TITLE PAGE

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MCP-103-312

A Phase 3b, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial of Linaclotide 290 µg Administered Orally for 12 Weeks Followed by a 4-week Randomized Withdrawal Period in Patients with Irritable Bowel Syndrome with Constipation

STATISTICAL ANALYSIS PLAN

Final Version 1.0: 27 November 2018

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APC	Abdominal Pain and Constipation
AST	aspartate aminotransferase
BM	bowel movement
BP	blood pressure
bpm	beats per minute
BSFS	Bristol Stool Form Scale
CBC	complete blood count
CDC HRQOL-4	CDC Healthy Days Core Module
CIC	chronic idiopathic constipation
CMH	Cochran-Mantel-Haenszel
CSBM	complete spontaneous bowel movement
eCRF	electronic case report form
eDiary	electronic diary
EOT	End-of-Treatment Period
HEENT	head, ears, eyes, nose, throat
IBS-C	Irritable Bowel Syndrome with Constipation
ICF	informed consent form
IPD	Important Protocol Deviations
ITT	Intent-to-Treat
IWRS	interactive web response system

LLN	lower limit of normal
LOCF	last observation carried forward
LS	least-squares
MCMC	Monte-Carlo Markov chain
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	Mixed Model Repeated Measures
NRS	numerical rating scale
OC	observed case
PCS	potentially clinically significant
PID	patient identification number
RM	rescue medication
RW	randomized withdrawal
SAE	serious adverse event
SAP	statistical analysis plan
SBM	spontaneous bowel movement
SD	standard deviation
SI	*Le Système International d'Unités* (International System of Units)
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

1.0 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and/or specified in the protocol of Study MCP-103-312 (dated 26 March 2018). Specifications for the tables, figures, and data listings are contained in a separate document.

2.0 STUDY OBJECTIVES

The objectives of this study are to evaluate the efficacy on abdominal symptoms (abdominal bloating, abdominal discomfort, and abdominal pain) and safety of linaclotide 290 µg administered orally to patients with irritable bowel syndrome with constipation (IBS-C).

3.0 STUDY DESIGN

3.1 GENERAL DESCRIPTION

The MCP-103-312 study is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 16-week study, consisting of 4 distinct periods (Screening, Pretreatment, Treatment, and Randomized Withdrawal). The study will enroll patients who have IBS-C diagnosed using Rome III criteria. Approximately 600 eligible patients will be randomized in equal proportions to one of two treatments: linaclotide 290 μg or placebo.

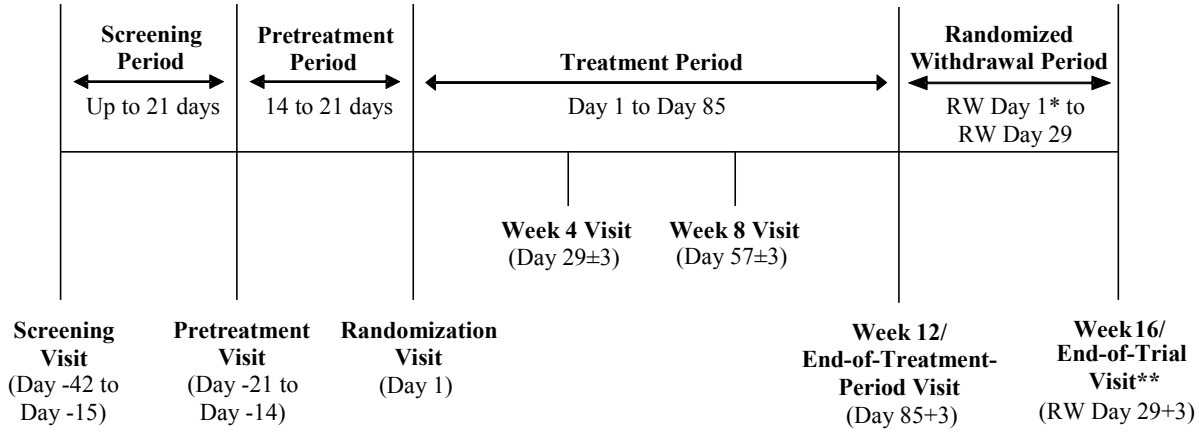
The length of this trial is 18-22 weeks, with 4 distinct periods, including up to 21 days of Screening, 14 to 21 days of Pretreatment, 12 weeks of double-blind treatment, and 4 weeks of randomized withdrawal. During the Pretreatment Period, patients will provide daily information on bowel habits, symptom severity, and use of Rescue Medicine. Patients meeting all of the entry criteria for this trial at the end of the Pretreatment Period will enter the Treatment Period. Patients who complete the 12-week Treatment Period and return for the Week 12/ETP Visit will enter the 4-week Randomized Withdrawal (RW) period and be allocated to study drug in a double-blind manner, as follows:

- Patients randomized to linaclotide 290 μg during the Treatment Period will be rerandomized to linaclotide 290 μg or placebo (1:1)
- Patients randomized to placebo during the Treatment Period will be allocated to linaclotide 290 μg

3.2 DISCUSSION OF STUDY DESIGN, INCLUDING CHOICE OF CONTROL GROUPS

A double-blind, placebo-controlled, parallel-group study design was chosen in accordance with the concepts in ICH E10, Choice of Control Groups and Related Issues in Clinical Trials, in order to provide comparable treatment groups and minimal chance of selection or investigator bias. The study has a 14- to 21-day Pretreatment Period to establish a baseline without therapy and to familiarize patients with data collection methodology (i.e., electronic diary [eDiary]), and a 12-week Treatment Period to compare the test treatment to the placebo control, and a 4-week RW period to evaluate persistence of treatment effect, the incidence of rebound (or worsening of symptoms from baseline) or other withdrawal effects, and potential need for retreatment.

Figure 3.2-1 Overview of Study Design



Note: there is no Day 0.
RW=Randomized Withdrawal

*RW Day 1 is the day after the Week 12/End-of-Treatment-Period Visit
**This visit represents the end of the trial.

3.3 TREATMENTS ADMINISTERED

Patients will be instructed to take one capsule in the morning at least 30 minutes before breakfast. Study drug in the form of 290 ug linaclotide or placebo oral capsules will be provided by Ironwood or designee. For the double-blind Treatment Period and RW Period.

