STATISTICAL ANALYSIS PLAN

Protocol No.:	SPD476-319
Protocol Title:	A Phase 3, Multicenter, Randomized, Double-blind Study to Determine the Safety and Efficacy of MMX Mesalamine/Mesalazine in Pediatric Subjects with Mild to Moderate Ulcerative Colitis, in both Acute and Maintenance Phases
Drug:	SPD476, MMX Mesalamine/mesalazine
Sponsor:	Shire Development LLC. 300 Shire Way Lexington, MA 02421
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ABBREVIATIONS

5-ASA	5-aminosalicylic acid
AE	adverse event
ATC	anatomical therapeutic class
BMI	body mass index
CMH	Cochran-Mantel-Haenszel
DUCS	Daily Ulcerative Colitis Scale
DMC	data monitoring committee
eCRF	electronic case report form
e-diary	electronic diary
FDA	Food and Drug Administration
FoTA	Final on Treatment Assessment
IRT	interactive response technology
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMX®	Multi Matrix System
PCI	potentially clinically important
PGA	Physician's Global Assessment
PRO	patient reported outcome
PUCAI	Pediatric Ulcerative Colitis Activity Index
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TEAE	treatment-emergent adverse event
UC	ulcerative colitis
UC-DAI	Ulcerative Colitis Disease Activity Index
WHO-DRUG	World Health Organization Drug Dictionary

1. INTRODUCTION

1.1 Purpose of the Statistical Analysis Plan

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy and safety data as described in the final study protocol SPD476-319 Version 6.0 dated 10 Apr 2017. Specifications for tables, figures, and listings are contained in a separate document.

1.2 Background

This is a phase 3, multicenter, randomized, double blind study to determine the safety and efficacy of Multi Matrix System (MMX) mesalamine/mesalazine in pediatric subjects (aged 5-17 years) with mild to moderate ulcerative colitis (UC). This study is comprised of an 8-week Double-blind Acute Phase and a 26-week Double-blind Maintenance Phase. Each phase includes 2 arms, and subjects will be randomized to 1 of 2 doses (low or high) of MMX mesalamine/mesalazine (900-4800mg/day, given once daily) at the beginning of each phase. Randomization will be in a 1:1 ratio stratified by body weight group.

The data from this study will:

- Aid in selection of appropriate doses in the pediatric population
- Determine whether MMX mesalamine/mesalazine is safe and effective for use in children and adolescents (aged 5-17 years) with mild to moderate UC or who are in remission.

The study allows all subjects to receive active MMX mesalamine/mesalazine. The doses for the study were determined from pharmacokinetic modeling using data from the SPD476-112 study, a pharmacokinetic study in children and adolescents with mild to moderate UC.

1.3 Study Rationale

MMX mesalamine/mesalazine is approved for both the induction of remission in adult patients with mild to moderate UC and for maintenance of remission of UC. Currently, limited data are available on the safety and efficacy of MMX mesalamine/mesalazine in children and adolescents with UC.

This study, a PREA post approval commitment with FDA, is designed to determine the appropriate dosage of MMX mesalamine/mesalazine for once-daily dosing across a range of weight groups, in children and adolescents aged 5-17 years with mild to moderate UC or who are in remission.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective of the Double-blind Acute Phase of the study is to assess clinical response to MMX mesalamine/mesalazine between a low and high dose in children and adolescents aged 5-17 years with mild to moderate UC.

The primary objective of the Double-blind Maintenance Phase of the study is to assess clinical response to MMX mesalamine/mesalazine between a low and high dose in children and adolescents aged 5-17 years who are in remission.

2.2 Secondary Objectives

2.2.1 Double-blind Acute Phase

- To assess clinical and endoscopic response to treatment with MMX mesalamine/mesalazine between a low and high dose in children and adolescents aged 5-17 years with mild to moderate UC in the Double-blind Acute Phase.
- To assess changes in the Daily Ulcerative Colitis Scale (DUCS) for children and caregivers between a low and high dose of MMX mesalamine/mesalazine in children and adolescents aged 5-17 years with mild to moderate UC in the Double-blind Acute Phase.
- To assess improvement in Pediatric Ulcerative Colitis Activity Index (PUCAI) score between a low and high dose of MMX mesalamine/mesalazine in children and adolescents aged 5-17 years with mild to moderate UC in the Double-blind Acute Phase.

2.2.2 Double-blind Maintenance Phase

- To assess clinical and endoscopic response to treatment with MMX mesalamine/mesalazine between a low and high dose in children and adolescents aged 5-17 years who are in remission in the Double-blind Maintenance Phase.
- To assess changes in the DUCS for children and caregivers between a low and high dose of MMX mesalamine/mesalazine in children and adolescents aged 5-17 years who are in remission in the Double-blind Maintenance Phase.
- To assess remission using the PUCAI score between a low and high dose of MMX mesalamine/mesalazine in children and adolescents aged 5-17 years who are in remission in the Double-blind Maintenance Phase.

2.2.3 Safety

To evaluate the safety and tolerability of a low and high dose of MMX mesalamine/mesalazine in children and adolescents aged 5-17 years with mild to moderate UC, in the Double-blind Acute Phase, the Open-label Acute Phase, and the Double-blind Maintenance Phase.

2.3 Exploratory Objectives

[redacted]

3. STUDY DESIGN

3.1 General Description

This study will be conducted in children and adolescents (aged 5-17 years) to collect data on the safety and efficacy of MMX mesalazine/mesalamine in this population. This study is a PREA post-approval commitment with the US FDA and is intended to provide estimates of clinical response for 2 doses (low and high) across a range of weight groups.

This study will enroll male and female children and adolescents aged 5-17 years. This is a prospective, parallel-group study with an 8-week Double-blind Acute Phase, and a 26-week Double-blind Maintenance Phase. More than 100 subjects will be screened, and up to 80 subjects will be enrolled in the Double-blind Acute Phase of the study. After agreement with FDA, the sample size for the Double-blind Acute Phase has been reduced to 53 subjects due to difficulties with recruitment.

More than 65 subjects will be screened (in addition to an expected 28 subjects who will enter the Double-blind Maintenance Phase from one of the Acute Phases) and at least 80 subjects will be enrolled in the Double-blind Maintenance Phase of the study.

Each phase includes 2 treatment arms, and subjects will be randomized at the beginning of each phase to 1 of 2 doses (low and high dose) of MMX mesalamine/mesalazine (900-4800mg/day, given once daily), stratified by weight group. There is an additional 8-week, Open-label Acute Phase for subjects who do not achieve a clinical response or who have withdrawn from the Double-blind Acute Phase and have met certain criteria (see Figure 1). Clinical response is defined as partial Ulcerative Colitis Disease Activity Index (UC-DAI) ≤1 (with rectal bleeding=0 and stool frequency ≤1 and Physician's Global Assessment [PGA] =0) at the end of the Double-blind Acute Phase. In this Open-label Acute Phase, subjects are treated with the high dose of MMX mesalamine/mesalazine for their weight group.

Subjects with a clinical response after completion of treatment in either the Double-blind Acute Phase or the Open-label Acute Phase will be eligible to enter the Double-blind Maintenance Phase based on partial UC-DAI score (i.e., without additional endoscopy).

Subjects without a clinical response after completion of acute treatment in the Open-label Acute Phase must be withdrawn.

Subjects may enter the Double-blind Maintenance Phase directly following the Baseline Visit (Visit 2) if they have a partial UC-DAI ≤1 (with rectal bleeding=0 and stool frequency ≤1 and PGA=0) and with mucosal appearance (endoscopy score) = 0 or 1 at that visit.

MMX mesalamine/mesalazine is dosed once daily by mouth. The selection of doses in this study is based on an approximate average of 43mg/kg for the low dose and 85mg/kg for the high dose in the 3 lower weight groups (18 to ≤23kg, >23 to ≤35kg and >35 to ≤50kg). These doses were selected based on standard of care dosing for other 5-ASA products in the pediatric population and pharmacokinetic dosing results. The dosing for the highest weight group (>50 to ≤90kg) is based on adult UC experience.

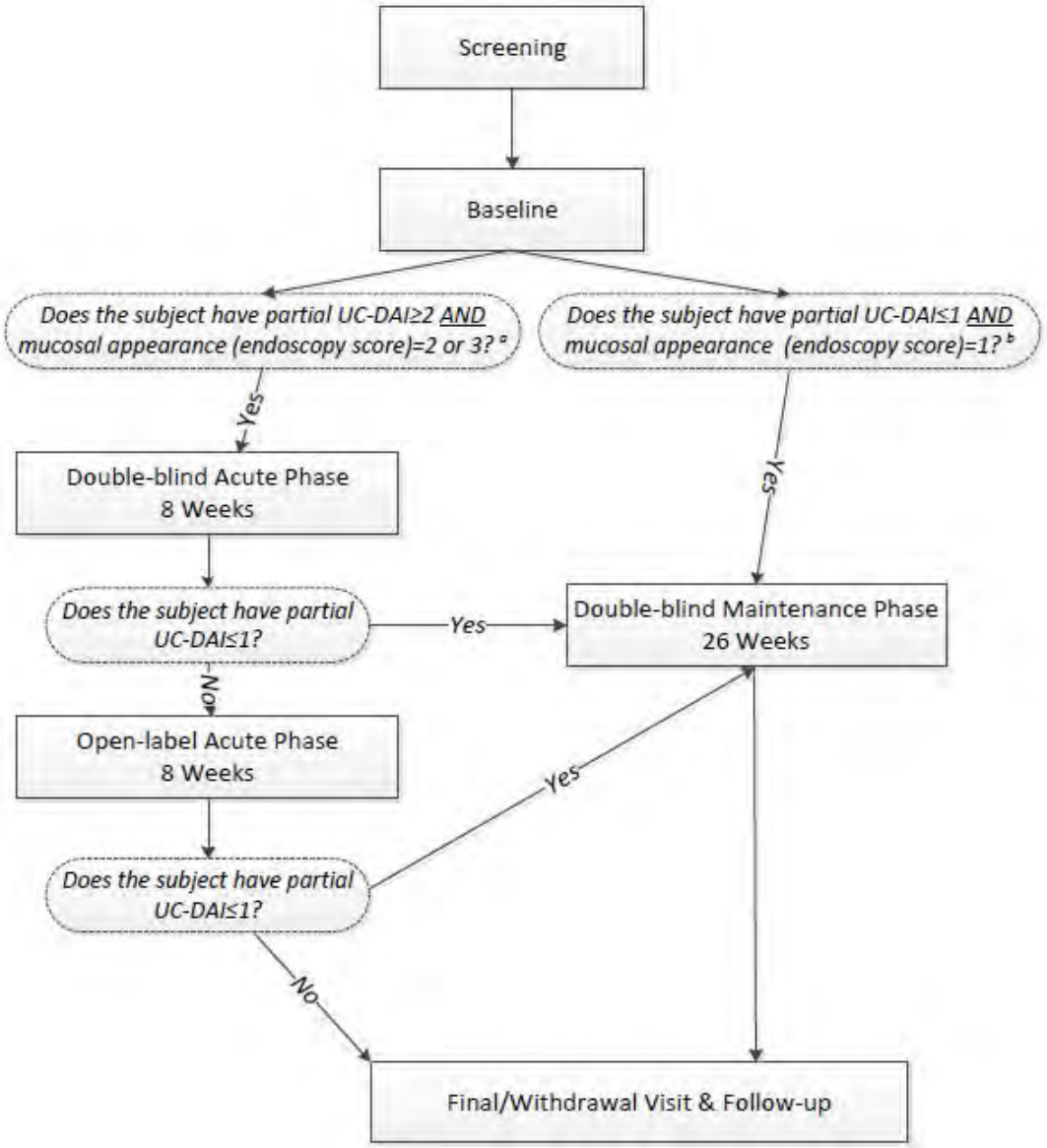
Minimum enrollment criteria have been agreed with FDA as follows, based on subject weight group:

Table 1: Minimally Required Number of Subjects per Weight Group

Weight Group	Low Dose (mg/day)	High Dose (mg/day)	Number of Subjects in Combined Low and High Dose[a]
18 to ≤23kg	900	1800	2
>23 to ≤35kg	1200	2400	12
>35 to ≤50kg	1800	3600	18
>50 to ≤90kg	2400	4800	36

[a] Randomization will be stratified by weight group with the aim of creating balance between the 2 dose groups within a weight group

Figure 1: Study Design Flow Chart



PGA=Physician's Global Assessment; UC-DAI=Ulcerative Colitis Disease Activity Index.

[a] Subjects with partial UC-DAI ≥2 (with a combined rectal bleeding and stool frequency score ≥1 and PGA=1 or 2) and with mucosal appearance (endoscopy score)=2 or 3.

[b] Subjects with partial UC-DAI ≤1 (with rectal bleeding=0 and stool frequency ≤1 and PGA=0) and with mucosal appearance (endoscopy score)=0 or 1.

Notes: Solid boxes indicate study phases. Dashed ellipses indicate decision points.

Subjects will initially be randomized into either the 8-week Double-blind Acute Phase or the 26-week Double-blind Maintenance Phase based on partial UC-DAI and mucosal appearance scores. Subjects who do not achieve a clinical response or who have withdrawn from the Double-blind Acute Phase after a minimum of 2 weeks and, in the investigator's opinion, have not benefited from treatment in the Double-blind Acute Phase may enter the Open-label Phase. Subjects without a clinical response after completion of acute treatment in the Open-label Acute Phase must be withdrawn.

3.2 Discussion of Study Design, Including the Choice of Control Groups

The inclusion of placebo and standard of care arms were considered in the design of this study. The use of placebo was considered not feasible given the alternative treatments currently available to children and adolescents with UC. As standard of care varies and there is no standard formulation or dose of 5-ASA licensed and approved across regions, a standard of care/comparator arm was not included.

3.3 Method of Assigning Subjects to Treatment Groups

This study includes 2 double-blind phases with low- and high-dose MMX mesalamine/mesalazine. The actual double-blind treatment given to individual subjects is determined by a randomization schedule stratified by weight group. Randomization will be a 1:1 ratio between low and high doses.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

The randomization number represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined.

Subjects eligible for either the Double-blind Acute or the Double-blind Maintenance Phase can be re-randomized if they initially failed randomization for the following reasons: incorrect use of IVRS, late or missing central laboratory or endoscopy results, or other reasons of this type as long as they meet inclusion and exclusion criteria. Re-randomization can only take place after consultation with the medical monitor.

Individual subject doses in the Double-blind Acute Phase are automatically assigned by the interactive response technology (IRT) based on subject weight group at the Baseline Visit (Visit 2). If the subject is directly entering the Double-blind Maintenance Phase, individual doses are also automatically assigned by the IRT based on subject weight group at the Baseline Visit (Visit 2).

Individual subject open-label treatment is automatically assigned by the IRT and will be the high dose based on the subject's weight group at Visit 3.2 (Week 8/Withdrawal of the Double-blind Acute Phase).

Individual subject double-blind doses for subjects being re-randomized to the Double-blind Maintenance Phase after completion of treatment at Visit 3.2 (Week 8 of the Double-blind Acute Phase) or Visit 4.2 (Week 8 of the Open-label Acute Phase) are automatically assigned by the IRT based on subject weight group at the time of re-randomization.

