomized analysis set will be conducted according to the randomized treatment regardless of the actual treatment received.

6.2 Intention-To-Treat Analysis Set

The intention-to-treat (ITT) analysis set includes all randomized subjects who were assigned to mesalamine 4 g extended release granules in the 000174 trial or randomized via Pathways 2 or 3. Analyses for the ITT analysis set will be conducted according to the randomized treatment regardless of the actual treatment received.

6.3 Modified ITT Analysis Set

The modified ITT (mITT) analysis set includes all subjects who receive at least 1 dose of IMP in the ITT analysis set. Analyses for the mITT analysis set will be conducted according to the randomized treatment regardless of the actual treatment received.

6.4 Per Protocol Analysis Set

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

6.5 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.

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.

Following categorical summaries will be made:

- < 14 days, 14 - < 28 days, 28 - <56 days, 56 - <84 days, 84 - <112 days, 112 - <140 days, 140 - <168 days, and 168 days or more
- At least 1 day, at least 14 days, at least 28 days, at least 56 days, at least 84 days, at least 112 days, at least 140 days, and at least 168 days

8.2 Treatment Compliance

The overall compliance 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.

All secondary endpoints will be tested without adjustment for multiplicity.

Randomization strata will be included in stratified analyses for efficacy endpoints. For the ITT, mITT, and PP analysis sets, randomization strata will be defined as follows:

- Stratum 1: Pathway 1 (mesalamine 4 g extended release granules arm in the 000174 trial)
- Stratum 2: Pathway 2
- Stratum 3: Pathway 3

Randomization strata for the all randomized analysis set will be defined as follows:

- Stratum 1: Pathway 1a (placebo arm in the 000174 trial)
- Stratum 2: Pathway 1b (mesalamine 4 g extended release granules arm in the 000174 trial)
- Stratum 3: Pathway 2
- Stratum 4: Pathway 3

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). Handling of 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 shows the scheduled trial day and window for each analysis visit.

Table 2 Scheduled trial day and window for analysis visits

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

Analysis visit	Scheduled trial day	Window
Week 2	Day 14	Day 1 to Day 35
Month 2	Day 56	Day 36 to Day 84
Month 4	Day 112	Day 85 to Day 140
Month 6	Day 168	Day 141 or after

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.

9.2 Primary Endpoint(s)

9.2.1 Primary Variable(s) Analysis

The primary efficacy analysis will be based on the ITT analysis set. The proportion of subjects in remission, defined as rectal bleeding of 0 and stool frequency scores of 0 or 1 with an endoscopic score of 0 or 1 in the Clinical and Endoscopic Response Score at Month 6, will be assessed by the Mantel-Haenszel test stratified by the randomization strata at a two-sided 0.05 significance level. Subjects who discontinue the double-blind regimen before Month 6, as well as subjects with missing remission assessment at Month 6, will be considered not having met the remission criteria. The common odds ratio will be estimated using the Mantel-Haenszel adjusted odds ratio estimate, and its 95% confidence interval will be provided. The homogeneity of odds ratios across the randomization strata will be tested by the Breslow-Day test at a 0.05 significance level, and the odds ratio for each stratum will be presented in forest plots. The quantitative or qualitative nature of the possible treatment by stratum interaction will be assessed and discussed.

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 all randomized analysis set
- Analysis on the mITT analysis set
- Analysis on the PP analysis set
- Analysis using the last observed Clinical and Endoscopic Response Score

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 Months 2, 4, and 6 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 Month 6 Clinical Response scores have been imputed, Month 6 Endoscopic Response score will be imputed by regression-based imputation models using treatment group, baseline characteristics, and Month 6 Clinical Response scores as the predictors. Based on the imputed Clinical and Endoscopic Response scores, the remission status at Month 6 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)(6) .

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 Month 6 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(7); Ratitch & O'Kelly, 2011(8)).

The primary endpoint will also be analyzed for the following subgroups for the ITT analysis set using the same method as the primary efficacy analysis. 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)
- Geographical region (North America including US and Canada or rest of the world)

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

9.3 Secondary Endpoint(s)

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

- The proportion of subjects in clinical remission at Months 2, 4, and 6, defined as a score of 0 for both rectal bleeding and stool frequency based on Clinical Response Score subset of the Clinical and Endoscopic Response Score
- Time to relapse, defined as number of days from randomization to the day of withdrawal due to escalation of therapy (i.e., surgical therapy, use of steroids, immunosuppressive or immunomodulating drugs, biologics, increase dose of 5 ASA in any form)

- The proportion of subjects with an increase from baseline in the Clinical and Endoscopic Response Score by 2 or more points in at least 1 component or by 1 or more points in at least 2 components at Month 6
- The change from baseline in serum CRP levels at Months 2, 4, and 6
- The change from baseline in fecal calprotectin levels at Months 2, 4, and 6

The proportion of subjects in clinical remission at Months 2, 4, and 6 will be analyzed by the generalized estimating equations (GEE) approach as longitudinal binary outcomes. The model will include the randomization strata, 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 6 months 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 relapse will be analyzed by the log-rank test stratified by the randomization strata. If a subject does not have the relapse by Day 168, the time to relapse will be censored at the earlier of the day that the last visit day or Day 168. The hazard ratio of relapse for mesalamine relative to placebo will be estimated (including the 95% CI) using the stratified Cox proportional hazards model with treatment group as a factor and the randomization strata as a stratification variable.