3.4 METHODS OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

Patients who meet all the inclusion criteria and none of the exclusion criteria will be randomized into the study at the Randomization Visit on Day 1. Approximately 600 patients will be randomized in equal proportions to either linaclotide 290 µg or placebo.

Patients receiving linaclotide 290 µg during the Treatment Period who complete the 12-week Treatment Period and agree to continue into the 4-week RW period will be randomized in equal proportion to either remain on linaclotide 290 µg or switch to placebo; all patients receiving placebo during the Treatment Period will be allocated to linaclotide 290 µg for the RW Period.

Randomization numbers will be assigned by interactive web response system (IWRS).

3.5 BLINDING

This study is a double-blind study.

4.0 DETERMINATION OF SAMPLE SIZE

The sample size of 600 patients (300 patients per treatment group) was chosen to ensure adequate power for testing the fixed-sequence procedure for the primary and secondary efficacy endpoints (Section 6.6).

The power calculations for the primary endpoint are based on the placebo and linaclotide 290 µg treatment groups from the Phase 3 trial LIN-MD-31. The patients in LIN-MD-31 are considered representative of the patient population for this trial. Using a resampling with replacement-based simulation (1000 iterations) and controlling for multiplicity as outlined above, the trial will have >99% power to reject the primary endpoint and ~94% power to reject all primary and secondary hypotheses defined in the testing process.

5.0 PHARMACOKINETICS, EFFICACY AND SAFETY ASSESSMENTS

5.1 STUDY SCHEMATIC AND SCHEDULE OF ASSESSMENT

The schedule of evaluations for Study MCP-103-312 is presented in Table 5.1-1.

Table 5.1-1 Schedule of Evaluations

MCP-103-312							
Trial Period →	**Screening Period (Up to 21 days)**	**Pretreatment Period (14 to 21 days)**	**Treatment Period (12 weeks)**				**Randomized Withdrawal (RW) Period (4 weeks)[q]**
Visit →	**Screening Visit**	**Pretreatment Visit**	**Randomization Visit**	**Week 4 Visit**	**Week 8 Visit**	**Week 12/End-of-Treatment-Period Visit**	**Week 16/ End-of-Trial Visit [r]**
Visit Days →	**Day -42 through Day -15**	**Day -21 to Day -14**	**Day 1**	**Day 29±3**	**Day 57±3**	**Day 85+3**	**RW Day 29+3**
Visit Number →	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
Trial Procedure ↓							
Signature of ICF	X						
Inclusion and Exclusion Criteria Verification	X	X	X*				
IWRS Registration [a]	X	X	X†	X	X	X	X
Medical History [b]	X						
Prior IBS-C Symptom Management Assessment [c]	X						
Physical Examination [d]	X					X*	X
Body Weight and Height [e]	X	X	X*	X	X	X*	X
Seated Vital Signs [f]	X	X	X*	X	X	X*	X
Prior and Concomitant Medicines [g]	X	X	X*	X	X	X*	X
Clinical Laboratory Tests [h]	X		X*			X*	X
Pregnancy Test [i]	X		X*			X*	X
Laxative/Suppository/ Enema Washout Instructions [j]	X						
AE Evaluations [k]		X	X*	X	X	X*	X
eDiary Registration and Training [l]		X	X*	X	X	X*	X
Daily and Weekly Assessments [m]		X	X*	X	X	X*	X

MCP-103-312							
Trial Period →	**Screening Period (Up to 21 days)**	**Pretreatment Period (14 to 21 days)**	**Treatment Period (12 weeks)**				**Randomized Withdrawal (RW) Period (4 weeks)[q]**
Visit →	**Screening Visit**	**Pretreatment Visit**	**Randomization Visit**	**Week 4 Visit**	**Week 8 Visit**	**Week 12/End-of-Treatment-Period Visit**	**Week 16/ End-of-Trial Visit [r]**
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Visit Number →	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
Trial Procedure ↓							
eDiary Compliance Verification and Reminder [n]			X*	X	X	X*	X
Rescue Medicine Dispensed [o]		X	X	X	X	X	
Patient eDiary Entry, in Clinic			X*	X	X	X*	X
Randomization			X†			X	
IBS-QOL			X†	X	X	X	X
CDC HRQOL-4			X†			X	X
Study Drug Dispensed			X†	X	X	X[s]	
Study Drug Administration [p]			X				
Study Drug Accountability				X	X	X	X

AE=adverse event; BM=bowel movement; CBC=complete blood count; CDC HRQOL-4=Centers for Disease Control and Prevention Healthy Days Core Module; CIC=chronic idiopathic constipation; eDiary=electronic diary; EOT=End-of-Trial; ETP=End-of-Treatment-Period; IBS-C=irritable bowel syndrome with constipation; IBS-QOL=irritable bowel syndrome quality of life questionnaire; ICF=informed consent form; IWRS=interactive web response system; RW=randomized withdrawal.

* Done prior to randomization; † Done predose

a. Site personnel will interact with IWRS to register the patient visit. Refer to the IWRS User Manual.
b. Includes diagnosis using Rome IV criteria for IBS, which will be collected as part of the patient's disease-specific history. Rome IV diagnosis has no bearing on patient eligibility to participate in the trial (patients will be enrolled based Rome III criteria).
c. Prior IBS-C symptom management assessment includes prior treatments taken for IBS-C, lifestyle and diet modifications for alleviating symptoms of IBS-C, assessment of satisfaction with prior interventions' ability to relieve bowel and abdominal symptoms, and primary reason for stopping use.
d. A physical examination includes the following: general appearance, HEENT (head, ears, eyes, nose, and throat), neck, cardiovascular, thorax/lungs, breasts, abdomen, rectal, genitourinary, musculoskeletal, lymph nodes, skin, neurologic, and mental status. A rectal examination should be performed during the

Screening Period on all patients who do not require a colonoscopy. After the Screening Period, the rectal examination is optional and may be performed at the discretion of the investigator. Breast and genitourinary examinations are optional at the discretion of the investigator.