3.4 Blinding the Treatment Assignment

This study includes double-blind treatment in the Double-blind Acute Phase and Double-blind Maintenance Phase.

The actual double-blind treatment given to individual subjects is determined by a randomization schedule which will be automatically assigned by the interactive response technology (IRT). Placebo, which exactly matches the investigational product, will be used in the blister packs to provide the same number and size tablets for each of the doses within a weight group and maintain the blind between the low and high dose groups.

3.5 Determination of Sample Size

This will be an estimation study with no formal hypothesis testing; therefore, this study is not powered to detect differences between treatment groups. More than 100 subjects will be screened and up to 80 subjects will be enrolled in the Double-blind Acute Phase of the study. After agreement with FDA, the sample size for the Double-blind Acute Phase has been reduced to 53 subjects due to difficulties with recruitment.

More than 65 subjects will be screened (in addition to an expected 28 subjects who will enter the Double-blind Maintenance Phase from one of the Acute Phases) and at least 80 subjects will be enrolled in the Double-blind Maintenance Phase of the study.

The sample size was chosen based on practical considerations and on agreement with the US FDA.

4. EFFICACY AND SAFETY VARIABLES

4.1 Schedule of Assessments

Table 5, Table 6, and Table 7 in Section 11 present schematics of the study separately for each treatment phase.

4.2 Efficacy Assessments

4.2.1 Modified Full UC-DAI Score

The full UC-DAI is widely used to assess treatment efficacy in subjects with mild to moderate UC (Schroeder et al., 1987; Sutherland et al., 1987). It consists of 4 individual parameters: stool frequency, rectal bleeding, endoscopy score (mucosal appearance), and PGA. For the purpose of this study, the standard UC-DAI scale has been modified so that an endoscopy score of mild disease does not include friability; instead, friability will be scored as 2: moderate disease.

Please see a description of stool frequency, rectal bleeding and PGA in Section 4.2.2.

All 4 parameters will be assessed individually on a scale from 0-3; the maximum total modified full UC-DAI score is 12.0.

Stool Frequency Score:
- 0 = Normal
- 1 = 1-2 more than normal/day
- 2 = 3-4 more than normal/day
- 3 = >4 more than normal day

Rectal bleeding (most severe bleeding of the day) Score:
- 0 = None
- 1 = Streaks of blood
- 2 = Obvious blood
- 3 = Mostly blood

Mucosal Appearance (endoscopy score):
- 0 = Normal (intact vascular pattern; no friability or granulation)
- 1 = Mild (erythema, decreased vascular pattern, minimal granularity)
- 2 = Moderate (marked erythema, granularity, friability, absent vascular pattern, bleeding with minimal trauma, no ulcerations)
- 3 = Severe (ulceration, spontaneous bleeding)

Physician's Global Assessment:
- 0 = No active disease
- 1 = Mild disease
- 2 = Moderate disease
- 3 = Severe disease

The modified full UC-DAI score will be calculated at Baseline (Visit 2), Week 8 of the Double-blind Acute Phase (Withdrawal) for subjects not entering into the Open-label Acute Phase, Week 8 of the Open-label Acute Phase (Withdrawal) for subjects who have not had endoscopy at the end of the Double-blind Acute Phase, and Week 26 of the Double-blind Maintenance Phase (Withdrawal) visits. The total score will be calculated by summing the individual scores for the 4 parameters (endoscopy score will be based on the central reader's score). The site is not required to calculate the full UC-DAI; this will be calculated centrally using e-diary and eCRF data.

For determination of the modified full UC-DAI, the average of the symptom scores of the last available 3 days within the 5-day period immediately prior to study visits where endoscopic data are available, will be used. No symptom data older than 5 days prior to the study visit will be used. Data collected on days when bowel preparations have been administered or when endoscopy has been performed will be excluded.

An endoscopy must be performed and mucosal appearance scored within 21 days prior to the Screening Visit (Visit 1), during the Screening period or at the Baseline Visit (Visit 2) depending on the subject's UC history and phase of the study into which they are entering. All efforts should be made to perform endoscopy at Week 8 of the Double-blind Acute Phase (or Week 8 of the Open-label Acute Phase, as applicable), Week 26 of the Double-blind Maintenance Phase, or the subject's withdrawal if different from these visits.

Endoscopies will be centrally read and scored for this study and endoscopic video or photographs must be provided to the central reader for each endoscopy performed. Video images are preferred; however, photographic images will be accepted when video images are not of sufficient quality, as determined by the central reader during individual site image evaluation prior to enrollment at the site. Further details of requirements for video and photographic images will be provided to study sites under separate cover by the central reader. All endoscopies should be performed by the same investigator/endoscopist, if possible, to ensure consistency in endoscopy.

4.2.2 Partial UC-DAI Score

The partial UC-DAI score is based on the individual parameters of the modified full UC-DAI without the endoscopic component. (Please see Section 4.2.1 for a description of the modified full UC-DAI.) It includes stool frequency, rectal bleeding, and PGA only. All 3 parameters will be assessed individually on a scale from 0-3; the maximum total partial UC-DAI score is 9.0.

Subjects' symptoms (rectal bleeding and stool frequency) will be reported by the subjects/caregivers in the e-diary once a day before bedtime starting from the evening of the Screening Visit (Visit 1) through the Baseline Visit (Visit 2). Subjects' symptoms are completed once a day before bedtime for the 5 days immediately prior to Visits 3, 3.1, and 3.2 of the Double-blind Acute Phase, Visits 4, 4.1, 4.2 of the Open-label Acute Phase and Visits 5.1 and 5.2 of the Double-blind Maintenance Phase. Symptom data should also be reported as soon as a subject's symptoms suggest that they might be experiencing an acute flare during the Double-blind Maintenance Phase, and they should contact the site to arrange for an unscheduled visit. In this case, symptoms should be entered for 5 days immediately prior to the unscheduled visit, if possible.

Stool frequency and rectal bleeding will be assessed on a scale from 0-3. Scores will be based on 1 of 2 versions of e-diary questions. One version is for children and adolescents aged 11-17 years and the other is for caregivers of children aged 5-10 years. Subject age at the beginning of their current study phase will determine which version of the e-diary will be completed for the entire phase; the version being completed will not change from caregiver to subject completion during a phase. However, the version should change from caregiver completion to subject completion for the next phase, if applicable based on a subject's age change.

Questions and responses for children and adolescents aged 11-17 years:

How many more times did you poop than you normally do since you went to bed last night?

- I didn't poop more than I normally do
- I pooped 1 or 2 more times than normal
- I pooped 3 or 4 more times than normal
- I pooped 5 or more times than normal.

Did you have blood in your poop?

- I didn't see any blood in my poop
- I saw streaks of blood (a small amount) in my poop
- I saw some blood (more than a small amount) in my poop
- I saw mostly blood (a lot) in my poop.

Questions and responses for caregivers of children aged 5-10 years:

Based on what you observed, how many more times did your child have a bowel movement than they normally do since they went to bed last night?

- They didn't have more bowel movements than they normally do
- They had 1 or 2 more bowel movements than normal
- They had 3 or 4 more bowel movements than normal
- They had 5 or more bowel movements than normal

Based on what you observed, did your child have blood in their stool?

- I didn't see any blood in my child's stool
- I saw streaks of blood (a small amount) in my child's stool
- I saw some blood (more than a small amount) in my child's stool
- I saw mostly blood (a lot) in my child's stool.

For determination of the partial UC-DAI, the average of the symptom scores of the last available 3 days within the 5-day period immediately prior to the study visit will be used. No symptom data older than 5 days prior to the study visit will be used. Data collected on days when bowel preparations have been administered or when endoscopy has been performed will be excluded.

Approximately 4 to 7 days prior to the Baseline Visit (Visit 2) and prior to each subsequent visit, it is recommended that site staff telephone the subject or the subject's caregiver to remind them to enter UC-DAI symptoms (rectal bleeding and stool frequency) into the e-diary every night, even if the subject has no symptoms. A missed day's data may be entered until 12:00 hours the following day.

A minimum of 1 score each for stool frequency and rectal bleeding must be available in order to randomize subjects into either the Double-blind Acute Phase or the Double-blind Maintenance Phase. If no data are available, the average value will be considered missing and the subject will be considered a screen failure.

Calculations of average stool frequency and rectal bleeding scores will proceed as follows:

- If symptom scores from the last 3 days are available, average = (x1+x2+x3)/3; the average value should be rounded up to 1 decimal place:
    - For example: (0+1+0)/3 = 0.3333; value = 0.3; (1+0+1)/3=0.666666; value=0.7; (2+2+2)/3=2.0
- If symptom scores from the last 2 days are available, average = (x1+x2)/2; the average value should be rounded up to 1 decimal place.
- If symptom scores from only 1 day are available, average = (x1/1) = x1.

The PGA will be performed at all visits where the partial UC-DAI score is calculated by the study site, and is scored on a scale from 0-3, where 0=no active disease, 1=mild disease, 2=moderate disease, and 3=severe disease. The PGA should be performed by the same investigator at all visits, if possible, for consistency in evaluation.

Scoring of the PGA by the investigator should take into account the following parameters:

- Rectal bleeding
- Stool frequency and consistency
- Night-time bowel movements
- Abdominal pain
- Impact to daily activities
- Physical findings
- Endoscopic findings (if endoscopy is performed).

The PGA is to be recorded in source documentation and added to the average stool frequency and average rectal bleeding scores to calculate the partial UC-DAI score. Sites should not perform rounding of partial UC-DAI scores. The average stool frequency and rectal bleeding scores will be calculated and available to the investigator through a report from the e-diary provider.

4.3 Other Clinical Outcomes Assessments

4.3.1 Daily Ulcerative Colitis Scale for Children and Caregivers (DUCS)

Shire has developed an electronic daily sign and symptom diary, the DUCS. Two versions have been developed: 1 PRO to be self-completed by children aged 8-17 years and 1 ObsRO to be completed by caregivers of children aged 5-10 years. Both the PRO and ObsRO will be completed by children aged 8-10 years; however, the ObsRO will be used for the secondary endpoint analysis. The data obtained from the PRO in this age group will provide information for future use to determine if children/adolescents can reliably complete the PRO.

A separate SAP has been developed for DUCS.

4.3.2 Overall Current Health

An Overall Current Health item will be included in the e-diary. The Overall Current Health item has been tested in cognitive debriefing interviews with the DUCS.

4.3.3 Global Change in Health

The Global Change in Health item assesses the subject's (aged 11-17 years) or caregiver's (for children aged 5-10 years) perception of change in health since starting the study and will be administered via paper in this study. This item has been tested in cognitive debriefing interviews with the DUCS.

4.3.4 Pediatric Ulcerative Colitis Activity Index

The PUCAI is a physician-administered measure that focuses on 6 key signs and symptoms of UC and activity limitations (Turner et al., 2007). The PUCAI yields a total score ranging from 0-85 with higher scores being worse. Recommended cut-off scores to differentiate disease activity are <10 (remission); 11-30 (mild); 31-64 (moderate) and >65 (severe) (Turner et al., 2009). Evaluation of the construct validity of the PUCAI revealed that it was highly correlated with physician's global assessment of disease activity and PUCAI scores were highly predictive of the need for escalating medical therapy (Turner et al., 2009).

Only sites who have executed a sub-license with Shire for PUCAI use will be able to collect PUCAI data for the study.

Item	Points
1. Abdominal pain	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
2. Rectal bleeding	
None	0
Small amount only, in less than 50% of stools	10
Small amount with most stools	20
Large amount (>50% of the stool content)	30
3. Stool consistency of most stools	
Formed	0
Partially formed	5
Completely unformed	10
4. Number of stools per 24 hours	
0–2	0
3–5	5
6–8	10
>8	15
5. Nocturnal stools (any episode causing wakening)	
No	0
Yes	10
6. Activity level	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
Sum of PUCAI (0–85)	

4.3.5 IMPACT III

The IMPACT questionnaire is a disease-specific health-related quality-of-life questionnaire developed for use in pediatric inflammatory bowel disease through a process of patient interviews and analysis of patient responses to an item-reduction questionnaire. This is a self-administered questionnaire, and data will be collected via paper in this study.

The IMPACT questionnaire has been studied to determine its feasibility, reliability, and validity. It was found to be a valid and reliable reflection of health-related quality of life of older children and adolescents with both UC and Crohn's disease (Otley et al., 2002).

In this study, the IMPACT III will be used. This is the current version of the questionnaire, adapted from IMPACT II, which was developed in 2002. The original version of IMPACT was developed in 1999. IMPACT III contains 35 items in 6 domains. The Bowel Symptoms domain and the 4 matching symptom items between the IMPACT III and the DUCS will be used to evaluate convergent validity of the DUCS.

The IMPACT III questionnaire has 35 questions, each with 5 Likert responses that are scored 1, 2, 3, 4, or 5, such that a higher score corresponds to a better quality of life. The questions are grouped into 5 domains, each of which is scored by adding the scores of the questions therein. A total score is obtained by adding the scores of all of the questions. The total score and the domain scores are computed only if the number of missing responses is no more than the maximum number in the table below.

Domain Name (range of scores)	**Question numbers (Maximum number of missing responses)**
Body Image (3 – 15)	7, 15, 33 (0)
Bowel Symptoms (7 – 35)	1, 3, 10, 19, 21, 25, 31 (1)
Emotional Functioning (7 – 35)	4, 5, 11, 12, 13, 16, 29 (1)
Social Functioning (12 – 60)	8, 9, 14, 17, 18, 20, 23, 26, 27, 30, 34, 35 (1)
Systemic Symptoms (3 – 15)	6, 28, 32 (0)
Treatment/Interventions (3 - 15)	2, 22, 24 (0)
Total Score (35 – 175)	1 – 35 (3)

The IMPACT is valid for children and adolescents aged 9-17 years old and is completed by the subject. Children/adolescent aged 9-17 years who cannot complete the questionnaire independently, may be assisted by an adult who is not the child's guardian or relative. Children who are 8 years old may complete the IMPACT with assistance from an adult who is not the child's guardian or relative. Children under the age of 8 years old will not complete the IMPACT.

4.4 Safety Assessments

4.4.1 Medical and Medication History

At screening, the subject's medical history (including UC history) and concomitant medications will be reviewed. Any new medical events or changes in intensity from the Screening Visit (Visit 1) noted during the study should be evaluated for report as an AE. New medications or changes to existing medications must be added or updated as appropriate. Adverse Event Assessments

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (e.g., "Have you had any health problems since your last visit?"). Adverse events are collected from the time informed consent is signed.

In addition, any symptoms/conditions reported during assessments or collected via structured data collection will be evaluated by the investigator at each study visit to determine whether these are AEs.

4.4.2 Vital Signs

Vital signs include blood pressure and pulse. Blood pressure should be determined by cuff (using the same method, the same arm, and in the same position throughout the study). Any clinically significant deviations from the Baseline Visit (Visit 2) vital signs which are deemed clinically significant in the opinion of the investigator are to be recorded as an AE.

Measurements of vital signs (blood pressure and pulse) will be performed at all study visits. Blood pressure and pulse will be determined in the sitting position (after 5 minutes).

4.4.3 Height and Weight

Height will be assessed at the Screening Visit (Visit 1) and at the final visit of each phase. Weight will be assessed at the Screening Visit (Visit 1), the Baseline Visit (Visit 2) and at the final visit of each phase.