The proportion of subjects with an increase from baseline in the Clinical and Endoscopic Response Score by 2 or more points in at least 1 component or by 1 or more points in at least 2 components at Month 6 will be analyzed using the same statistical method used for the primary efficacy analysis.

The change from baseline in serum CRP levels and fecal calprotectin levels at Months 2, 4, and 6 will be analyzed by repeated-measures analysis of covariance (ANCOVA) models that include the randomization strata, 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 6 months 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.

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)(9) 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)(10). 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.

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 Months 2, 4, and 6 will be analyzed by repeated-measures ANCOVA models that include treatment, randomization strata, 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.

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 Medical Dictionary for Regulatory Activities (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.

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

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.

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 treatment will include the last post-baseline observation during the treatment 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 treatment 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, Week 2, Months 2, 4, and 6 for each laboratory variable. The Week 2, Months 2, 4, and 6 measurements for the analysis will be identified based on the method described in Section 9.1.

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 treatment 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)

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 treatment for each laboratory variable will be summarized by the baseline category (i.e., low, normal, high, absent, or present).

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, and treatment 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 treatment will include the last post-baseline observation during the treatment.

10.4.1.1 Summary Statistics

Change and percentage change from baseline at end of treatment 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, Week 2, Months 2, 4, and 6 for each vital sign variable. The Weeks 2, Months 2, 4, and 6 measurements for the analysis will be identified based on the method described in Section 9.1.

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 treatment for each vital sign variable will be summarized.

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, and treatment 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 variables measured after the first dose of IMP. End of treatment will include the last post-baseline observation during the treatment 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 treatment 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 Month 6 for each ECG variable. The Month 6 measurement for the analysis will be identified based on the method described in Section 9.1.

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 treatment for each ECG variable will be summarized.

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, and treatment 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

	Screening[a]	Baseline/ Randomization[b]	Intermediate	Intermediate	Intermediate	End of Treatment/ Early Withdrawal
Visit	**0**	**1**	**2**	**3**	**4**	**5**
Month[c]	**Week - 3**	**Month 0**	**Week 2**	**Month 2**	**Month 4**	**Month 6**
Trial Day (visit window)	**Up to Day -21**	**Day 0**	**Day 14 (±3 days)**	**Day 56 (±5 days)**	**Day 112 (±5 days)**	**Day 168 (±5 days)**
Written informed consent	X	X[d]				
Inclusion/exclusion criteria review	X	X				
Medical history	X	X				
Physical examination, including weight	X	X	X	X	X	X
Height	X					
Vital signs	X	X	X	X	X	X
12-lead electrocardiogram	X					X
Demographic data	X					
Serum/urine pregnancy test[e]	X	X				X
Standard urinalysis[f]	X[g]					X
Drug and alcohol history	X					
Immunological testing for HBV, HCV, and HIV	X					
Estimated creatinine clearance	X[g]		X	X	X	X
Safety hematology, coagulation, and chemistry	X[g]		X[m]	X	X	X
Randomization		X				
Prior and concomitant medications	X	X	X	X	X	X
Serum CRP		X[a]		X	X	X
Fecal calprotectin stool sample		X[a]		X	X	X
Clinical Response Score (stool frequency and rectal bleeding scores)	X			X	X	
Calculation of clinical and Endoscopic Response Score		X[h]				X
Flexible sigmoidoscopy[i] / Central reading	X					X
HRQoL questionnaire: IBDQ		X[a]		X	X	X
Adverse event recording[j]	X	X	X	X	X	X
Distribution of trial medication		X		X	X	
First administration of trial medication		X[l]				
Trial medication collection/distribution			X[n]	X	X	X
Trial medication compliance			X	X	X	X
Subject diary activation	X	X[d]				
Subject diary data review[k]		X	X	X	X	X

Note: All subjects who discontinue treatment will complete end-of-treatment assessments.

a For Pathway 3 - *de novo* subjects only (a complete screening visit, including flexible sigmoidoscopy, which will be scheduled at screening and completed at least (4) days prior to randomization).

b Subjects in Pathways 1 and 2 will be consented at Visit 1/Baseline. The complete screening assessments will be taken from Study 000174 end-of-treatment visit and eligibility (all inclusion/exclusion criteria) will be reassessed.

c Month equals 4 weeks; week equals 7 days.

d Pathways 1 and 2 only.

e For females of childbearing age or <1 year postmenopausal; if positive, the subject will not be enrolled in the trial. A serum pregnancy test will be performed at Visit 0 (screening) for Pathway 3 – *de novo* only. Urine pregnancy tests will be performed for all subjects at Visit 1 (baseline/Day 0) and Visit 5 (Month 6) or early withdrawal.
f If positive for blood, leucocytes, or nitrite, perform microscopic urinalysis.
g Results must be available at randomization (Visit 1).
h For all subjects; Study 000174 end-of-treatment Clinical and Endoscopic Response Score assessments will be utilized for Pathways 1 and 2 only.
i Baseline flexible sigmoidoscopy/colonoscopy for Pathway 3 – *de novo* subjects will be scheduled at screening (Visit 0) and completed at least 4 days prior to randomization (Visit 1) to allow sufficient time for the central reading.
j Adverse events are collected from the signing of informed consent.
k Subject daily diary data will be collected electronically and daily diary compliance will be assessed.
l IMP to be distributed at Day 0, and will be taken the following day (Day 1).
m No coagulation panel.
n Subjects will bring IMP kit to site for assessment of compliance; this same kit will be used until Visit 3.