e. Height is measured only at the Screening Visit.
f. Vital signs must be obtained in the seated position and include oral temperature, respiratory rate, blood pressure, and pulse. Pulse and blood pressure readings will be taken after the patient has been sitting for five minutes.
g. At the Screening Visit, information related to concomitant medicine that patients are taking on the day of the visit will be captured as well as their prior use of certain IBS-C or CIC (approved or unapproved) prescription medications.
h. Chemistry, CBC, and urine drug screen. The urine drug screen will be performed at the Screening Visit only.
i. To be eligible to continue in the trial, a negative serum pregnancy test must be documented at the Screening Visit. A negative urine pregnancy test must be documented at the Randomization Visit and the Week 12/ETP Visit (prior to randomization), and a negative serum pregnancy test must be documented at the Week 16/End-of-Trial (EOT) Visit.
j. Study coordinator will instruct patients about the use of laxatives, suppositories, and enemas.
k. All AEs occurring after the patient signs the ICF will be captured.
l. At the Pretreatment Visit and all subsequent visits, the study coordinator will register the patient visit to the clinic in the patient's eDiary. At the Pretreatment Visit, the study coordinator will instruct the patients about the use of the eDiary. Refer to the eDiary User Manual.
m. An eDiary will be used for recording Daily BM-related Symptom Severity Assessments, Daily Abdominal Symptom-severity Assessments, Weekly Assessments, and Use of Bisacodyl or Other Laxatives, Suppositories, or Enemas. Patients will enter BMs and laxative use in the eDiary on an event-driven basis, and will complete an evening entry each day to record daily abdominal assessments and any BMs and/or laxative use not previously recorded for that day.
n. At the Randomization Visit and all subsequent visits, the study coordinator will review the eDiary entry information to verify patient compliance with the daily eDiary completion requirement. After determining the patient's compliance, the study coordinator will remind patients to complete the eDiary daily (except at the Week 16/EOT visit). eDiary questions may be found in the eDiary User Manual.
o. Rescue Medicine (oral bisacodyl or bisacodyl suppositories) will be supplied to patients at the Pretreatment Visit and, if needed, at subsequent study drug dispensing visits.
p. Study drug will be administered in the clinic at the Randomization Visit. Patients are instructed to fast for 2 hours before this clinic visit. On all other days, study drug will be taken once daily in the morning at least 30 minutes before breakfast.
q. The RW Period will start the day after the Week 12/ETP Visit (this will be considered RW Day 1).
r. Patients who are randomized but do not complete the Treatment Period or RW Period (withdraw consent or are discontinued before they have completed 12 weeks or 4 weeks of treatment, respectively), will be considered Treatment Period or RW Period withdrawals, respectively, and should complete the procedures required at the EOT Visit (even if out of window).
s. Patients will take their first dose of study drug in the RW Period on RW Day 1 (ie, the day after the Week 12/ETP Visit).

5.2 PHARMACOKINETIC ASSESSMENTS

There are no pharmacokinetic assessments planned for this study.

5.3 EFFICACY ASSESSMENTS

5.3.1 Primary Efficacy Assessments

The efficacy assessments that will be used to determine the primary efficacy endpoint are the daily patient assessments of abdominal bloating, abdominal discomfort, and abdominal pain at their worst (ie, the components of the abdominal score).

Daily Patient Assessment of Abdominal Pain at its Worst

Patient assessment of abdominal pain at its worst will be collected via a daily evening report in the eDiary. The rating of abdominal pain at its worst during the previous 24 hours on an 11-point NRS will be provided by the patient answering the following question:

"How would you rate your worst abdominal pain in the past 24 hours?"

<eDiary presents NRS where 0 is anchored with "No abdominal pain" and 10 is anchored with "Worst possible abdominal pain">

Daily Patient Assessment of Abdominal Discomfort at its Worst

Patient assessment of abdominal discomfort at its worst will be collected via a daily evening report in the eDiary. The rating of abdominal discomfort at its worst during the previous 24 hours on an 11-point NRS will be provided by the patient answering the following question:

"How would you rate your worst abdominal discomfort in the past 24 hours?"

<eDiary presents NRS where 0 is anchored with "No abdominal discomfort" and 10 is anchored with "Worst possible abdominal discomfort">

Daily Patient Assessment of Abdominal Bloating at its Worst

Patient assessment of abdominal bloating at its worst will be collected via a daily evening report in the eDiary. The rating of abdominal bloating at its worst during the previous 24 hours on an 11-point NRS will be provided by the patient answering the following question:

"How would you rate your worst abdominal bloating in the past 24 hours?"

<eDiary presents NRS where 0 is anchored with "No abdominal bloating" and 10 is anchored with "Worst possible abdominal bloating">

5.3.2 Secondary Efficacy Assessments

The efficacy assessments that will be used to determine the secondary efficacy endpoints are the daily patient assessments of abdominal pain, abdominal discomfort, and abdominal bloating at their worst, as described in Section 5.3.1.

5.3.3 Additional Efficacy Assessment

In addition to the primary/secondary efficacy assessments, the following efficacy assessments are used in determining the additional efficacy endpoints.

Complete Spontaneous Bowel Movement

The CSBM assessment is based on the eDiary questions that determine whether a BM is a CSBM:

BM Day and Time

Patients will report BMs on an event-driven basis. An evening report will ask whether the patient entered all BMs for that day, and collect BMs not previously entered for that day.

Association with a Sense of Complete Evacuation

This is assessed by the patient answering the following eDiary question for each BM:

"Did you feel like you completely emptied your bowels after your bowel movement?"

1=Yes
2=No

Day of Any Laxative Use

Patients will report use of bisacodyl or other laxatives, suppositories, or enemas on an event-driven basis. An evening report will ask whether the patient entered all laxative use for that day, and collect bisacodyl or other laxatives, suppositories, or enemas not previously entered for that day.

Each day of the Pretreatment, Treatment, and RW Periods, the patient will complete eDiary entries on an event-driven basis to report BMs, and whether the BM was associated with a sense of complete evacuation. (The patient is also asked to provide assessments of stool consistency and straining, which are described below.) The patient will also complete eDiary entries on an event-driven basis to report use of protocol-permitted bisacodyl (tablets or suppositories) or other laxatives, suppositories, or enemas to treat their symptoms. Patients will complete a daily evening report to enter any BMs and laxative usage not previously reported by the patient for that day (recall is limited to 24 hours or to the time of the previous evening's report).

Spontaneous Bowel Movement

The SBM assessment is based on the eDiary questions (described above) that determine whether a BM is an SBM:

- BM day and time
- Day of Any Laxative Use

Stool Consistency

Patient assessment of stool consistency will be collected using two questions by eDiary entry on an event-driven basis (ie, for each BM reported in the eDiary).