4.4.4 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the laboratory's normal procedures. Reference ranges are to be supplied by the laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes.

The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

The following routine clinical laboratory assessments will be performed:

Biochemistry	**Hematology**
ALT Albumin Alkaline phosphatase AST Bilirubin, total Bicarbonate Calcium Chloride Cholesterol, total Creatinine, enzymatic CK (creatine kinase) CRP standard (C-reactive protein) Direct bilirubin Gamma GT Glucose random, serum Lactate dehydrogenase Magnesium Phosphate Potassium Sodium Total protein Triglycerides Urea (BUN, blood urea nitrogen) Uric acid	Complete blood count (RBC [red blood cells], WBC [white blood cells], platelets, HGB [hemoglobin]) HCT (hematocrit) White blood cell differential **Urinalysis** pH Specific gravity Protein Glucose Ketones Bilirubin Blood

Microscopic examination will be conducted if protein and/or blood is/are detected during urinalysis. The microscopic examination will consist of red blood cells, white blood cells, casts, and bacteria.

4.4.5 Pregnancy Test

A serum β-HCG pregnancy test is performed for all females of childbearing potential at the following visits as applicable to the subject's participation in the study:

- Screening Visit (Visit 1)
- Double-blind Acute Phase: Week 8 (Visit 3.2)
- Open-label Acute Phase: Week 8 (Visit 4.2)
- Double-blind Maintenance Phase: Week 26 (Visit 5.2)
- If pregnancy is suspected
- On withdrawal of the subject from the study

A urine pregnancy test is performed for all females of childbearing potential at all other visits as indicated in Table 5, Table 6, and Table 7.

4.4.6 Stool Assessments

Collection of stool samples for all assessments must occur before administration of any bowel preparations for endoscopy if samples are collected on the same day as bowel preparation administration.

If a standard of care stool sample has been collected within 24 hours prior to the Screening Visit (Visit 1), this sample may be used for screening assessments and evaluations provided that written informed consent/assent has been collected before the stool is sent for laboratory analysis.

Screening Assessments

A stool sample will be collected during the Screening Visit (Visit 1), which is a period of 3 to 21 days. If a standard of care stool sample was collected within 24 hours prior to the Screening Visit (Visit1), this sample may be used for screening assessments and evaluations. The sample must be collected in sufficient time to ensure results reporting within the Screening Visit (Visit 1) period Stool samples collected for culture may be processed by local laboratories; however, results from the central laboratory analysis will prevail and will be entered into the eCRF. The following parameters will be assessed:

- Culture for enteric pathogens including Salmonella, Shigella, Yersinia, Aeromonas, Plesiomonas, and Campylobacter
- Presence of Clostridium difficile toxin
- Microscopic examination of stool for ova and parasites.

If the stool sample is positive for any of the above parameters, the subject will not be eligible for the study.

[redacted]

4.4.7 Physical Examinations

Abnormalities identified at the Screening Visit (Visit 1) will be documented in the subject's source documents. Changes after the Screening Visit (Visit 1) will be captured as AEs, as deemed by the investigator.

4.4.8 Pharmacokinetic Assessments

Blood samples will be collected at the times specified in Table 5, Table 6, and Table 7 to allow measurement of plasma concentrations of 5-ASA and its major metabolite Ac-5-ASA. Pharmacokinetic sampling will occur only at participating sites that have been appropriately assessed and qualified for pharmacokinetic sampling.

5. STATISTICAL ANALYSIS

5.1 General Methodology

All statistical analyses will be performed using SAS® Version 9.2 or higher (SAS Institute, Cary, North Carolina, USA).

Unless otherwise specified, summary tabulations using the Double-blind Acute Phase and Double-blind Maintenance Phase Safety Analysis Sets will be presented by treatment arm and overall. Summary tabulations using the Open-label Acute Phase Safety Analysis Set will be presented by high-dose only. Summary tabulations using the Overall will be presented by overall only.

For categorical variables, the number and percentage of subjects within each category (with a category for missing data as needed) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, standard deviation (SD), Q1, Q3, minimum, and maximum values will be presented.

This is an estimation study intended to provide estimates of clinical response for 2 doses (low and high) across a range of weight groups and not powered to detect differences between treatment groups. P-values will be presented as descriptive statistics.

All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

5.2 Subject Population Sets

Note that as the efficacy analysis sets are identical to the safety sets for this study, only one set of definitions will be used. All efficacy analyses will be based on the Safety Analysis Sets.

5.2.1 Screened Set

The Screened Set will consist of all subjects who have signed an informed consent.

5.2.2 Enrolled Set

The enrolled Set will consist of all subjects who have signed informed consent and also passed inclusion/exclusion criteria.

5.2.3 Overall Randomized Analysis Set

The Overall Randomized Analysis Set will consist of randomized subjects.

5.2.4 Overall Safety Analysis Set

The Overall Safety Analysis Set will consist of randomized subjects who have taken at least 1 dose of investigational product.

5.2.5 Double-blind Acute Phase Safety Analysis Set

The Double-blind Acute Phase Safety Analysis Set will consist of randomized subjects who have taken at least 1 dose of investigational product during the Double-blind Acute Phase.

5.2.6 Open-label Acute Phase Safety Analysis Set

The Open-label Acute Phase Safety Analysis Set will consist of all subjects who have taken at least 1 dose of investigational product during the Open-label Acute Phase.

5.2.7 Double-blind Maintenance Phase Safety Analysis Set

The Double-blind Maintenance Phase Safety Analysis Set will consist of randomized subjects who have taken at least 1 dose of investigational product during the Double-blind Maintenance Phase.

5.3 Subject Disposition

A listing of all Screen Failures (i.e., subjects who were screened but not randomized) will be presented along with reasons for screen fail and details of any adverse events (AEs).

The number of subjects included in each analysis set (i.e., Screened Set, Enrolled Set, Overall Randomized Analysis Set, Overall Safety Analysis Set, Double-blind Acute Phase Safety Analysis Set, Open-label Acute Phase Safety Analysis Set, and Double-blind Maintenance Phase Safety Analysis Set) will be summarized as a whole. For the Double-blind Maintenance Phase Safety Analysis Set, this will also include the subjects who entered directly, and subjects who entered via the Acute Phase (Double-blind/Open-label) as well as the total.

For Double-blind Acute Phase and Double-blind Maintenance Phase Safety Analysis Sets, the number and percentage of subjects who completed, and discontinued from the phase will be presented by treatment arm and overall. For the Open-label Acute Phase Safety Analysis Set, the number and percentage of subjects who completed, and discontinued from the phase will be presented by high dose only. The Primary reasons for discontinuation as recorded on the termination page of the electronic case report form (eCRF) will also be summarized (number and percentage) by treatment arm, separately for each phase. All subjects who discontinued will be listed by discontinuation reason, separately for each phase.

The number of subjects enrolled, randomized, received at least 1 dose of investigational product and completed will be tabulated by site and country for the Overall Randomized Analysis Set. In addition, the duration of enrollment in days, will be summarized for each site, country, and overall. Duration of enrollment will be calculated as (last date of contact for any subject at that site - the first date of informed consent for any subject at that site + 1).

5.4 Protocol Violations and Deviations

Protocol major/minor deviations will be recorded by the site separately from the clinical database. The Shire study team will review and classify all protocol deviations and violations into categories before database lock.

Protocol deviations will be summarized by site for Overall Safety Analysis Set and Open-Label Acute Phase Safety Analysis Set. Protocol deviations will also be summarized by site and treatment arm for the Double-blind Acute Phase Safety Analysis Set and the Double-blind Maintenance Phase Safety Analysis Set separately. Protocol major/minor deviations will be also listed.

5.5 Demographic and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented separately for each Safety Analysis Set (Overall, Double-blind Acute Phase, Open-label Acute Phase and Double-blind Maintenance Phase). For the Double-blind Acute Phase and Double-blind Maintenance Phase Safety Analysis Sets, summaries will be presented by treatment arm and overall. For the Overall Safety Analysis Set, summaries will be presented by overall, and for the Open-label Acute Phase Safety Analysis Set, summaries will be presented for high-dose only.

Demographic characteristics include age, age group (5-10 years and 11-17 years), sex, ethnicity, and race. Baseline characteristics include weight, weight group (18 to ≤23kg, >23 to ≤35kg, >35 to ≤50kg and >50 to ≤90kg), height, and body mass index (BMI). Height will be presented in cm and weight will be presented in kg. Any height measurements recorded in the CRF in inches will be multiplied by 2.54 to convert to cm. Body mass index will be presented in kg/m^2.

Ulcerative colitis history will be presented separately for each Safety Analysis Set (Overall, Double-blind Acute Phase, Open-label Acute Phase, and Double-blind Maintenance Phase). For the Double-blind Acute Phase and Double-blind Maintenance Phase Safety Analysis Sets, summaries will be presented by treatment arm and overall. For the Overall Safety Analysis Set, summaries will be presented overall only, and for the Open-label Acute Phase, summaries will be presented for high-dose only.

The following parameters will be summarized:

- Time (in months) since diagnosis ([screening date - diagnosis date] +1 / 30)
- Method of diagnosis
- Diagnosis state (i.e., is the subject newly diagnosed)

For subjects who are not newly diagnosed:

- Number of acute episodes of UC in the last year
- Number of acute episodes of UC since diagnosis
- Typical duration of past acute episodes (days [where this is recorded in weeks the value will be multiplied by 7])
- Time (in days) since current acute episode of UC ([screening date - onset date] +1)
- Full extent of disease measured from anal margin (cm) at the time of the most recent endoscopy
- The classification of the extent of disease at the most recent endoscopy
- Subjects with rectal involvement
- Subjects with extra-intestinal manifestations
- Subjects with any history of significant GI surgery

Medical history will be listed.

5.6 Extent of Exposure and Treatment Compliance

For the Double-blind Acute and Double-blind Maintenance Phase, summaries will be presented by treatment arm and overall. For the Open-label Acute Phase, summaries will be presented by treatment arm only.

5.6.1 Exposure to Investigational Product

Exposure to investigational product will be summarized separately for each of the three Safety Analysis Sets (Double-blind Acute Phase, Open-label Acute Phase and Double-blind Maintenance Phase). Summary statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for the duration of treatment exposure will also be presented.

Exposure will be summarized in terms of total dose, average daily dose, and length of exposure for each phase, calculated for each subject as:

- Total Dose (mg) = sum of doses within phase of interest
- Average Daily Dose (mg/day) = Total Dose / total days of dosing within phase of interest
- Length of Exposure (weeks) = (Date of last dose within phase of interest – date of first dose within phase of interest + 1) / 7

Additionally, to examine subject-level exposure across study phases, these parameters will be listed by subject and phase.

5.6.2 Measurement of Treatment Compliance

Summaries of compliance will be produced for each of the three Safety Analysis Sets (Double-blind Acute Phase, Open-label Acute Phase and Double-blind Maintenance Phase).

Frequencies and percentages of subjects will be presented for the following categories: <80%, 80-120%, and >120%. Any treatment compliance calculations conducted at the site will be used for study management purposes. Therefore, those values will not be reconciled with values calculated during data analysis. Summary statistics (n, mean, SD, median, Q1, Q3, minimum, maximum) will also be presented.

Compliance is calculated for each phase and defined as:

$$\frac{\text{Overall Number of tablets dispensed - Overall Number of tablets returned}}{[\text{Date of Last Dose - Date of First Dose} + 1] \text{ x Number of Tablets Per Day}} \text{ x } 100\ \%$$

The number of tablets per day is 4 for subjects in the weight groups of 18 to ≤23kg, >23 to ≤35kg, and >50 to ≤90kg regardless of treatment arm or phases. The number of tablets per day is 6 for subjects in the >35 to ≤50kg weight group regardless of treatment arm or phases.

Additionally, to examine subject-level compliance across study phases, these parameters will be listed by subject and phase.

5.7 Prior and Concomitant Medication

World Health Organization Drug Dictionary (WHO-DRUG) 2013SEP01 (or newer) and the Anatomical Therapeutic Chemical (ATC) classification system will be used to classify prior and concomitant medications by therapeutic class.

Prior medication is defined as any medication with the start date prior to the date of the first dose of investigational product. Prior treatment given for the subject's UC was recorded for the year prior to the Screening Visit, where available. All other prior treatment, including but not limited to herbal treatments and vitamins, received within 21 days of the date of first dose of investigational product was recorded.

Concomitant medication is defined as any medication with a start date prior to the date of the first dose of investigational product and continuing after the first dose of investigational product or with a start date between the dates of the first dose of investigational product and the end of the follow-up period, inclusive. Any medication with a start date after the date of the end of the follow-up period will not be considered a concomitant medication.

Both prior and concomitant medication usage will be summarized by the number and proportion of subjects receiving each medication within each therapeutic class and preferred term. Medications can be counted both as prior and concomitant medication. Multiple medication usage by a subject in the same category will be counted only once.

Separate summaries for both prior and concomitant medication usage will be produced for both the Double-blind Acute and Double-blind Maintenance Phase Safety Analysis Sets by treatment arm and overall. For the Overall Safety Analysis Set, summaries for both prior and concomitant medication usage will be presented overall only. For the Open-label Acute Phase Safety Set, summaries for concomitant medication usage will be presented by high-dose.

All prior and concomitant medication will be listed.

5.8 Analysis of Efficacy

All efficacy analyses will be based on the Safety Analysis Set specific to the study phase. Baseline is defined as the last observation prior to first dose of investigational product in the study. The Double-blind Acute Phase Week 8/Withdrawal visit (Visit 3.2) is treated as the Open-label Acute Phase Week 0 for subjects continuing into the Open-label Acute Phase from this visit. The Double-blind Acute Phase Week 8/Withdrawal visit (Visit 3.2) is treated as the Double-blind Maintenance Phase Week 0 for subjects continuing into the Double-blind Maintenance Phase from this visit. The Open-label Acute Phase Week 8/Withdrawal visit (Visit 4.2) is treated as the Double-blind Maintenance Phase Week 0 for subjects continuing into the Double-blind Maintenance Phase from this visit. For subjects who enter the Double-blind Maintenance Phase directly, the Baseline Visit (Visit 2) is treated as the Double-blind Maintenance Phase Week 0.

The final on treatment assessment (FoTA) for the Double-blind Acute phase is defined as data from the Double-blind Acute phase Week 8, or early withdrawal visit if subject withdrew prior to Week 8. The FoTA for the Open-label Acute phase is defined as data from the Open-label Acute phase Week 8, or early withdrawal visit if subject withdrew prior to Week 8. The FoTA for the Double-blind Maintenance phase is defined as data from the Double-blind Maintenance phase Week 26, or early withdrawal visit if subject withdrew prior to Week 26.

Details of the derivation of the composite endpoints (partial and full UC-DAI scores) are included in Section 8.2.

5.8.1 Primary Efficacy Endpoints and Analysis

The primary endpoints for this study are defined separately for both the Double-blind Acute Phase and Double-blind Maintenance Phases and will be conducted using the appropriate Safety Analysis Set for the phase:

5.8.1.1 Double-blind Acute Phase

The primary efficacy endpoint for the Double-blind Acute Phase is defined as the proportion of subjects with a clinical response (defined as partial UC-DAI≤1 with rectal bleeding=0, stool frequency ≤1, and PGA=0) at Week 8.