BSFS

For each BM, the patient assesses his/her stool using the BSFS which depicts the stool consistency characteristics along with descriptions for each of them. The 7-point ordinal BSFS is provided below (see Appendix 1 for full scale including pictures):

"Please describe the form of your stool using the following scale where:"

1=Separate hard lumps like nuts (difficult to pass)
2=Like a sausage but lumpy
3=Like a sausage but with cracks on the surface
4=Like a sausage or snake, smooth and soft
5=Soft pieces with clear-cut edges (easy to pass)
6=Fluffy pieces with ragged edges, a mushy stool
7=Watery, no solid pieces (entirely liquid)

5-point ordinal scale

Patients will also assess stool consistency by daily eDiary entry on an event-driven basis using a 5-point ordinal scale:

"How would you describe the consistency of your stool?"

1=Very hard
2=Hard
3=Neither too hard nor too soft
4=Loose but not watery
5=Very loose and watery

Straining

Patient assessment of straining will be collected by eDiary entry on an event-driven basis (ie, for each BM reported in the eDiary). For each BM, degree of straining will be assessed by the patient using the following 5-point ordinal scale:

"How much did you strain during your bowel movement?"

1=Not at all
2=A little (mild straining)
3=A fair amount (moderate straining)
4=A large amount (severe straining)
5=An extreme amount (extremely severe straining)

Weekly Patient Assessment of Constipation Severity

Patient assessment of constipation severity will be reported weekly by eDiary entry. The rating of constipation severity during the previous 7 days on a 5-point ordinal scale will be provided by the patient answering the following question:

"On average, how would you rate your constipation during the past 7 days?"

1=None
2=Mild
3=Moderate
4=Severe
5=Very severe

Weekly Patient Assessment of IBS Symptom Severity

Patient assessment of IBS symptom severity will be reported weekly by eDiary entry. The rating of IBS symptom severity during the previous 7 days on a 5-point ordinal scale will be provided by the patient answering the following question:

"On average, how would you rate your IBS symptoms during the past 7 days?"

1=None
2=Mild
3=Moderate
4=Severe
5=Very severe

Weekly Patient Assessment of Adequate Relief

Patient assessment of adequate relief of IBS symptoms will be reported weekly by eDiary entry. The rating of adequate relief during the previous 7 days on a binary scale will be provided by the patient answering the following question:

"Overall, have you had adequate relief from your IBS symptoms during the past 7 days?"

1=Yes
2=No

Weekly Patient Assessment of Treatment Satisfaction

Patient assessment of treatment satisfaction will be reported weekly by eDiary entry each week after the Randomization Visit. Patients will answer the following question on a 5-point ordinal scale:

"Overall, how satisfied are you with the study medication's ability to relieve your IBS symptoms?"

1=Not at all satisfied
2=A little satisfied
3=Moderately satisfied
4=Quite satisfied
5=Very satisfied

5.3.4 Health Outcomes Assessments

5.3.4.1 IBS-QOL

The IBS-QOL is an instrument for assessing the impact of IBS on a patient's quality of life (Appendix 2).(1) The IBS-QOL will be completed at the Randomization Visit prior to the patient receiving study drug and at subsequent visits as specified in the Schedule of Evaluations (Table 5.1-1). At each of the designated visits, the assessment will be triggered by site personnel on the patient's eDiary for the questionnaire to be self-administered by the patient.

5.3.4.2 CDC Healthy Days Core Module (CDC HRQOL-4)

The CDC Healthy Days Core Module (CDC HRQOL-4; Appendix 3) assesses a person's perceived health status through 4 questions that assess self-rated health, numbers of recent days when physical health or mental health was not good, and number of recent days with limitations due to poor physical or mental health.(2) For the CDC HRQOL-4 items, recent is defined as during the past 30 days. The CDC HRQOL-4 will be completed at the Randomization Visit prior to the patient receiving study drug and at subsequent visits as specified in the Schedule of Evaluations (Table 5.1-1). At each of the designated visits, the assessment will be triggered by site personnel on the patient's eDiary for the questionnaire to be self-administered by the patient.

5.4 SAFETY ASSESSMENTS

The safety parameters will include adverse events (AEs), clinical laboratory and vital sign parameters, and physical examination.

5.4.1 Adverse Events

The AE assessment (interview) will be collected from the time the patient signed the informed consent obtained until completion of trial participation (eg, early termination or Week 16/EOT Visit). At each trial visit, the investigator will inquire about the occurrence of AEs/SAEs since the last visit.

5.4.1.1 Causality Assessment

Causal relationship must be assessed according to the following scale:

- Related — An AE is attributed to the study medication if:
  - A temporal relationship to study drug administration makes a causal relationship plausible (eg, the event occurred within a reasonable time frame following administration of study medication); and/or
  - Other causative factor(s) (eg, the subject's clinical condition, other concomitant treatments) either do not explain the event or are less equally likely to have led to the occurrence of the event, or
  - The event improved with stopping of the investigational product, and/or
  - The event recurred upon re-exposure with investigational product
- Not Related — Any other event (refer to Section 8.2.1.2.2 of the protocol for details)

5.4.1.2 Severity Assessment

Severity will be assessed according to the following scale:

- Mild — A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate — A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research participant.
- Severe — A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

5.4.1.3 Serious Adverse Events

All adverse events will be categorized as Serious (as defined in the MCP-103-312 Protocol, Section 8.2.1.1) or Non-Serious.

5.4.2 Medical History

A complete medical history will be performed as defined in the Schedule of Evaluations (Table 5.1-1).

5.4.3 Physical Examination

A complete physical examination will be performed as defined in the Schedule of Evaluations (Table 5.1-1). A physical examination will include the following assessments: general appearance; head, ears, eyes, nose, and throat (HEENT); neck; cardiovascular; thorax/lungs; abdomen; musculoskeletal; lymph nodes; skin; neurologic; and mental status. Breast, genitourinary, and rectal examinations are optional at the discretion of the investigator, except as described in the Schedule of Evaluations (Table 5.1-1).

5.4.4 Vital Signs

Vital sign measurements will be performed as defined in the Schedule of Evaluations (Table 5.1-1). Vital sign measurements include oral temperature (°C), respiratory rate, systolic and diastolic blood pressure (BP), and pulse. Pulse and BP readings will be taken after the patient has been seated for at least 5 minutes.

5.4.5 Clinical Laboratory Data

Fasted blood and urine samples for clinical laboratory tests will be collected at the days and times defined in the Schedule of Evaluations (Table 5.1-1). A central laboratory will be used to evaluate all blood and urine samples (except the urine pregnancy test).

The following clinical laboratory tests will be performed:

Hematology: Absolute and differential white blood cell count, erythrocyte count, hemoglobin, hematocrit, platelet count, and red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration)

Chemistry: Sodium, magnesium, potassium, calcium, chloride, glucose, blood urea nitrogen, creatinine, total protein, alkaline phosphatase, albumin, total bilirubin, aspartate aminotransferase, alanine aminotransferase, bicarbonate, phosphate, cholesterol, and uric acid

Other: Urine drug screening (cocaine, barbiturates, amphetamines, opiates, benzodiazepine, alcohol, and cannabinoids) (Screening Visit only). Clinical significance of a positive urine drug screen will be assessed by the investigator; positive results for cocaine, barbiturates, and cannabinoids are exclusionary.

Pregnancy test: Serum human chorionic gonadotropin pregnancy test (for women of childbearing potential only) should be conducted at the Screening Visit and Week 16/EOT Visit. A negative urine pregnancy test must be documented at the Randomization Visit and the Week 12/ETP Visit for the patient to be eligible for randomization and dosing with study drug. Positive results on the pregnancy test will exclude a patient from participating or continuing in the trial.

6.0 STATISTICAL METHODS

6.1 GENERAL METHODS

Efficacy outcomes from the Treatment Period will be based on the ITT Population and will be summarized by treatment group assigned at the Randomization Visit. Efficacy outcomes from the RW Period only or from the Combined Treatment and RW Period will be based on the RW Population and will be summarized by treatment sequence determined at the Week 12/ETP Visit. Treatment periods will be summarized for safety in the same manner as efficacy; however, safety summaries (Safety Population) will be based on the actual treatment received.

Descriptive statistics including the number of patients, mean, minimum and maximum, and standard deviation (SD) will be calculated for continuous variables. Frequencies and percentages for each category will be calculated for categorical variables. Percentages will be based on the total number of non-missing values. The number missing will be presented, but without a percentage. All hypothesis tests will be two-sided with a 5% significance level, and 95% confidence intervals (CIs) will be used, unless stated otherwise.

All statistical analyses will be performed using SAS Version 9.3 (or later) for Windows.

6.2 ADJUSTING FOR COVARIATES

As a general approach, the baseline values will be included in the mixed model for repeated measures (MMRM) and analysis of covariance (ANCOVA) as a covariate when the postbaseline or change scores are analyzed. Heterogeneity of slopes will be explored (e.g., review of residuals, inclusion of an interaction term, comparison of group differences at the 25th and 75th percentiles).

6.3 HANDLING OF DROPOUTS/MISSING DATA IMPUTATION METHOD

For responder endpoints, a patient will be deemed a weekly non-responder for all weeks following the patient's discontinuation from the study. The responder definition will be applied to the week the patient discontinues. Unless stated otherwise, missing data will not be imputed.

6.4 INTERIM ANALYSIS AND DATA MONITORING

No formal interim analyses are planned to compare treatment groups with respect to efficacy or safety prior to formal completion of the trial.

6.5 MULTICENTER STUDIES

This study is being conducted in approximately 80 centers. Due to the potential of small numbers of patients per center, data will be pooled into the following 5 geographic regions (as listed in Section 9.3): Northeast, Southeast, Midwest, Southwest, and West.

All analyses using trial center will use this 5-category geographic region variable.

6.6 MULTIPLE COMPARISONS/MULTIPLICITY

The overall family-wise Type I error rate for the primary and secondary efficacy analyses will be controlled at the α=0.05 level by employing a fixed-sequence procedure as described below. Following the fixed-sequence procedure, if the primary hypothesis between the placebo group and the linaclotide 290 µg group is statistically significant (α=0.05) in the ITT Population, then the primary objective of the trial will have been achieved and the next hypothesis can be tested; otherwise, testing will stop. The testing of each sequential hypothesis is conditional on all the previous hypotheses being rejected at the 0.05 level of significance. If a hypothesis is not rejected at the 0.05 level of significance, then all remaining hypotheses are deemed not statistically significant. All hypothesis testing will be two-sided.

1. Linaclotide vs. placebo – Change from Baseline in Abdominal Score
2. Linaclotide vs. placebo – Change from Baseline in 12-week Abdominal Score (CDF)
3. Linaclotide vs. placebo – 6/12 Week Abdominal Score Responder
4. Linaclotide vs. placebo – Change from Baseline in Abdominal Score at Week 12
5. Linaclotide vs. placebo – Change from Baseline in Abdominal Score at Week 10
6. Linaclotide vs. placebo – Change from Baseline in Abdominal Score at Week 8
7. Linaclotide vs. placebo – Change from Baseline in Abdominal Score at Week 6
8. Linaclotide vs. placebo – Change from Baseline in Abdominal Score at Week 4
9. Linaclotide vs. placebo – Change from Baseline in Abdominal Score at Week 2
10. Linaclotide vs. placebo – Change from Baseline in Abdominal Score at Week 1

6.7 USE OF AN EFFICACY SUBSET

Not applicable

6.8 ACTIVE CONTROL TO SHOW EQUIVALENCE

Not applicable.

6.9 EXAMINATION OF SUBGROUPS

Subgroup analyses will be performed on the primary and secondary efficacy endpoints, as well as treatment emergent adverse events by preferred term using the subgroups defined in Table 6.9-1.

Table 6.9-1 Subgroup Variables

Subgroup Variable	***Subgroups***
Age	(1) <65; ≥65 (2) <65; ≥65 to <75; ≥75
Sex	Female; Male
Race	Caucasian; Black/African American; Other
Ethnic Origin	Hispanic; Non-Hispanic
Body Mass Index (BMI)	<30 kg/m^2; ≥30 kg/m^2

7.0 ANALYSIS METHODS

7.1 PATIENT POPULATIONS

7.1.1 Screened Population

The Screened Population consists of all patients who signed informed consent and received a patient identification (PID) number.

7.1.2 Safety Population

The Safety Population consists of all patients who received at least one dose of study drug.

7.1.3 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population consists of all randomized patients. Efficacy analysis will be based on the ITT population, in which patients are evaluated according to the treatment group to which they were assigned at randomization.