- Subjects with missing data at Week 8 will be assumed not to have had a clinical response. The primary efficacy endpoint will be compared between treatment arms using a continuity corrected chi-squared test on the Double-blind Acute Phase Safety Analysis Set. If any of the expected cell counts are very low (i.e., less than 5), then Fisher's Exact Test will be used as an alternative analysis method.
- The null hypothesis to be tested is that there is no difference in the proportion of subjects with a clinical response at Week 8 between low and high doses of MMX mesalamine/mesalazine.
- The number (n, %) of subjects with a clinical response at Week 8 and the difference between treatment arms, together with the 95% CI (2-sided), and associated p-value will be presented. The odds ratio comparing the two treatments, together with the 95% CI (2-sided) will also be presented.

5.8.1.2 Double-blind Maintenance Phase

The primary efficacy endpoint for the Double-blind Maintenance Phase is defined as the proportion of subjects who have maintained a clinical response (defined as partial UC-DAI≤1 with rectal bleeding=0 and stool frequency ≤1 and PGA=0) at Week 26.

- Subjects with missing data at Week 26 will be assumed not to have had a clinical response. The primary efficacy endpoint will be compared between treatment arms using a Cochran-Mantel-Haenszel (CMH) test stratifying for 3 levels of Week 8 responder status (entered Maintenance Phase directly, responder at Week 8 of the Double-blind Acute Phase, or responder at Week 8 of the Open-label Acute Phase) on the Double-blind Maintenance Phase Safety Analysis Set.

- The null hypothesis to be tested is that there is no difference in the proportion of subjects with a clinical response at Week 26 between low and high doses of MMX mesalamine/mesalazine.
- The number (n, %) of subjects with a clinical response at Week 26 and the difference between treatment arms, together with the 95% CI (2-sided), and associated p-value will be presented. The odds ratio comparing the two treatments, together with the 95% CI (2-sided) will also be presented.

5.8.2 Secondary Efficacy Endpoints and Analysis

The secondary endpoints for this study are defined separately for both the Double-blind Acute and Double-blind Maintenance Phases and will be conducted using the appropriate Safety Analysis Set for the phase.

5.8.2.1 Double-blind Acute Phase

- The proportion of subjects with a clinical and endoscopic response at Week 8, defined as UC-DAI ≤2 with rectal bleeding=0 and stool frequency ≤1 and PGA=0, and with mucosal healing (endoscopy score ≤1) based on central reading. In addition, there must be at least a 1-point reduction in endoscopy score from baseline. This endpoint will be compared between treatment arms using a continuity corrected chi-squared test. If any of the expected cell counts are very low (i.e., less than 5), then Fisher's Exact Test will be used as an alternative analysis method. Subjects with missing data at Week 8 will be assumed not to have had a clinical response. Subjects who completed week 8 but who did not have central reading endoscopies at both baseline and week 8 will be excluded.
- The proportion of subjects with a clinical and endoscopic response at Week 8, defined as UC-DAI ≤2 with rectal bleeding=0 and stool frequency ≤1 and PGA=0, and with mucosal healing (endoscopy score ≤1) based on local reading. In addition, there must be at least a 1-point reduction in endoscopy score from baseline. This endpoint will be compared between treatment arms using a continuity corrected chi-squared test. If any of the expected cell counts are very low (i.e., less than 5), then Fisher's Exact Test will be used as an alternative analysis method. Subjects with missing data at Week 8 will be assumed to be treatment failures. Subjects with missing data at Week 8 will be assumed not to have had a clinical response. Subjects who completed week 8 but who did not have local reading endoscopies at both baseline and week 8 will be excluded.
- The change in the DUCS score from baseline to Week 8 of the Double-blind Acute Phase. This endpoint will be compared between treatment arms using an analysis of covariance (ANCOVA), including treatment arm as a factor and the baseline DUCS score as a covariate in the model.
- The percentage of subjects with an improvement (change of ≥20 points) in PUCAI score from baseline to Week 8 of the Double-blind Acute Phase. This endpoint will be compared between treatment arms using a continuity corrected chi-squared test. If any of the expected cell counts are very low (i.e., less than 5), then Fisher's Exact Test will be used as an alternative analysis method. Subjects with missing data at Week 8 will be assumed not to have had a clinical response.

5.8.2.2 Double-blind Maintenance Phase

- The proportion of subjects who have maintained a clinical and endoscopic response at Week 26, defined as UC-DAI ≤2 with rectal bleeding=0 and stool frequency ≤1 and PGA=0 and with mucosal healing (endoscopy score ≤1) based on central reading. This endpoint will be compared between treatment arms using a CMH test stratifying by Week 8 responder status Subjects with missing data at Week 26 will be assumed not to have had a clinical response. If there are an insufficient number of subjects with central reading endoscopy data, then the CMH test will not be performed. The number and percentage of subjects with clinical and endoscopic response – based on central response will be presented by treatment arm.
- The proportion of subjects who have maintained a clinical and endoscopic response at Week 26, defined as UC-DAI ≤2 with rectal bleeding=0 and stool frequency ≤1 and PGA=0, and with mucosal healing (endoscopy score ≤1) based on local reading. This endpoint will be compared between treatment arms using a CMH test stratifying by Week 8 responder status. Subjects with missing data at Week 26 will be assumed not to have had a clinical response. If there are an insufficient number of subjects with central reading endoscopy data, then the CMH test will not be performed. The number and percentage of subjects with clinical and endoscopic response – based on local response will be presented by treatment arm.
- The change in the DUCS score from Double-blind Maintenance Phase Week 0 to Week 26. This endpoint will be compared between treatment arms using an analysis of covariance, including treatment arm as a factor, the DUCS score at Double-blind Maintenance Phase Week 0 and Week 8 responder status as covariates in the model.
- The percentage of subjects in remission (PUCAI <10) at Double-blind Maintenance Phase Week 26. This endpoint will be compared between treatment arms using a CMH test stratifying by Week 8 responder status. Subjects with missing data at Week 26 will be assumed not to have had a clinical response.

5.8.3 Other Efficacy Endpoint(s) and Analysis

Other efficacy endpoints will be summarized by study phase (Double-blind Acute Phase, Open-label Acute Phase, and Double-blind Maintenance Phase) using the appropriate Safety Analysis Set for that phase.

5.8.3.1 UC-DAI

- The partial UC-DAI (continuous version, calculated as the sum of symptoms plus PGA score) and the full UC-DAI (continuous version, calculated as the sum of partial UC-DAI plus endoscopy) will be summarized by visit and treatment arm (as applicable) for each study phase. These tables will include both continuous and categorical summaries. Separate summaries will be produced for the full UC-DAI using endoscopy results from central and local readings.
- The components of the UC-DAI (average stool frequency score, average rectal bleeding score, PGA score and endoscopy score) will be summarized individually as continuous and categorical variables by visit and treatment arm (as applicable) for each study phase.

These tables will include separate summaries of endoscopy scores using results from central and local readings.

- The change from baseline to Week 2, Week 4, Week 8, and FoTA for the Double-blind Acute phase and change from Week 0 to Week 13 and Week 26 for the Double-blind Maintenance Phase for the components of the UC-DAI will be summarized individually as categorical variables by treatment arm (as applicable) using shift tables for each study phase.
- To examine concordance between PGA and endoscopy scores (central and local readings), cross-tabulations of the assessment results at each study visit will be displayed. A weighted Kappa statistic will be presented to serve as measure of the degree or amount of agreement between the two assessments.

5.8.3.2 PUCAI

- The PUCAI will be summarized by visit and treatment arm (as applicable) for each study phase. These tables will include both continuous and categorical [<10 (remission); 10-34 (mild); 35-64 (moderate) and 65 or above (severe)] summaries.
- The components of the PUCAI score (abdominal pain, rectal bleeding, stool consistency, number of stools in 24 hours, nocturnal stools, and activity level) will be summarized individually by visit and treatment arm (as applicable) for each study phase.

5.8.3.3 IMPACT III

- The IMPACT III domains (body image, bowel symptoms, emotional functioning, social functioning, systemic symptoms, and treatment/interventions) and total score and change from baseline will be summarized by visit and treatment arm (as applicable) for each study phase.

5.8.3.4 DUCS

- Listings of the responses to each of the items collected as part of the electronic daily sign and symptom diary (DUCS) will be presented by treatment, subject, visit, and visit date. These listings will include items for overall current health and global change in health.

5.8.4 Exploratory Efficacy Endpoint(s) and Analyses

- [redacted].
- [redacted].
- [redacted]

5.9 Analysis of Safety

All summaries of safety data will be produced separately for each phase of the study, for the Double-blind Acute Safety Analysis Set (overall and by treatment arm), Open-label Acute Safety Analysis Set (by treatment arm only), and Double-blind Maintenance Phase Safety Analysis Set (overall and by treatment arm).

Baseline is defined as the last observation prior to first dose of investigational product in the study. If an assessment occurs on same day as the first dose of investigational product, the assessment will be considered the Baseline assessment. The Double-blind Acute Phase Week 8/Withdrawal visit (Visit 3.2) is treated as the Open-label Acute Phase Week 0 for subjects continuing into the Open-label Acute Phase from this visit. The Double-blind Acute Phase Week 8/Withdrawal visit (Visit 3.2) is treated as the Double-blind Maintenance Phase Week 0 for subjects continuing into the Double-blind Maintenance Phase from this visit. The Open-label Acute Phase Week 8/Withdrawal visit (Visit 4.2) is treated as the Double-blind Maintenance Phase Week 0 for subjects continuing into the Double-blind Maintenance Phase from this visit. For subjects who enter the Double-blind Maintenance Phase directly, the Baseline Visit (Visit 2) is treated as the Double-blind Maintenance Phase Week 0.

Safety variables include AEs, clinical laboratory variables and vital signs variables. For each safety variable, the last value collected prior to the first dose of investigational product (during phase of interest) will be used as baseline/Week 0 for the analyses of that safety variable. A Final on-Treatment Assessment (FoTA) will be defined as the last valid assessment obtained after baseline/Week 0 and whilst on investigational product.

5.9.1 Adverse Events

Adverse events will be coded using Version 16.1 (or newer) of Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with an event, as well as the number of events will be reported for each summary.

An AE (classified by preferred term) that occurs during the study will be considered a treatment-emergent AE (TEAE) if it has a start date on or after the first dose of investigational product or if it has a start date before the date of the first dose of investigational product, but increases in severity on or after the date of the first dose of investigational product. If more than 1 AE with the same preferred term is reported before the date of the first dose of investigational product, then the AE with the greatest severity will be used as the benchmark for comparison to the AEs occurring during the study under the preferred term. An AE that occurs more than 7 days after the date of the last dose of investigational product of that phase will not be counted as a TEAE.

An overall summary of the number of subjects with TEAEs and number of TEAEs will be presented overall for the Overall Safety Analysis Set, an overall summary of the number of subjects with TEAEs and number of TEAEs will be presented for High-dose MMX only for Open Label Acute Phase Safety Analysis Set, and by treatment group and overall for the Double-blind Acute and Double-blind Maintenance Phase Safety Analysis Sets. The summary will include the number and percentage of subjects with any TEAEs, serious TEAEs, TEAEs related to investigational product, TEAEs leading to discontinuation of investigational product and TEAEs leading to death.

The number and percentage of subjects reporting TEAEs, as well as the number of events, will be tabulated by system organ class (SOC) and preferred term for Overall Safety Analysis set, the Double-blind Acute and Double-blind Maintenance Phase Safety Analysis Sets, and also for Open-label Acute Phase Safety Analysis Set.

The number and percentage of subjects reporting TEAEs will also be tabulated by SOC, preferred term, and maximum severity for Overall Safety Analysis set, Double-blind Acute and Double-blind Maintenance Phase Safety Analysis Sets, and also for Open-label Acute Phase Safety Analysis Set.

Treatment-emergent adverse events considered related to investigational product will also be summarized by SOC and preferred term for Overall Safety Analysis set, Double-blind Acute and Double-blind Maintenance Phase Safety Analysis Sets, and also for Open-label Acute Phase Safety Analysis Set.

If more than 1 AE occurs with the same preferred term for the same subject, then the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to investigational product.

The incidence of frequently occurring TEAEs (≥5% of subjects in any treatment arm) will be summarized by preferred term for Overall Safety Analysis set, the Double-blind Acute and Double-blind Maintenance Phase Safety Analysis Sets, and also for Open-label Acute Phase Safety Analysis Set.

TEAEs related to investigational product, serious TEAEs, TEAEs leading to discontinuation of investigational product, and serious TEAEs leading to death will be summarized by SOC and preferred term.

Treatment-emergent adverse events of special interest (including renal toxicity, hepatic toxicity, pericarditis, myocarditis, pancreatitis, gastritis, and cholecystitis) will also be summarized by SOC and preferred term for Overall Safety Analysis set, Double-blind Acute and Double-blind Maintenance Phase Safety Analysis Sets, and also for Open-label Acute Phase Safety Analysis Set.

Renal Toxicity

- Acute renal failure - (SMQ- Broad)
- Chronic kidney disease – (SMQ- Broad)

Hepatic Toxicity

- Drug related hepatic disorders- comprehensive search – (SMQ)
- Cholestasis and jaundice of hepatic origin (SMQ)
- Drug related hepatic disorders – severe events only (SMQ)
- Liver related investigations, signs and symptoms (SMQ)
- Liver related coagulation and bleeding disturbances (SMQ)

Pericarditis

- Pericarditis (PT)
- Pleuropericarditis (PT)

Myocarditis

- Myocarditis (PT)
- Allergic Myocarditis (PT)
- Eosinophilic myocarditis (PT)

Pancreatitis

- Acute pancreatitis (SMQ)

Gastritis

- Gastrointestinal nonspecific inflammation (SMQ)
- Gastrointestinal nonspecific dysfunction (SMQ)

Cholecystitis

- Cholecystitis (PT)
- Cholecystitis acute (PT)
- Cholecystitis chronic (PT)
- Cholecystectomy (PT)
- Cholecystocholangitis (PT)

Subject listings will be presented for all deaths, serious AEs (SAEs), and subjects withdrawn due to AEs.

5.9.2 Clinical Laboratory Variables

Descriptive statistics for clinical laboratory values (in SI units) and changes from baseline at each assessment time point as well as shift tables from baseline/week 0 to each visit for quantitative variables will be presented for the following clinical Hematology and Biochemistry laboratory variables (Note: Urinalysis is only collected at screening and will be listed but not summarized) for Double-blind Acute and Double-blind Maintenance Phase Safety Analysis Sets, and also for Open-label Acute Phase Safety Analysis Set .