7.1.4 Randomized Withdrawal Population

The RW Population consists of all patients who were re-randomized or allocated to study drug upon completion of the Treatment Period. For the RW Period, there are 3 treatment sequences as follows:

1. **290 µg-290 µg** (290 µg linaclotide administered in the Treatment Period, followed by 290 µg linaclotide in the RW Period)
2. **290 µg-Placebo** (290 µg linaclotide administered in the Treatment Period, followed by placebo in the RW Period)
3. **Placebo-290 µg** (placebo administered in the Treatment Period, followed by 290 µg linaclotide in the RW Period)

Randomized Withdrawal Safety Population

The RW Safety Population consists of all patients who were re-randomized to or assigned to double-blind RW treatment and received at least one dose of RW treatment.

7.2 PROTOCOL DEVIATIONS

Protocol deviations and Important Protocol Deviations (IPD) will be identified and documented for all randomized patients prior to unblinding through programmatic checks of the study data and select individual data reviews. IPDs will be determined based on review of all protocol deviations and protocol deviation categories (i.e., Use of Disallowed Medication); this review will be performed by members of the Ironwood Clinical Trials team, including but not limited to the Clinical Medical Researcher and study Biostatistician. IPD categories include, but are not limited to:

- those who entered the study even though they did not satisfy the entry criteria
- those who developed withdrawal criteria during the study but were not withdrawn
- those who received the wrong treatment or incorrect dose

- those who received an excluded concomitant treatment

The number and percentage of subjects with IPDs will be presented by study treatment and IPD category. Protocol deviations and IPDs will be provided by patient in data listings.

7.3 PATIENT DISPOSITION

The number and percentage of patients included in each of the Safety, and ITT populations will be summarized overall and by treatment group for each trial center within each geographic region. The number of patients in the Screened Population will be summarized by geographic region (See Section 9.3 for definition of geographic region) and by study center.

The number and percentage of screen failure patients (i.e., patients who entered the Screening Period but not the Pretreatment Period) and the number and percentage of pretreatment failures (i.e., patients who entered the Pretreatment Period but were not randomized), along with the associated reasons for failure, will be tabulated overall for the Screened Population. Patients who initially failed screening and were re-screened will only be counted once, that is, the PID used for the rescreened subject will be summarized and listed for patient disposition.

The number and percentage of ITT patients, the number and percentage of patients who completed the Treatment Period, as well as the number and percentage of patients who prematurely discontinued treatment will be presented for each treatment group and pooled across treatment groups. The reasons for premature discontinuation from the Treatment Period as recorded on the trial completion forms of the electronic case report forms (eCRFs) will be summarized (number and percentage) by treatment group for the Randomized Population. The number and percentage of patients who prematurely discontinued treatment will be summarized for each treatment group by time of discontinuation, defined as the number of days from first dose of study drug to the date of last dose during the Treatment Period, categorized into weeks (Week 1 through Week 12). All patients who prematurely discontinue during the Treatment Period will be listed by discontinuation reason for the Randomized Population.

Similar to the Treatment Period, the number and percentage of patients who are re-randomized into the RW Period, complete the RW Period, and prematurely discontinue from the RW Period will be presented overall and by treatment sequence. The reason for premature discontinuation from the RW Period as recorded on the trial completion forms of the eCRFs will be summarized (number and percentage) by treatment sequence and overall.

7.4 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters (age, age group, race, ethnicity, sex), and baseline characteristics (weight; height; and body mass index, calculated as weight in kg/[height in m]^2) will be summarized descriptively for the Safety and ITT Populations. Baseline efficacy parameters (including the abdominal score, abdominal bloating, abdominal discomfort, abdominal pain, SBM frequency, CSBM frequency, BSFS score, stool consistency, and straining) will be summarized descriptively for the ITT Population.

Abnormalities in patients' medical and surgical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0. The number and percentage of patients with abnormalities in medical and surgical histories in each system organ class (SOC) and preferred term will be summarized by treatment group for the Safety Population.

7.5 MEASUREMENT OF TREATMENT COMPLIANCE

Dosing compliance for a specified period is defined as the total number of capsules taken by a patient during that period divided by the number of capsules that were expected to be taken during the same period, multiplied by 100. The total number of capsules taken will be calculated based on the following equation: total number of capsules dispensed – (number of capsules returned + number of capsules lost). The total number of capsules expected to be taken during a specified period equals the number of days in the period.

Descriptive statistics for study drug compliance for the Treatment Period overall, and for each of the 3 consecutive 4-week periods (weeks 1-4, 5-8, 9-12) in the Treatment Period (consistent with study drug dispensing) will be presented for the Safety Population. Similarly, descriptive statistics for the RW Period (RW weeks 1-4) will be presented for the RW Population.

7.6 EXTENT OF EXPOSURE

Exposure to study drug will be calculated as the number of days from the date of first dose taken to the date of last dose taken.

Exposure to study drug for the Safety Population during the double-blind treatment period will be summarized descriptively by treatment group. Overall treatment duration will also be categorized as 1 Day; >1 Day to ≤ 7 Days; >7 Days to ≤30 Days; >30 Days to ≤90 Days; and >90 Days and the number and percent of patients in each category will be summarized. In addition, a cumulative distribution graph of exposure to study drug by treatment will be provided.

Patient-years, defined as exposure to the study drug in years, will be summarized by treatment group for the Safety Population.

Similar summaries will be provided by treatment sequence for the RW period with the Overall treatment duration categorized as 1 Day; >1 Day to ≤7 Days; >7 Days to ≤21 Days; >21 Days to ≤28 Days, and >28 Days.

7.7 PRIOR AND CONCOMITANT MEDICATION

Prior medication is defined as any medication taken before the date of the first dose of double-blind study drug. Concomitant medicines are defined as any medicines taken on or after the date of first dose of study drug during the defined period (Treatment/RW). Any medicines started after the date of last dose of study drug for the defined period (Treatment/RW) will be excluded from the summaries related to concomitant medicines for that period.

Both prior and concomitant medications will be coded by drug name and therapeutic class using WHO Drug B2 March 2018 version or above. The use of prior and concomitant medications will be summarized for the Safety Population by the number and percentage of patients in each treatment group and for the RW Population by treatment sequence receiving each medication within each therapeutic class. If a patient took a specific medication multiple times or took multiple medications in the same category (based on Anatomical-Therapeutic-Chemical classification), that patient would be counted only once for the coded drug name or therapeutic class. The use of per-protocol rescue medicines is collected separately in the eDiary and will be summarized as described in Section 7.9.3.

7.8 EDIARY COMPLIANCE

Patients are required to enter their evening diary assessments into the eDiary each evening during the pretreatment, treatment, and RW periods. An evening assessment is considered complete if all questions, excluding the weekly assessments, are answered.

eDiary compliance will be calculated for baseline (pretreatment period), the treatment period (weeks 1-12), RW period (RW weeks 1-4), and for each week. For each time period, eDiary percent compliance will be calculated as 100* the number of completed evening assessments divided by the expected number of days in the period. Percent compliance will also be dichotomized as ≥80% and <80% for each period, as well as the number and percentage of patients with ≥4 / <4 complete eDiary entries each week. Descriptive statistics (number of patients, mean, SD, median, minimum, and maximum) for eDiary compliance will be presented for the ITT population by treatment; n and percent will be presented for the dichotomous categories.

7.9 EFFICACY ANALYSIS

All efficacy analyses will be based on the ITT Population for the Treatment Period and based on the RW Population for the RW Period.

Baseline values for efficacy parameters will be derived from the eDiary daily data collected in the Pretreatment Period, specifically the period of time from 14 days prior to randomization up to the time of randomization.

A patient's daily abdominal score is calculated as the average of the daily abdominal pain, abdominal bloating, and abdominal discomfort assessments. If two or more of these individual daily abdominal symptoms are missing, then the Abdominal Score for that day will be missing.

Baseline values for patient symptom severity parameters (e.g., abdominal score, abdominal discomfort, abdominal bloating, abdominal pain, and constipation severity) will be the average of the non-missing severity scores reported during this period.

An SBM is defined as a BM that occurs in the absence of laxative, enema, or suppository use on either the calendar day of the BM or the calendar day before the BM. CSBM is defined as an SBM associated with a sense of complete evacuation.

The baseline CSBM and SBM weekly rates will be derived based on the number of CSBMs and SBMs a patient had during this period.

Baseline stool consistency and straining will be calculated as the average of the non-missing values from the SBMs reported by the patient during this period. A patient's baseline Stool Consistency and straining cannot be assessed if the patient does not have at least one SBM during the Pretreatment Period. Patients with missing baseline Stool Consistency will be excluded from Stool Consistency analyses that involve change from baseline. Similarly, patients with missing baseline straining will be excluded from straining analyses that involve change from baseline.

For weekly responder parameters based on daily eDiary assessments, a patient with less than 4 complete evening reports during an analysis week will not be considered a responder for that week.

Trial centers will be pooled by geographic region (details provided in Section 9.3). In lieu of trial center, geographic region will be used in analyses adjusting for center-to-center variability.

All hypotheses will be tested at a two-sided 0.05 significance level (Section 6.6). All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

7.9.1 Primary Endpoint

The primary endpoint is the Change from Baseline in Abdominal Score at Each Week during the Treatment Period. The weekly Abdominal Score is the average of the non-missing daily Abdominal Scores during in a week. Change from baseline will be calculated as the weekly score minus the baseline score.

7.9.1.1 Analyses of the Primary Endpoint

Inferential testing between the linaclotide 290 µg and placebo groups with regard to the change from baseline in abdominal score over the Treatment Period will be evaluated employing a mixed model with repeated measures (MMRM) framework with week (categorical), treatment, geographic region, and week-by-treatment fixed effects, patient as the random effect, and baseline value as a covariate. An unstructured covariance structure will be utilized to model the covariance matrix. Descriptive statistics based on the MMRM model will include least-squares (LS) mean change from baseline for each treatment, the LS mean difference between linaclotide 290 µg and placebo, corresponding 95% CIs, and the p-value associated with the comparison.

7.9.1.2 Sensitivity Analyses of the Key Efficacy Parameters

If warranted, for the primary efficacy and secondary endpoints/analyses (defined in Section 7.9.2), the potential impact of missing data on the estimates of treatment effect will be assessed using a sensitivity analysis approach based on multiple imputations (MI).

In order to characterize the extent of missing data associated with the key efficacy parameter, the number and percentage of patients with <4 completed evening diaries will be presented by treatment group for the ITT Population for each week of the Treatment Period (Please refer to Section 7.8 for additional details).

Weekly data for a patient with <4 complete evening diaries in a week will be classified as missing for that week. Sensitivity analyses will utilize a pattern-mixture model using a placebo-based method (3).

The placebo-based MI imputes missing data after dropout (monotonic) based on the placebo group data using multiple imputation methodology for all subjects (including active treatment subjects).

The steps to implement placebo-based MI are as follows:

1. **Create a Monotonic Dataset**: One-thousand (1000) datasets will be generated where missing outcome data at intermittent week (s) (non-monotonic) will be first imputed for each treatment using non-missing data from all subjects within the treatment group by a Monte Carlo Markov Chain (MCMC) imputation model with treatment, baseline score, geographic region and weekly score. The MCMC statement (mcmc chain=multiple impute=monotone) in the SAS PROC MI procedure will be used. As a result, each of the 1000 datasets will only have missing ending data, or a monotone missing data pattern.
2. For each of the 1000 datasets with monotonic missing data, the monotonic missing weekly data will be imputed one week at a time by a sequence of MIs, as follows. Imputation will utilize data from all Placebo subjects and Active treatment with the week of interest (week currently being imputed) missing.
    a. For week 1, create two datasets: one containing all placebo patients and active patients with the week 1 value - missing, referred to as Mono_imp1; one containing all other patients, referred to as Mono_rest1.
    b. For Mono_imp1, impute the missing values at week 1 utilizing Proc MI:

```
PROC MI data=mono_imp1 out=reg_imp1 nimpute=1 seed=XXXX;
   By imputation;  /*note 1000 imputation performed in step 1*/
   Var base siteid change1 ;
   Monotone Regression (change1);
Run;
```

    c. Set Mono_rest1 and reg_imp1 Call this dataset IMP1.
    d. Repeat Steps 2a-2c for weeks 2 through 12, respectively

Note: for Week i, i>1,

```
PROC MI data=mono_impi out=reg_impi nimpute=1 seed=XXXX;
   By imputation;  /*note 1000 imputation performed in step 1*/
   Var base siteid change1 change2 . . . change(i-1) change(i);
   Monotone regression (change(i));
Run;
```

3. Analyze each of the 1000 imputed complete datasets.
    a. For continuous endpoints, perform same statistical analyses (MMRM) as described in Section 7.9.1.1 for observed case.
    b. For responder endpoint:
        a. Using the abdominal score data imputed above, recalculate the responder

b. For each imputed dataset, perform Cochran-Mantel-Haenszel (CMH) analyses as described in Section 7.9.2.1.