Hematology	Complete blood count (RBC [red blood cells], WBC [white blood cells], platelets, HGB [hemoglobin]), HCT (hematocrit), white blood cell differential
Biochemistry	ALT, albumin, alkaline phosphatase, AST, bilirubin (total), bicarbonate, calcium, chloride, cholesterol (total), creatinine (enzymatic), CK (creatine kinase), CRP standard (C-reactive protein), direct bilirubin, gamma glutamyl transpeptidase (GGT), glucose random (serum), lactate dehydrogenase, magnesium, phosphate, potassium, sodium, total protein, triglycerides, urea (BUN, blood urea nitrogen), uric acid
Urinalysis	Bilirubin, blood, glucose, ketones, pH, protein, specific gravity

Clinical laboratory test values are potentially clinically important (PCI) if they meet either the low or high PCI criteria listed in Table 2. The number and percentage of subjects with post-baseline/Week 0 PCI values during phase of interest will be tabulated. The percentages will be calculated relative to the number of subjects with available baseline/Week 0 values and at least 1 post-baseline/Week 0 assessment during phase of interest.

The numerator is the total number of subjects with at least 1 post-baseline/Week 0 PCI value during phase of interest. A supportive listing of subjects with post-baseline PCI values will be provided including the subject number, site, baseline/Week 0, and post-baseline/Week 0 values.

Table 2: Criteria for Potentially Clinically Important Laboratory Tests

Parameter	SI Unit	Lower Limit	Higher Limit
Biochemistry			
Sodium	mmol/L	<130	>150
Potassium	mmol/L	<3.0	>5.5
Glucose	mmol/L	<3.1	>8.6
Blood Urea Nitrogen	mmol/L	-	>1.5 x ULN
Creatinine	µmol/L	-	>1.5 x ULN
Calcium	mmol/L	<2.20 (2-11 yrs) <2.10 (12-17 yrs) <2.00 (>17 yrs)	>2.82 (2-11 yrs) >2.67 (12-17 yrs) >2.87 (>17 yrs)
Total Protein	g/L	<54	>86
Albumin	g/L	<33 (5-14 yrs) <33 (15-17 yrs, F) <30 (15-17 yrs, M) <30 (>17 yrs)	-
Aspartate Transaminase (AST)	U/L	-	>1.5 x ULN
Alanine Transaminase (ALT)	U/L	-	>1.5 x ULN
Gamma Glutamyl Transferase (GGT)	U/L	-	>1.5 x ULN
Alkaline Phosphatase	U/L	-	>1.5 x ULN
Total Bilirubin	µmol/L	-	>1.5 x ULN
Bicarbonate	mmol/L	<16	>30
Chloride	mmol/L	<90	>115
Uric acid	µmol/L	-	>532 (F) >591 (M)
Phosphate	mmol/L	<1.01 (3-9 yrs) <1.04 (10-15 yrs) <0.75 (>15 yrs)	>2.06 (3-9 yrs) >1.93 (10-15 yrs) >1.61 (>15 yrs)
Triglycerides	U/L	-	>2.5 x ULN
Lactate dehydrogenase (LDH)	U/L	-	>2.5 x ULN
Creatine kinase	U/L	-	>1.5 x ULN
Magnesium	mmol/L	<0.74	-

Table 2: Criteria for Potentially Clinically Important Laboratory Tests

Parameter	SI Unit	Lower Limit	Higher Limit
Cholesterol	mmol/L	-	>7.77
Hematology			
White Blood Cell Count – Total (WBC)	10^9/L	<4.10 (3-4 yrs) <3.60 (5-6 yrs) <3.10 (7-8 yrs) <3.00 (>8 yrs)	>19.20 (3-4 yrs) >18.00 (5-6 yrs) >17.00 (7-8 yrs) >16.50 (9-10 yrs) >16.20 (11-15 yrs) >16.00 (>15 yrs)
Red Blood Cells (RBC)	10^{12}/L	<3.0	-
Hemoglobin	g/L	<100	-
Hematocrit	L/L	<0.32	>0.50
Platelet Count	10^9/L	<75	>500
Neutrophils/Leukocytes	%	<20 (2-5 yrs) <25 (6-11 yrs) <30 (12-17 yrs) <40 (>17 yrs)	>65 (2-11 yrs) >70 (12-17 yrs) >75 (>17 yrs)
Lymphocytes/ Leukocytes	%	<12 (2-17 yrs) <15 (>17 yrs)	>63 (2-5 yrs) >57 (6-11 yrs) >52 (12-17 yrs) >47 (>17 yrs)
Monocytes/Leukocytes	%	-	> 15
Eosinophils/Leukocytes	%	-	> 10
Basophils/Leukocytes	%	-	> 10

LLN: Lower limit of normal value provided by the laboratory
ULN: Upper limit of normal value provided by the laboratory

5.9.3 Vital Signs

Descriptive statistics for vital signs (e.g., systolic and diastolic blood pressure, and pulse rate) and their changes from baseline/Week 0 at each post-baseline/Week 0 visit will be presented for Double-blind Acute and Double-blind Maintenance Phase Safety Analysis Sets, and also for Open-label Acute Phase Safety Analysis Set.

Vital sign values will be considered PCI if they meet either the low or high PCI criteria listed in Table 3. The number and percentage of subjects with PCI post-baseline values will be tabulated. The percentages will be calculated relative to the number of subjects with baseline and at least 1 post-baseline/Week 0 assessment during phase of interest. The numerator is the total number of subjects with at least 1 PCI post-baseline/Week 0 vital sign value during phase of interest.

A supportive listing of subjects with post-baseline/Week 0 PCI values will be provided including the subject number, site, baseline/Week 0, and post-baseline/Week 0 PCI values.

Table 3: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign Parameter	Age (yrs)		
		Lower Limit	Upper Limit
Systolic blood pressure (mmHg)	5 - 6	<89	>125
	7 – 12	<92	>135
	≥13	<100	>140
Diastolic blood pressure (mmHg)	5 - 6	<50	>84
	7 – 12	<55	>90
	≥13	<60	>90
Pulse rate (beats per minute)	5 - 6	<50	>130
	7 – 12	<50	>125
	≥13	<50	>120

5.10 Analysis of Pharmacokinetic Data

Blood samples will be collected for determination of 5-ASA and Ac-5-ASA plasma concentrations, and the plasma samples will be assayed for 5-ASA and Ac-5-ASA using validated analytical methods.

Plasma concentrations reported as BLQ (below the limit of quantification) of the assay will be reported as zero on the data listings, and BLQ concentrations are treated as zero in the calculation of summary statistics.

The plasma concentrations of 5-ASA and Ac-5-ASA will be summarized by treatment and visit using descriptive statistics (number of observations, mean, standard deviation, coefficient of variation, median, Q1, Q3, maximum, and minimum) using the Safety Analysis Set for each study phase.

A population pharmacokinetic model was developed based on the 5-ASA and Ac-5-ASA plasma concentration data (full pharmacokinetic profiles) from SPD476-112. The plasma concentration data from this study (sparse pharmacokinetic sampling) will be pooled with the plasma concentration data from SPD476-112 to update the original population pharmacokinetic analysis. The population pharmacokinetic methods will be described in a separate document from this statistical analysis plan.

6. CHANGES TO ANALYSES SPECIFIED IN THE PROTOCOL

- Changes to the analyses specified in the protocol are as follows: The observed-case sensitivity analysis has been removed from the SAP, since the observed-case analysis would be identical to the complete-case analysis. The model-based imputation method sensitivity analysis has been omitted from the SAP as this study is not powered to detect differences between treatment groups and other sensitivity analysis (LOCF and complete case) intended to examine the robustness of the treatment estimate (under the assumption that the subjects with missing Week 8 or Week 26 results are treatment failures) have been included.
- Statements were added to the SAP to clarify that this is an estimation study intended to provide estimates of clinical response for 2 doses (low and high) across a range of weight groups and not powered to detect differences between treatment groups.
- After agreement with FDA, the sample size for the Double-blind Acute Phase has been reduced to 53 subjects due to difficulties with recruitment.
- Subgroup analyses for the primary endpoint were added to the SAP to explore efficacy by weight group and Week 8 responder status.
- For maintenance phase secondary endpoints, the proportion of subjects who have maintained a clinical and endoscopic response at Week 26, using central reading and using local reading endoscopies, if there are an insufficient number of subjects with central reading endoscopy data, then the CMH test will not be performed. The number and percentage of subjects with clinical and endoscopic response will be presented by treatment arm.
- To conduct psychometric analysis of the DUCS would require more data, and thus will be considered in the future.

7. STATISTICAL/ANALYTIC ISSUES

7.1 Adjustment for Covariates

The analysis of the primary efficacy endpoint for the Double-blind Acute Phase does not include adjustment for covariates.

The analysis of the primary efficacy endpoint for the Double-blind Maintenance Phase includes adjustment for prior response status (entered Maintenance Phase directly, responder at Week 8 in Double-blind Acute Phase, responder at Week 8 in Open-label Acute Phase).

The analysis of the secondary efficacy endpoint, change in DUCS score from baseline to Week 8 for the Double-blind Acute Phase includes adjustment for the baseline DUCS score.

The analysis of the secondary efficacy endpoint, change in DUCS score from Week 0 to Week 26 for the Double-blind Maintenance Phase includes adjustment for the baseline DUCS score and prior response status (entered Maintenance Phase directly, responder at Week 8 in Double-blind Acute Phase, responder at Week 8 in Open-label Acute Phase).

7.2 Handling of Dropouts or Missing Data

For the primary analysis of the primary efficacy endpoint, subjects with missing data at Week 8 or Week 26 for the Double-blind Acute Phase or Double-blind Maintenance Phase, respectively, will be assumed not to have had a clinical response and will be considered treatment failures.

Sensitivity analyses to examine the handling of missing data for the primary efficacy endpoint include complete-case analysis and last observation carried forward. These are described in Section 7.7.

7.3 Interim Analysis and Data Monitoring

A safety review team will review safety data twice a year according to the Data Review Plan.

There is no interim efficacy analysis planned for this study. An independent Data Monitoring Committee (DMC) will monitor safety data generated by the study at regular intervals for the duration of the study. Their role is to protect the interests of subjects in the study and of future subjects who may enroll, by reviewing the accumulating safety and tolerability data generated in this study. DMC meetings will be held on 3 occasions—the first time after one-fourth of the targeted sample size is evaluable for analysis, the second time after two-fourth are evaluable, and third time after three-fourth are evaluable. The data provided to the DMC will not be considered ‘clean’ until the database is locked. Data will be provided to the DMC by an independent statistical reporting group not assigned to the project.

Further details regarding the DMC and meeting frequency can be found in the DMC charter. The DMC charter will define the primary responsibilities of the DMC, guide its activities, its relationship with other trial components, its membership, and the purpose and timing of its meetings. It will provide the procedures for ensuring confidentiality, formal communication, an outline of the content of the Open and Closed Reports that will be provided to the DMC.

7.4 Multicenter Studies

Data from all centers that participate in this protocol will be combined so that an adequate number of subjects will be available for analysis.

7.5 Multiple Comparisons/Multiplicity

This is an estimation study intended to provide estimates of clinical response for 2 doses (low and high) across a range of weight groups and not powered to detect differences between treatment groups. No adjustment for multiplicity will be performed.

7.6 Examination of Subgroups and Interactions

As indicated for each subgroup analysis, efficacy endpoints will be summarized by study phase (Double-blind Acute Phase, Open-label Acute Phase, and Double-blind Maintenance Phase) using the appropriate Safety Analysis Set for that phase.

7.6.1 Weight Group

The primary efficacy endpoint will be summarized for each study phase by weight group (18 to ≤23kg, >23 to ≤35kg, >35 to ≤50kg and >50 to ≤90kg).

7.6.2 Prior Response Status

The primary and secondary efficacy endpoints will be summarized for the Double-blind Maintenance Phase by prior response status (entered Maintenance Phase directly, responder at Week 8 in Double-blind Acute Phase, responder at Week 8 in Open-label Acute Phase). This analysis will provide information on the durability of response with respect to the prior treatment with either MMX or other 5-ASA treatment.

In addition, the primary and secondary efficacy endpoints will be summarized for the Double-blind Maintenance Phase by prior response status (entered Maintenance Phase directly, responder at Week 8 in Double-blind Acute Phase, responder at Week 8 in Open-label Acute Phase) and prior treatment (low-dose MMX, high-dose MMX, and 5-ASA by medication preferred term). This analysis will provide information on the durability of response with respect to the prior MMX dose group or other 5-ASA treatments by preferred term.

The number (n, %) of subjects with a clinical response at Week 26 and difference between treatment arms for each stratum, together with the 95% CI (2-sided), and associated p-value will be presented.

7.7 Sensitivity Analyses

7.7.1 Sensitivity Analyses of the Primary Endpoint

The following sensitivity analyses will be performed for both the Double-blind Acute and Double-blind Maintenance Phase primary endpoint:

- A modified clinical response, defined as partial UC-DAI≤1 with rectal bleeding=0 and stool frequency ≤1 will be analyzed in a similar way to the primary endpoint analysis in order to investigate the effect of removing the PGA component from the responder definition.

- A modified clinical response, defined as partial UC-DAI≤1 with rectal bleeding=0 and stool frequency=0, and PGA=0 will be analyzed in a similar way to the primary endpoint to support extrapolation to adult efficacy.
- A complete-case analysis (where subjects who withdraw early from the study are excluded) will be performed in a similar way to the primary endpoint analysis.
- A last observation carried forward analysis (LOCF), using data from the final on-treatment assessment (FoTA) for the appropriate phase, will be performed in a similar way to the primary endpoint analysis. Specifically, the values of the individual components of the partial UC-DAI (rectal bleeding, stool frequency and PGA scores) will be imputed using the last observation carried forward (LOCF) method.
- Logistic modeling will be conducted to investigate the effect of doses in mg/kg on the clinical response in the Double-blind Acute and Double-blind Maintenance Phases. The logistic regression model will adjust for doses in mg/kg, sex, and age. For the Double-blind Maintenance Phase primary endpoint, the logistic regression model will also adjust for Week 8 responder status.

8. DATA HANDLING CONVENTIONS

8.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation, Q1, Q3, minimum, maximum. Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in each category.

See TFLs4Shire for rules on the number of decimal places to present data and p-values.

8.2 Derived Efficacy Endpoints

- Stool frequency and rectal bleeding score:
  - For both stool frequency and rectal bleeding, the symptom score (collected via the electronic diary [e-diary]) is defined as the average of the scores from the last available 3 days from the 5 days immediately prior to the visit (days -1 to -5). If there are fewer than 3 days of data available during days -1 to -5, the average will be calculated from any available days within the period. If there are no available days during the period, then the symptom score will be missing for that visit. Data collected on days when bowel preparations have been administered or when endoscopy has been performed will be excluded.
  - For stool frequency and rectal bleeding, the symptom score will be grouped into a category (0, >0 - <1, 1 - <2, 2 - <3, and 3).
- Partial UC-DAI score:
  - Sum of rectal bleeding score, stool frequency score and PGA score
- Full UC-DAI score:
  - Sum of rectal bleeding score, stool frequency score, PGA score and endoscopy score
- Clinical response: partial UC-DAI ≤1 (rectal bleeding=0 and stool frequency ≤1 and PGA=0)
- Clinical and endoscopic response: UC-DAI ≤2 with rectal bleeding=0 and stool frequency ≤1 and PGA=0, and mucosal healing (endoscopy score ≤1) based on central reading
- Week 8 responder status is defined based on clinical response: entered Maintenance Phase directly, responder at Week 8 of the Double-blind Acute Phase, or responder at Week 8 of the Open-label Acute Phase.

8.3 Repeated or Unscheduled Assessments of Safety Parameters

If a subject has repeated assessments before the start of investigational product, then the results from the final assessment made prior to the start of investigational product during phase of interest will be used as baseline/Week 0. If end of phase assessments are repeated or unscheduled, the last post-baseline/Week 0 assessment will be used as the end of phase assessment for generating descriptive statistics. However, all post-baseline/Week 0 assessments will be used for PCI value determination and all assessments will be presented in the data listings.

8.4 Incomplete Date of Diagnosis

When computing the time since diagnosis, any missing days (of month) will be imputed as the 15th for diagnosis dates that precede screening. If imputed date is after screening, then screening date will be used as imputed diagnosis date.

8.5 Missing Date of Investigational Product

When the date of the last dose of investigational product is missing for a subject in the Safety Set for the acute or maintenance phases, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last visit date when investigational product was returned will be used in the calculation of treatment duration.

8.6 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, incomplete (i.e., partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, the start date will be imputed first.

8.6.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing day and month

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day.
- If either the year is before the year of the date of the first dose of investigational product or if both years are the same but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of the first dose of investigational product or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

8.6.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of investigational product is missing, then the last visit date will be imputed. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the same as the year of the date of the last dose of investigational product, then the day and month of the date of the last dose of investigational product will be assigned to the missing fields.
- If the year of the incomplete stop date is before the year of the date of the last dose of investigational product, then 31 December will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the date of the last dose of investigational product will be assigned to the missing day.

- If either the year is before the year of the date of the last dose of investigational product or if both years are the same but the month is before the month of the date of the last dose of investigational product, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the last dose of investigational product or if both years are the same but the month is after the month of the date of the last dose of investigational product, then the first day of the month will be assigned to the missing day.

8.7 Missing Date Information for Adverse Events

For AEs, only incomplete (i.e., partially missing) start dates will be imputed, to determine if the event is treatment emergent.

8.7.1 Incomplete Start Date

Follow same rules as in Section 8.6.1.

8.7.2 Incomplete Stop Date

Not applicable as duration of AEs is not presented.

8.8 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of investigational product, then a severity of "Mild" will be assigned. If the severity is missing for a TEAE starting on or after the date of the first dose of investigational product, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

8.9 Missing Relationship to Investigational Product for Adverse Events

If the relationship to investigational product is missing for a TEAE starting on or after the date of the first dose of investigational product, a causality of "Related" will be assigned. The imputed values for relationship to double-blind investigational product will be used for incidence summaries, while the actual values will be presented in data listings.

8.10 Character Values of Clinical Laboratory Variables

If the reported value of a clinical laboratory variable cannot be used in a statistical analysis (e.g., if a character string is reported for a numerical variable), then the appropriately determined coded value will be used in the statistical analysis. However, the actual values as reported in the database will be presented in data listings.

Table 4: Examples for Coding of Special Character Values for Clinical Laboratory Variables

Clinical Laboratory Test	Possible Results (in SI units)	Coded Value for Analysis
Chemistry: ALT	<5	0
Chemistry: AST	<5	0
Chemistry: Total Bilirubin	<2	0
Urinalysis: Glucose	≥55	Positive
	≤0	Negative
Urinalysis: pH	≥8.0	8.0
[redacted]	[redacted]	[redacted]

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14.2.2.1.19	Proportion of Subjects in Remission (<10 Points) PUCAI Score from Week 0 to Week 26 of Double-Blind Maintenance Phase by Treatment Arm, Prior Response Status and Prior Treatment [Double-Blind Maintenance Phase Safety Analysis Set]
14.2.2.1.20	Proportion of Subjects in Remission (<10 Points) PUCAI Score from Week 0 to Week 26 of Double-Blind Maintenance Phase by Treatment Arm and Prior Treatment (Preferred Term) [Double-Blind Maintenance Phase Safety Analysis Set – Subjects who Entered the Maintenance Phase Directly]

Table Number	Table Title
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14.2.2.2.1	UC-DAI (Partial, Full based on Central Reading, and Full based on Local Reading) by Treatment Arm and Study Visit for the Double-Blind Acute Phase [Double-Blind Acute Phase Safety Analysis Set]
14.2.2.2.2	Components of UC-DAI (Average Stool Frequency, Average Rectal Bleeding, PGA, Endoscopy based on Central Reading, and Endoscopy based on Local Reading) by Treatment Arm and Study Visit for the Double-Blind Acute Phase [Double-Blind Acute Phase Safety Analysis Set]
14.2.2.2.3	Components of UC-DAI (Average Stool Frequency, Average Rectal Bleeding, PGA, Endoscopy based on Central Reading, and Endoscopy based on Local Reading) Shift from Baseline to Double-Blind Acute Phase Week 8 by Treatment Arm [Double-Blind Acute Phase Safety Analysis Set]
14.2.2.2.4	PGA Score versus Endoscopy Score (Based on Central Reading) during Double-Blind Acute Phase by Treatment Arm and Study Visit [Double-Blind Acute Phase Safety Analysis Set]
14.2.2.2.5	PGA Score versus Endoscopy Score (Based on Local Reading) during Double-Blind Acute Phase by Treatment Arm and Study Visit [Double-Blind Acute Phase Safety Analysis Set]
14.2.2.2.6	PUCAI by Treatment Arm and Study Visit for the Double-Blind Acute Phase [Double-Blind Acute Phase Safety Analysis Set]
14.2.2.2.7	Components of PUCAI Score by Treatment Arm and Study Visit for the Double-Blind Acute Phase [Double-Blind Acute Phase Safety Analysis Set]
14.2.2.2.8	IMPACT III Domains by Treatment Arm and Study Visit for the Double-Blind Acute Phase [Double-Blind Acute Phase Safety Analysis Set]
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14.2.2.2.9	UC-DAI (Partial, Full based on Central Reading, and Full based on Local Reading) by High-Dose MMX and Study Visit for the Open-Label Acute Phase [Open-Label Acute Phase Safety Analysis Set]
14.2.2.2.10	Components of UC-DAI (Average Stool Frequency, Average Rectal Bleeding, PGA, Endoscopy based on Central Reading, and Endoscopy based on Local Reading) by High-Dose MMX and Study Visit for the Open-Label Acute Phase [Open-Label Acute Phase Safety Analysis Set]

Table Number	Table Title
14.2.2.2.11	Components of UC-DAI (Average Stool Frequency, Average Rectal Bleeding, PGA, Endoscopy based on Central Reading, and Endoscopy based on Local Reading) Shift from Week 0 to Open-Label Acute Phase Week 8 by High-Dose MMX [Open-Label Acute Phase Safety Analysis Set]
14.2.2.2.12	PGA Score versus Endoscopy Score (Based on Central Reading) during Open-Label Acute Phase by High-Dose MMX and Study Visit [Open-Label Acute Phase Safety Analysis Set]
14.2.2.2.13	PGA Score versus Endoscopy Score (Based on Local Reading) during Open-Label Acute Phase by High-Dose MMX and Study Visit [Open-Label Acute Phase Safety Analysis Set]
14.2.2.2.14	PUCAI by High-Dose MMX and Study Visit for the Open-Label Acute Phase [Open-Label Acute Phase Safety Analysis Set]
14.2.2.2.15	Components of PUCAI Score by High-Dose MMX and Study Visit for the Open-Label Acute Phase [Open-Label Acute Phase Safety Analysis Set]
14.2.2.2.16	IMPACT III Domains by High-Dose MMX and Study Visit for the Open-Label Acute Phase [Open-Label Acute Phase Safety Analysis Set]
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14.2.2.2.17	UC-DAI (Partial, Full based on Central Reading, and Full based on Local Reading) by Treatment Arm and Study Visit for the Double-Blind Maintenance Phase [Double-Blind Maintenance Phase Safety Analysis Set]
14.2.2.2.18	Components of UC-DAI (Average Stool Frequency, Average Rectal Bleeding, PGA, Endoscopy based on Central Reading, and Endoscopy based on Local Reading) by Treatment Arm and Study Visit for the Double-Blind Maintenance Phase [Double-Blind Maintenance Phase Safety Analysis Set]
14.2.2.2.19	Components of UC-DAI (Average Stool Frequency, Average Rectal Bleeding, PGA, Endoscopy based on Central Reading, and Endoscopy based on Local Reading) Shift from Week 0 to Double-Blind Maintenance Phase Week 26 by Treatment Arm [Double-Blind Maintenance Phase Safety Analysis Set]
14.2.2.2.20	PGA Score versus Endoscopy Score (Based on Central Reading) during Double-Blind Maintenance Phase by Treatment Arm and Study Visit [Double-Blind Maintenance Phase Safety Analysis Set]
14.2.2.2.21	PGA Score versus Endoscopy Score (Based on Local Reading) during Double-Blind Maintenance Phase by Treatment Arm and Study Visit [Double-Blind Maintenance Phase Safety Analysis Set]

Table Number	Table Title
14.2.2.2.22	PUCAI by Treatment Arm and Study Visit for the Double-Blind Maintenance Phase [Double-Blind Maintenance Phase Safety Analysis Set]
14.2.2.2.23	Components of PUCAI Score by Treatment Arm and Study Visit for the Double-Blind Maintenance Phase [Double-Blind Maintenance Phase Safety Analysis Set]
14.2.2.2.24	IMPACT III Domains by Treatment Arm and Study Visit for the Double-Blind Maintenance Phase [Double-Blind Maintenance Phase Safety Analysis Set]
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14.2.3.1.1	Summary of Plasma Concentration during Double-Blind Acute Phase by Treatment Arm [Double-Blind Acute Phase Safety Analysis Set]
14.2.3.1.2	Summary of Plasma Concentration during Open-Label Acute Phase by High-Dose MMX [Open-Label Acute Phase Safety Analysis Set]
14.2.3.1.3	Summary of Plasma Concentration during Double-Blind Maintenance Phase by Treatment Arm [Double-Blind Maintenance Phase Safety Analysis Set]
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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
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Adverse Events	
14.3.1.1.1	Overall Treatment-emergent Adverse Events (TEAEs) [Overall Safety Analysis Set]
14.3.1.1.2	Overall Treatment-emergent Adverse Events (TEAEs) during Double-Blind Acute Phase by Treatment Arm [Double-Blind Acute Phase Safety Analysis Set]
14.3.1.1.3	Overall Treatment-emergent Adverse Events (TEAEs) during Open-Label Acute Phase by High-Dose MMX [Open-Label Acute Phase Safety Analysis Set]
14.3.1.1.4	Overall Treatment-emergent Adverse Events (TEAEs) during Double-Blind Maintenance Phase by Treatment Arm [Double-Blind Maintenance Phase Safety Analysis Set]

Table Number	Table Title
14.3.1.2.1	Treatment-emergent Adverse Events (TEAEs) by System Organ Class, Preferred Term [Overall Safety Analysis Set]
14.3.1.2.2	Treatment-emergent Adverse Events (TEAEs) during Double-Blind Acute Phase by System Organ Class, Preferred Term and Treatment Arm [Double-Blind Acute Phase Safety Analysis Set]
14.3.1.2.3	Treatment-emergent Adverse Events (TEAEs) during Open-Label Acute Phase by System Organ Class, Preferred Term and High-Dose MMX [Open-Label Acute Phase Safety Analysis Set]
14.3.1.2.4	Treatment-emergent Adverse Events (TEAEs) during Double-Blind Maintenance Phase by System Organ Class, Preferred Term and Treatment Arm [Double-Blind Maintenance Phase Safety Analysis Set]
14.3.1.3.1	Frequently Occurring (>=5%) Treatment-emergent Adverse Events (TEAEs) by Preferred Term [Overall Safety Analysis Set]
14.3.1.3.2	Frequently Occurring (>=5%) Treatment-emergent Adverse Events (TEAEs) during Double-Blind Acute Phase by Preferred Term and Treatment Arm [Double-Blind Acute Phase Safety Analysis Set]
14.3.1.3.3	Frequently Occurring (>=5%) Treatment-emergent Adverse Events (TEAEs) during Open-Label Acute Phase by Preferred Term and High-Dose MMX [Open-Label Acute Phase Safety Analysis Set]
14.3.1.3.4	Frequently Occurring (>=5%) Treatment-emergent Adverse Events (TEAEs) during Double-Blind Maintenance Phase by Preferred Term and Treatment Arm [Double-Blind Maintenance Phase Safety Analysis Set]
14.3.2.1.1	Treatment-emergent Adverse Events (TEAEs) by Maximum Severity, System Organ Class, Preferred Term and Treatment Arm [Overall Safety Analysis Set]
14.3.2.1.2	Treatment-emergent Adverse Events (TEAEs) during Double-Blind Acute Phase by Maximum Severity, System Organ Class, Preferred Term and Treatment Arm [Double-Blind Acute Phase Safety Analysis Set]
14.3.2.1.3	Treatment-emergent Adverse Events (TEAEs) during Open-Label Acute Phase by Maximum Severity, System Organ Class, Preferred Term and High-Dose MMX [Open-Label Acute Phase Safety Analysis Set]
14.3.2.1.4	Treatment-emergent Adverse Events (TEAEs) during Double-Blind Maintenance Phase by Maximum Severity, System Organ Class, Preferred Term and Treatment Arm [Double-Blind Maintenance Phase Safety Analysis Set]
14.3.2.2.1	Treatment-emergent Adverse Events (TEAEs) Considered Related to Investigational Product by System Organ Class, Preferred Term and Treatment Arm [Overall Safety Analysis Set]

Table Number	Table Title
14.3.2.2.2	Treatment-emergent Adverse Events (TEAEs) Considered Related to Investigational Product during Double-Blind Acute Phase by System Organ Class, Preferred Term and Treatment Arm [Double-Blind Acute Phase Safety Analysis Set]
14.3.2.2.3	Treatment-emergent Adverse Events (TEAEs) Considered Related to Investigational Product during Open-Label Acute Phase by System Organ Class and Preferred Term [Open-Label Acute Phase Safety Analysis Set]
14.3.2.2.4	Treatment-emergent Adverse Events (TEAEs) Considered Related to Investigational Product during Double-Blind Maintenance Phase by System Organ Class, Preferred Term and Treatment Arm [Double-Blind Maintenance Phase Safety Analysis Set]
14.3.3.1.1	Serious Treatment-emergent Adverse Events (TEAEs) Leading to Death by System Organ Class, Preferred Term and Treatment Arm [Overall Safety Analysis Set]
14.3.3.1.2	Serious Treatment-emergent Adverse Events (TEAEs) Leading to Death during Double-Blind Acute Phase by System Organ Class, Preferred Term and Treatment Arm [Double-Blind Acute Phase Safety Analysis Set]
14.3.3.1.3	Serious Treatment-emergent Adverse Events (TEAEs) Leading to Death during Open-Label Acute Phase by System Organ Class, Preferred Term and High-Dose MMX [Open-Label Acute Phase Safety Analysis Set]
14.3.3.1.4	Serious Treatment-emergent Adverse Events (TEAEs) Leading to Death during Double-Blind Maintenance Phase by System Organ Class, Preferred Term and Treatment Arm [Open-Label Acute Phase Safety Analysis Set]
14.3.3.2.1	Treatment-emergent Adverse Events (TEAEs) Leading to Discontinuation of Investigational Product by System Organ Class, Preferred Term and Treatment Arm [Overall Safety Analysis Set]
14.3.3.2.2	Treatment-emergent Adverse Events (TEAEs) Leading to Discontinuation of Investigational Product during Double-Blind Acute Phase by System Organ Class, Preferred Term and Treatment Arm [Double-Blind Acute Phase Safety Analysis Set]
14.3.3.2.3	Treatment-emergent Adverse Events (TEAEs) Leading to Discontinuation of Investigational Product during Open-Label Acute Phase by System Organ Class, Preferred Term and High-Dose MMX [Open-Label Acute Phase Safety Analysis Set]
14.3.3.2.4	Treatment-emergent Adverse Events (TEAEs) Leading to Discontinuation of Investigational Product during Double-Blind Maintenance Phase by System Organ Class, Preferred Term and Treatment Arm [Double-Blind Maintenance Phase Safety Analysis Set]

Table Number	Table Title
14.3.3.3.1	Treatment-emergent Adverse Events of Special Interest by System Organ Class, Preferred Term and Treatment Arm [Overall Safety Analysis Set]
14.3.3.3.2	Treatment-emergent Adverse Events of Special Interest during Double-Blind Acute Phase by System Organ Class, Preferred Term and Treatment Arm [Double-Blind Acute Phase Safety Analysis Set]
14.3.3.3.3	Treatment-emergent Adverse Events of Special Interest during Open-Label Acute Phase by System Organ Class, Preferred Term and High-Dose MMX [Open-Label Acute Phase Safety Analysis Set]
14.3.3.3.4	Treatment-emergent Adverse Events of Special Interest during Double-Blind Maintenance Phase by System Organ Class, Preferred Term and Treatment Arm [Double-Blind Maintenance Phase Safety Analysis Set]
14.3.3.4.1	Serious Treatment-emergent Adverse Events (TEAEs) by System Organ Class, Preferred Term and Treatment Arm [Overall Safety Analysis Set]
14.3.3.4.2	Serious Treatment-emergent Adverse Events (TEAEs) during Double-Blind Acute Phase by System Organ Class, Preferred Term and Treatment Arm [Double-Blind Acute Phase Safety Analysis Set]
14.3.3.4.3	Serious Treatment-emergent Adverse Events (TEAEs) during Open-Label Acute Phase by System Organ Class, Preferred Term and High-Dose MMX [Open-Label Acute Phase Safety Analysis Set]
14.3.3.4.4	Serious Treatment-emergent Adverse Events (TEAEs) during Double-Blind Maintenance Phase by System Organ Class, Preferred Term and Treatment Arm [Double-Blind Maintenance Phase Safety Analysis Set]
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14.3.4.1	Quantitative Clinical Laboratory Results during Double-Blind Acute Phase by Treatment Arm: Hematology [Double-Blind Acute Phase Safety Analysis Set]
14.3.4.2	Quantitative Clinical Laboratory Results during Open-Label Acute Phase: Hematology [Open-Label Acute Phase Safety Analysis Set]
14.3.4.3	Quantitative Clinical Laboratory Results during Double-Blind Maintenance Phase by Treatment Arm: Hematology [Double-Blind Maintenance Phase Safety Analysis Set]
14.3.4.4	Shift from Baseline in Clinical Laboratory Results during Double-Blind Acute Phase by Treatment Arm: Hematology [Double-Blind Acute Phase Safety Analysis Set]
14.3.4.5	Shift from Week 0 in Clinical Laboratory Results during Open-Label Acute Phase : Hematology [Open-Label Acute Phase Safety Analysis Set]

Table Number	Table Title
14.3.4.6	Shift from Week 0 in Clinical Laboratory Results during Double-Blind Maintenance Phase by Treatment Arm: Hematology [Double-Blind Maintenance Phase Safety Analysis Set]
14.3.4.7	Potentially Clinically Important (PCI) Laboratory Results during Double-Blind Acute Phase by Treatment Arm: Hematology [Double-Blind Acute Phase Safety Analysis Set]
14.3.4.8	Potentially Clinically Important (PCI) Laboratory Results during Open-Label Acute Phase : Hematology [Open-Label Acute Phase Safety Analysis Set]
14.3.4.9	Potentially Clinically Important (PCI) Laboratory Results during Double-Blind Maintenance Phase by Treatment Arm: Hematology [Double-Blind Maintenance Phase Safety Analysis Set]
14.3.4.10	Normal Ranges and Potentially Clinically Important (PCI) Criteria: Hematology
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14.3.4.11	Quantitative Clinical Laboratory Results during Double-Blind Acute Phase by Treatment Arm: Biochemistry [Double-Blind Acute Phase Safety Analysis Set]
14.3.4.12	Quantitative Clinical Laboratory Results during Open-Label Acute Phase: Biochemistry [Open-Label Acute Phase Safety Analysis Set]
14.3.4.13	Quantitative Clinical Laboratory Results during Double-Blind Maintenance Phase by Treatment Arm: Biochemistry [Double-Blind Maintenance Phase Safety Analysis Set]
14.3.4.14	Shift from Baseline in Clinical Laboratory Results during Double-Blind Acute Phase by Treatment Arm: Biochemistry [Double-Blind Acute Phase Safety Analysis Set]
14.3.4.15	Shift from Week 0 in Clinical Laboratory Results during Open-Label Acute Phase: Biochemistry [Open-Label Acute Phase Safety Analysis Set]
14.3.4.16	Shift from Week 0 in Clinical Laboratory Results during Double-Blind Maintenance Phase by Treatment Arm: Biochemistry [Double-Blind Maintenance Phase Safety Analysis Set]
14.3.4.17	Potentially Clinically Important (PCI) Laboratory Results during Double-Blind Acute Phase by Treatment Arm: Biochemistry [Double-Blind Acute Phase Safety Analysis Set]
14.3.4.18	Potentially Clinically Important (PCI) Laboratory Results during Open-Label Acute Phase: Biochemistry [Open-Label Acute Phase Safety Analysis Set]

Table Number	Table Title
14.3.4.19	Potentially Clinically Important (PCI) Laboratory Results during Double-Blind Maintenance Phase by Treatment Arm: Biochemistry [Double-Blind Maintenance Phase Safety Analysis Set]
14.3.4.20	Normal Ranges and Potentially Clinically Important (PCI) Criteria: Biochemistry
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14.3.5.1	Actual Values and Change from Baseline in Vital Signs during Double-Blind Acute Phase by Treatment Arm [Double-Blind Acute Phase Safety Analysis Set]
14.3.5.2	Actual Values and Change from Week 0 in Vital Signs during Open-Label Acute Phase [Open-Label Acute Phase Safety Analysis Set]
14.3.5.3	Actual Values and Change from Week 0 in Vital Signs during Double-Blind Maintenance Phase by Treatment Arm [Double-Blind Maintenance Phase Safety Analysis Set]
14.3.5.4	Potentially Clinically Important (PCI) Vital Signs Results during Double-Blind Acute Phase by Treatment Arm [Double-Blind Acute Phase Safety Analysis Set]
14.3.5.5	Potentially Clinically Important (PCI) Vital Signs Results during Open-Label Acute Phase [Open-Label Acute Phase Safety Analysis Set]
14.3.5.6	Potentially Clinically Important (PCI) Vital Signs Results during Double-Blind Maintenance Phase by Treatment Arm [Double-Blind Maintenance Phase Safety Analysis Set]
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14.3.8.1	Compliance during Double-Blind Acute Phase by Treatment Arm [Double-Blind Acute Phase Safety Analysis Set]
14.3.8.2	Compliance during Open-Label Acute Phase [Open-Label Acute Phase Safety Analysis Set]
14.3.8.3	Compliance during Double-Blind Maintenance Phase by Treatment Arm [Double-Blind Maintenance Phase Safety Analysis Set]
14.3.8.4	Investigational Product Exposure during Double-Blind Acute Phase by Treatment Arm [Double-Blind Acute Phase Safety Analysis Set]
14.3.8.5	Investigational Product Exposure during Open-Label Acute Phase [Open-Label Acute Phase Safety Analysis Set]
14.3.8.6	Investigational Product Exposure during Double-Blind Maintenance Phase by Treatment Arm [Double-Blind Maintenance Phase Safety Analysis Set]

Listing Number	Title
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16.1.7	Randomization Assignments [Overall Randomized Analysis Set]
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16.2.1.1.1	Overall Subject Disposition [Enrolled Set]
16.2.1.1.2	Subject Disposition during the Double-Blind Acute Phase [Enrolled Set]
16.2.1.1.3	Subject Disposition during the Open-Label Acute Phase [Enrolled Set]
16.2.1.1.4	Subject Disposition during the Double-Blind Maintenance Phase [Enrolled Set]
16.2.1.2	Subjects Who Terminated from the Study [Enrolled Set]
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16.2.1.3	Study Analysis Set Classification [Enrolled Set]
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16.2.2	Listing of Protocol Deviations [Enrolled Set]
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16.2.4.1	Subject Demographics [Enrolled Set]
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16.2.5.1	Investigational Product Accountability [Enrolled Set]
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[redacted]	[redacted]
16.2.5.4	Pharmacokinetic Blood Draw Times and Concentration Data [Enrolled Set]
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16.2.6.1	Clinical Response and/or Endoscopic Response [Enrolled Set]
16.2.6.2	Components of the UC-DAI by Timepoint - Rectal Bleeding and Stool Frequency Scores [Enrolled Set]
16.2.6.3	Components of the UC-DAI by Timepoint - Endoscopy Scores [Enrolled Set]
16.2.6.4	Components of the UC-DAI by Timepoint – PGA Score, Partial UC-DAI Score and Full UC-DAI Score [Enrolled Set]
16.2.6.5	Pediatric Ulcerative Colitis Activity Index (PUCAI) [Enrolled Set]
16.2.6.6	Global Change in Health (GCH) [Enrolled Set]
16.2.6.7.1	Subject Diary - Daily Ulcerative Colitis Scale (DUCS) – Child Questions and Responses

Listing Number	Title
16.2.6.7.2	Subject Diary - Daily Ulcerative Colitis Scale (DUCS) – Caregiver Questions and Responses
16.2.6.8	Subject Diary - Daily Ulcerative Colitis Scale (DUCS) – Scores [Enrolled Set]
16.2.6.9	Subject Diary - Overall Current Health [Enrolled Set]
16.2.6.10	IMPACT III: A Quality of Life Questionnaire for Children with Inflammatory Bowel Disease – Questions and Responses
16.2.6.11	IMPACT III: A Quality of Life Questionnaire for Children with Inflammatory Bowel Disease – Scores [Enrolled Set]
16.2.6.12	IMPACT III: Domains and Total Score [Enrolled Set]
Adverse Event Data	
16.2.7.1.1	Adverse Events [Enrolled Set]
16.2.7.1.2	Treatment-emergent Adverse Events (TEAEs) Considered Related to Investigational Product [Overall Safety Analysis Set]
16.2.7.2.1	Serious Treatment-emergent Adverse Events (TEAEs) [Overall Safety Analysis Set]
16.2.7.2.2	Serious Treatment-emergent Adverse Events Leading to Death [Overall Safety Analysis Set]
16.2.7.3	Treatment-emergent Adverse Events (TEAEs) Leading to Discontinuation of Investigational Product [Overall Safety Analysis Set]
16.2.7.4.1	Subjects Reporting Renal Toxicity Treatment-emergent Adverse Events (TEAEs) [Overall Safety Analysis Set]
16.2.7.4.2	Subjects Reporting Pericarditis Treatment-emergent Adverse Events (TEAEs) [Overall Safety Analysis Set]
16.2.7.4.3	Subjects Reporting Myocarditis Treatment-emergent Adverse Events (TEAEs) [Overall Safety Analysis Set]
16.2.7.4.4	Subjects Reporting Pancreatitis Treatment-emergent Adverse Events (TEAEs) [Overall Safety Analysis Set]
16.2.7.4.5	Subjects Reporting Gastritis Treatment-emergent Adverse Events (TEAEs) [Overall Safety Analysis Set]
16.2.7.4.6	Subjects Reporting Cholecystitis Treatment-emergent Adverse Events (TEAEs) [Overall Safety Analysis Set]
Laboratory Results	
16.2.8.1.1	Results for Pregnancy [Enrolled Set]
16.2.8.1.2.1	Clinical Laboratory Test Results: Hematology [Enrolled Set]
16.2.8.1.2.2	Clinical Laboratory Test Results: Biochemistry [Enrolled Set]
16.2.8.1.2.3	Clinical Laboratory Test Results: Urinalysis [Enrolled Set]

Listing Number	Title
[redacted]	[redacted]
16.2.8.1.2.5	Clinical Laboratory Test Results: Stool Sample Culture [Enrolled Set]
16.2.8.1.2.6	Clinical Laboratory Test Results: Stool Sample for Microbiome Analysis [Enrolled Set]
16.2.8.1.3.1	Subjects with Potentially Clinical Important (PCI) Laboratory Test Results: Hematology [Enrolled Set]
16.2.8.1.3.2	Subjects with Potentially Clinical Important (PCI) Laboratory Test Results: Biochemistry [Enrolled Set]
16.2.8.2.1	Vital Signs [Enrolled Set]
16.2.8.2.2	Subjects with Potentially Clinical Important (PCI) Vital Signs [Enrolled Set]

11. SCHEDULE OF EVENTS

Table 5: Double-blind Acute Phase

Visit	1 (Screening)	Recommended Telephone call[a]	2 (Baseline)	3[b]	3.1	3.2[c, d, e, f]	6[g]
Week/Month[h]	Day –21 to –3	Day –7 to –4	Week 0	Week 2	Week 4	Week 8/Withdrawal	Follow-up
Informed consent	✔						
Inclusion/exclusion criteria	✔		✔				
Demographics	✔						
Medical and medication history	✔						
Physical examination	✔					✔	
Height	✔					✔	
Weight	✔		✔			✔	
Vital signs	✔		✔	✔	✔	✔	
Biochemistry (includes C-reactive protein) and hematology	✔					✔	
Pregnancy test (for females of childbearing potential only)[i]	✔		✔	✔	✔	✔	
Pharmacokinetic blood sampling (at participating sites only)						✔	
[redacted]			✔				
Urinalysis	✔					✔[j]	
[redacted]	✔						
Stool sample (culture)[k, l]	✔						
[redacted]	✔					✔	

Table 5: Double-blind Acute Phase

Visit	1 (Screening)	Recommended Telephone call[a]	2 (Baseline)	3[b]	3.1	3.2[c, d, e, f]	6[g]
Week/Month[h]	**Day –21 to –3**	**Day –7 to –4**	**Week 0**	**Week 2**	**Week 4**	**Week 8/Withdrawal**	**Follow-up**
Review DUCS instructions, ability to read and understand e-diary with subject/caregiver	✔						
Subject/caregiver e-diary entry: rectal bleeding, stool frequency, DUCS, and Overall Current Health[m]	✔		✔	✔	✔	✔	
Assessment of e-diary compliance[a]		✔					
Global Change in Health[l]				✔	✔	✔	
IMPACT III[n]			✔			✔	
PUCAI (where applicable)			✔			✔	
Average stool frequency[o, p, q]			✔	✔	✔	✔	
Average rectal bleeding[o, p, q]			✔	✔	✔	✔	
PGA[p, q]			✔	✔	✔	✔	
Endoscopy (flexible sigmoidoscopy or colonoscopy) for study eligibility[h, q, r]	✔		✔				
Endoscopy (flexible sigmoidoscopy or colonoscopy), where possible for subjects who are not entering into the Open-label Acute Phase)[q]						✔	
Calculate partial UC-DAI			✔			✔	
IRT entry	✔		✔	✔	✔	✔	
Investigational product dispensed			✔	✔	✔	✔[s]	

Table 5: Double-blind Acute Phase

Visit	1 (Screening)	Recommended Telephone call[a]	2 (Baseline)	3[b]	3.1	3.2[c, d, e, f]	6[g]
Week/Month[h]	Day –21 to –3	Day –7 to –4	Week 0	Week 2	Week 4	Week 8/Withdrawal	Follow-up
Investigational product collected and compliance calculated				✔	✔	✔	
Adverse events	✔	✔	✔	✔	✔	✔	✔
Concomitant medication	✔		✔	✔	✔	✔	✔
Re-randomization (subjects entering Double-blind Maintenance Phase only)						✔	

Abbreviations: DUCS=Daily Ulcerative Colitis Scale for children and caregivers; eCRF=electronic case report form; e-diary=electronic diary; IRT= interactive response technology; PGA=Physician's Global Assessment; PUCAI=Pediatric Ulcerative Colitis Activity Index; UC-DAI=Ulcerative Colitis Disease Activity Index.

[a] Approximately 4 to 7 days prior to the Baseline Visit (Visit 2) and prior to each subsequent visit (Visits 3, 3.1, and 3.2), it is recommended that site staff telephone the subject or the subject's caregiver to remind them to enter UC-DAI symptoms (rectal bleeding and stool frequency) into the e-diary every night, even if the subject has no symptoms.

[b] Subjects may enter into the Open-label Acute Phase beginning at Visit 3 (after a minimum of 2 weeks double-blind treatment) and at any time until the end of the Double-blind Acute Phase provided all criteria have been met.

[c] Subjects will continue into the Open-label Acute Phase if they have not met the criteria to enter the Double-blind Maintenance Phase and are eligible to continue into the Open-label Acute Phase.

[d] Subjects will continue into the Double-blind Maintenance Phase if partial UC-DAI ≤1 (with rectal bleeding=0 and stool frequency ≤1 and PGA=0) and with mucosal healing (endoscopy score)=0 or 1, and are eligible to continue into the Double-blind Maintenance Phase.

[e] This will be the final visit for subjects not entering the Open-label Acute Phase or the Double-blind Maintenance Phase.

[f] The Baseline Visit (Visit 2) does not need to be repeated for subjects entering the Double-blind Maintenance Phase at the end of the Double-blind Acute Phase. Visit 3.2 will be considered the Week 0 visit for the next phase into which subjects are continuing.

[g] Follow-up assessment in this phase applies only to subjects who are discontinuing the study; may be performed via telephone call within 7 days of the last dose of investigational product.

[h] A visit window of ±3 days is permitted for all study visits except for the Screening Visit (Visit 1) and the Baseline Visit (Visit 2), which must occur 3 to 21 days following the Screening Visit (Visit 1). If the initial endoscopy is not adequate for mucosal healing score assignment due to inadequate bowel preparation, to allow for a repeat endoscopy to be conducted, the period of the Screening Visit (Visit 1) can be extended by an additional 14 days from the date of the initial endoscopy.

[i] The serum pregnancy test will be performed for all female subjects of childbearing potential at the screening visit (Visit 1) and Week 8/Withdrawal (Visit 3.2). Urine pregnancy tests will be performed at all other visits.

[j] Urinalysis performed at this visit only for subjects who are not continuing into the Open-label Acute Phase.

[redacted]

[l] Stool samples collected for culture may be processed by local laboratories; however, results from the central laboratory analysis will prevail and will be entered in the eCRF.

[m] Rectal bleeding, stool frequency, DUCS, and Overall Current Health e-diary entry is completed once a day before bedtime every day from the evening of the Screening Visit

Table 5: Double-blind Acute Phase

Visit	1 (Screening)	Recommended Telephone call[a]	2 (Baseline)	3[b]	3.1	3.2[c, d, e, f]	6[g]
Week/Month[h]	Day –21 to –3	Day –7 to –4	Week 0	Week 2	Week 4	Week 8/Withdrawal	Follow-up

(Visit 1), preferably for at least the 3 days immediately prior to the Baseline Visit (Visit 2). Rectal bleeding, stool frequency, DUCS and Overall Current Health e-diary entry is completed once a day before bedtime for the 5 days immediately prior to Visits 3, 3.1, and 3.2 of the Double-blind Acute Phase.

[n] Global Change in Health to be completed by caregivers of children aged 5-10 years and by children aged 11-17 years; IMPACT III to be completed by children aged 8-17 years only (see Section 4.3).

[o] The average stool frequency and rectal bleeding scores will be calculated and available to the investigator through a report from the e-diary provider.

[p] Components of the partial UC-DAI.

[q] Components of the modified full UC-DAI.

[r] For subjects entering the Double-Blind Acute Phase only: Subjects with an unconfirmed diagnosis of UC must have endoscopy performed during the Screening Visit (Visit 1). Subjects with a previously confirmed diagnosis must have endoscopy at the Screening Visit (Visit 1) or at the Baseline Visit (Visit 2) if endoscopy has not been performed within 21 days prior to the Screening Visit (Visit 1).

[s] Only for subjects continuing into the Open- label Acute or Double- blind Maintenance Phase.

Table 6: Open-label Acute Phase

Visit	Recommended Telephone call[a]	4	4.1	4.2[b, c, d, e]	6[f]
Week[g]	Day –7 to –4	Week 2	Week 4	Week 8/Withdrawal	Follow-up
Physical examination				✔	
Height				✔	
Weight				✔	
Vital signs		✔	✔	✔	
Biochemistry (includes C-reactive protein) and hematology				✔	
Pregnancy test (for females of childbearing potential only)[h]		✔	✔	✔	
Pharmacokinetic blood sampling (at participating sites only)				✔	
Urinalysis				✔	
[redacted]				✔	
Subject e-diary entry: rectal bleeding, stool frequency, DUCS, and Overall Current Health[i]		✔	✔	✔	
Assessment of e-diary compliance[a]	✔				
PUCAI (where applicable)				✔	
Average stool frequency[j,k,l]		✔	✔	✔	
Average rectal bleeding[j, k, l]		✔	✔	✔	
PGA[k, l]				✔	
Endoscopy (flexible sigmoidoscopy or colonoscopy), where possible[k]				✔	
IRT entry		✔	✔	✔	
Calculate partial UC-DAI				✔	

Table 6: Open-label Acute Phase

Visit	Recommended Telephone call[a]	4	4.1	4.2[b, c, d, e]	6[f]
Week[g]	Day –7 to –4	Week 2	Week 4	Week 8/Withdrawal	Follow-up
Investigational product dispensed		✔	✔	✔ [m]	
Investigational product collected and compliance calculated		✔	✔	✔	
Adverse events	✔	✔	✔	✔	✔
Concomitant medication		✔	✔	✔	✔
Re-randomization (subjects entering Double-blind Maintenance Phase only)				✔	

Abbreviations: DUCS=Daily Ulcerative Colitis Scale for children and caregivers; e-diary=electronic diary; IRT= interactive response technology; PGA=Physician's Global Assessment; PUCAI=Pediatric Ulcerative Colitis Activity Index; UC-DAI=Ulcerative Colitis Disease Activity Index.

[a] Approximately 4 to 7 days prior to Visit 4 and prior to each subsequent visit (Visits 4.1 and 4.2), it is recommended that site staff telephone the subject or the subject's caregiver to remind them to enter UC-DAI symptoms (rectal bleeding and stool frequency) into the e-diary every night, even if the subject has no symptoms.

[b] Subjects will continue into the Double-blind Maintenance Phase if partial UC-DAI ≤1 (with rectal bleeding=0 and stool frequency ≤1 and PGA=0) and are eligible to continue into the Double-blind Maintenance Phase.

[c] Subjects will be withdrawn from the study if they have not achieved a partial UC-DAI ≤1 (with rectal bleeding=0 and stool frequency ≤1 and PGA=0).

[d] This will be the final visit for subjects not continuing into the Double-blind Maintenance Phase.

[e] The Baseline Visit (Visit 2) does not need to be repeated for subjects entering the Double-blind Maintenance Phase at the end of the Open-label Acute Phase. Visit 4.2 will be considered the Week 0 visit for the Double-blind Maintenance Phase.

[f] Follow-up assessment in this phase applies only to subjects who are discontinuing the study; may be performed via telephone call within 7 days of the last dose of investigational product.

[g] A visit window of ±3 days is permitted for all study visits.

[h] The serum pregnancy test will be performed for all female subjects of childbearing potential at Week 8/Withdrawal (Visit 4.2). Urine pregnancy tests will be performed at all other visits.

[i] Rectal bleeding, stool frequency, DUCS, and Overall Current Health e-diary entry is completed once a day before bedtime every day for 5 days immediately prior to Visits 4, 4.1 and 4.2 of the Open-label Acute Phase.

[j] The average stool frequency and rectal bleeding scores will be calculated and available to the investigator through a report from the e-diary provider.

[k] Components of the partial UC-DAI.

[l] Components of the modified full UC-DAI.

[m] Only for subjects continuing into the Double-blind Maintenance Phase.

Table 7: Double-blind Maintenance Phase

Visit	1 (Screening)[a]	Recommended Telephone call[b]	2 (Baseline)[a]	5	5.1	5.2	6[c]
Day/Month[d]	Day –21 to –3	Day –7 to –4	Week 0	Weeks 2-4	Week 13	Week 26/ Withdrawal	Follow-up
Informed consent	✔						
Inclusion/exclusion criteria	✔		✔				
Demographics	✔						
Medical and medication history	✔						
Physical examination	✔				✔	✔	
Height	✔					✔	
Weight	✔		✔			✔	
Vital signs	✔		✔		✔	✔	
Biochemistry (includes C-reactive protein) and hematology	✔					✔	
Pregnancy test (for females of childbearing potential only)[e]	✔		✔	✔	✔	✔	
Pharmacokinetic blood sampling (at participating sites only)						✔	
Urinalysis	✔					✔	
[redacted]			✔				
[redacted]	✔						
Stool sample (culture)[f, g]	✔						
[redacted]	✔					✔	
Review DUCS instructions, ability to read and understand e-diary with subject/caregiver	✔						
Subject/caregiver e-diary entry: rectal bleeding, stool frequency, DUCS, and Overall Current Health[h]	✔		✔		✔	✔	
Assessment of e-diary compliance[a]		✔					

Table 7: Double-blind Maintenance Phase

Visit	1 (Screening)[a]	Recommended Telephone call[b]	2 (Baseline)[a]	5	5.1	5.2	6[c]
Day/Month[d]	**Day –21 to –3**	**Day –7 to –4**	**Week 0**	**Weeks 2-4**	**Week 13**	**Week 26/ Withdrawal**	**Follow-up**
Global Change in Health[i]						✔	
IMPACT III[i]			✔			✔	
PUCAI (where applicable)			✔			✔	
Average stool frequency [j, k, l]			✔		✔	✔	
Average rectal bleeding [j, k, l]			✔		✔	✔	
PGA [k, l]			✔			✔	
Endoscopy (flexible sigmoidoscopy or colonoscopy) for study eligibility[d, l, m]	✔		✔				
Endoscopy (flexible sigmoidoscopy or colonoscopy), where possible[l]						✔	
IRT entry	✔		✔	✔	✔	✔	
Calculate partial UC-DAI			✔			✔	
Investigational product dispensed			✔	✔	✔		
Investigational product collected and compliance calculated				✔	✔	✔	
Adverse events	✔	✔	✔	✔	✔	✔	✔
Concomitant medication	✔		✔		✔	✔	✔

Abbreviations: DUCS=Daily Ulcerative Colitis Scale for children and caregivers; eCRF=electronic case report form; e-diary=electronic diary; IRT= interactive response technology; PGA=Physician's Global Assessment; PUCAI=Pediatric Ulcerative Colitis Activity Index; UC-DAI=Ulcerative Colitis Disease Activity Index.

[a] The Screening Visit (Visit 1) and the Baseline Visit (Visit 2) in Table 7 apply only to subjects entering directly into the Double-blind Maintenance Phase.

[b] Approximately 4 to 7 days prior to the Baseline Visit (Visit 2) and prior to each subsequent visit (Visits 5, 5.1, and 5.2), it is recommended that site staff telephone the subject or the subject's caregiver to remind them to enter UC-DAI symptoms (rectal bleeding and stool frequency) into the e-diary every night, even if the subject has no symptoms.

[c] Follow-up assessment may be performed via telephone call within 7 days of the last dose of investigational product.

[d] A visit window of ±3 days is permitted for all study visits except for the Screening Visit (Visit 1) (must be 3 to 21 days) and the Baseline Visit (Visit 2), which must occur 3 to 21 days following the Screening Visit (Visit 1). If the initial endoscopy is not adequate for mucosal healing score assignment due to inadequate bowel preparation, to allow for a repeat endoscopy to be conducted, the period of the Screening Visit (Visit 1) can be extended by an additional 14 days from the date of the initial endoscopy.

[e] The serum pregnancy test will be performed for all female subjects of childbearing potential at the screening visit (Visit 1) and Week 26/Withdrawal (Visit 5.2). Urine pregnancy tests will be performed at all other visits.

[redacted]

Table 7: Double-blind Maintenance Phase

Visit	1 (Screening)[a]	Recommended Telephone call[b]	2 (Baseline)[a]	5	5.1	5.2	6[c]
Day/Month[d]	Day –21 to –3	Day –7 to –4	Week 0	Weeks 2-4	Week 13	Week 26/ Withdrawal	Follow-up

[redacted].

[g] Stool samples collected for culture may be processed by local laboratories in addition to the assessment by the central laboratory. Central laboratory results will prevail and, as such, they will be the data entered into the eCRF.

[h] Rectal bleeding, stool frequency, DUCS and Overall Current Health e-diary entry is completed once a day before bedtime every day during the Screening Visit (Visit 1), preferably for at least the 3 days immediately prior to the Baseline Visit (Visit 2). Rectal bleeding, stool frequency, DUCS and Overall Current Health e-diary entry is completed once a day before bedtime for the 5 days immediately prior to Visit 5.1 and Visit 5.2.

[i] Global Change in Health to be completed by caregivers of children aged 5-10 years and by children aged 11-17 years; IMPACT III to be completed by children aged 8-17 years only.

[j] The average stool frequency and rectal bleeding scores will be calculated and available to the investigator through a report from the e-diary provider.

[k] Components of the partial UC-DAI.

[l] Components of the modified full UC-DAI.

[m] For subjects entering the Double-blind Maintenance Phase directly: Subjects with a previously confirmed diagnosis must have endoscopy at the Screening Visit (Visit 1) or at the Baseline Visit (Visit 2). If the initial endoscopy is not adequate for mucosal healing score assignment due to inadequate bowel preparation, to allow for a repeat endoscopy to be conducted, the period of the Screening Visit (Visit 1) can be extended by an additional 14 days from the date of the initial endoscopy.