4. Estimation and Inference of the MI datasets will be performed using Rubin's combination rules (4) as implemented through the MIANALYZE procedure in SAS.

7.9.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Change from Baseline in 12-week Abdominal Score
  The 12-week Abdominal Score is the average of the non-missing Abdominal Scores reported over the course of the Treatment Period. Change from baseline will be calculated as the 12-week score minus the baseline score.
- 6/12 Week Abdominal Score Responder
  A 6/12 Week Abdominal Score Responder is a patient who meets the Weekly Abdominal Score Responder criteria for at least 6 out of the 12 weeks of the Treatment Period. For each week in the Treatment Period, a Weekly Abdominal Score Responder is a patient who has an improvement from baseline of at least 2 points (ie, a -2 change from baseline) in the respective weekly abdominal score.

7.9.2.1 Secondary Efficacy Analysis

The cumulative distribution functions (CDFs) for linaclotide 290 µg and placebo will be estimated for the Change from Baseline in 12-week Abdominal Score endpoint. The CDFs will be compared using the Wilcoxon rank sum test with Hodges-Lehmann estimator for the median difference.

For the secondary responder endpoint, the proportion of responders in the linaclotide 290 µg group will be compared to the proportion of responders in the placebo group using a Cochran-Mantel-Haenszel (CMH) test controlling for geographic region. The number and percent of responders, the difference in responder rates between the linaclotide 290 µg and placebo groups, the odds ratio relative to placebo controlling for geographic region, all corresponding 95% CIs, and the p-value associated with the CMH test will be presented. The 95% CIs for responder rates will be obtained using exact Clopper-Pearson method; 95% CIs for differences in responder rates will be obtained using the normal approximation to the binomial distribution.

A secondary time-course analysis of the Change from Baseline in Abdominal Score (see primary endpoint definition in Section 7.9.1.1) will also be conducted. Using the MMRM framework defined in the primary analyses, treatment difference between linaclotide 290 µg and placebo will be assessed at each individual week. For each week, descriptive statistics based on the MMRM model will include the LS mean change from baseline for each treatment, the LS mean difference between linaclotide 290 µg and placebo, corresponding 95% CIs, and the p-value associated with the treatment comparison. Only weeks 12, 10, 8, 6, 4, 2, and 1 are secondary analyses controlled for multiplicity.

7.9.3 Additional Efficacy Endpoints

Additional efficacy endpoints will be explored outside of the formal testing procedures and not controlled for multiplicity. These endpoints will include:

- 6/12 Week Abdominal Pain and Constipation (APC) +1 Responder

A 6/12 Week APC +1 Responder is a patient who meets the Weekly APC +1 Responder criteria for at least 6 out of the 12 weeks of the Treatment Period. For each week in the Treatment Period, a Weekly APC +1 Responder is a patient who has an increase from baseline of at least 1 in the respective CSBM weekly rate and has a decrease from baseline of at least 30% in the respective weekly abdominal pain score. If a patient did not enter information into the eDiary on at least 4 days for a particular Treatment Period week, the patient will not be considered a responder for that week.

- Change from Baseline in Abdominal Pain at Each Week

Abdominal pain is measured daily using an 11-point NRS. For each week on treatment, the weekly abdominal pain score is the mean of the non-missing daily values.

- Change from Baseline in CSBM Frequency Rate at Each Week

A patient's weekly CSBM frequency rate is the CSBM rate (CSBMs/week) calculated for that week.

- Change from Baseline in SBM Frequency Rate at Each Week

A patient's weekly SBM frequency rate is the SBM rate (SBMs/week) calculated for that week.

- Change from Baseline in BSFS (Stool Consistency) at Each Week

Stool consistency is measured using the 7-point BSFS. The patient's BSFS score for each week on treatment is the mean of the non-missing BSFS scores from the SBMs reported by the patient during the week.

- Change from Baseline in Stool Consistency at Each Week

Stool consistency is measured using a 5-point ordinal scale. The patient's stool consistency score for each week on treatment is the mean of the non-missing stool consistency scores from the SBMs reported by the patient during the week.

- Change from Baseline in Straining at Each Week

Straining is measured using a 5-point ordinal scale. The patient's straining score for each week on treatment is the mean of the non-missing straining scores from the SBMs reported by the patient during the week.

- Change from Baseline in Abdominal Discomfort at Each Week

Abdominal discomfort is measured daily using an 11-point NRS. For each week on treatment, the weekly abdominal discomfort score is the mean of the non-missing daily values.

- Change from Baseline in Abdominal Bloating at Each Week

Abdominal bloating is measured daily using an 11-point NRS. For each week on treatment, the weekly abdominal bloating score is the mean of the non-missing daily values.

- Percent Change from Baseline in Abdominal Pain at Each Week

Percent change will be calculated as 100 * the Change from Baseline in Abdominal Pain at Worst at each week divided by the baseline abdominal pain score.

- Change from Baseline in Percent of Days with Use of Rescue Medicine over the Treatment Period

The percent of days using per-protocol rescue medicine or any other laxative, suppository, or enema during each week will be calculated as 100 * the number of days rescue medicine was used during the week divided by the total number of days on treatment.

- SBM Within 24 Hours After First Dose Responder

A patient meets the SBM Within 24 Hours After First Dose Responder criteria if the amount of time between the randomization date and time and the time of first reported SBM is less than or equal to 24 hours. For patients who did not take their first dose of study medication on the randomization visit, then the first reported SBM must occur on the same study day as the first dose study day. Randomization date and time is utilized as a surrogate for the date and time of first dose because only first dose date, not time, is captured.

- 6/12 Week Abdominal Pain 30% Responder

A 6/12 Week Abdominal Pain 30% Responder is a patient who meets the Weekly Abdominal Pain 30% Responder criteria for at least 6 out of the 12 weeks of the Treatment Period. For each week in the Treatment Period, a Weekly Abdominal Pain 30% Responder is a patient who has a decrease from baseline of at least 30% in the respective weekly abdominal pain score. If a patient did not enter information into the eDiary on at least 4 days for a particular Treatment Period week, the patient will not be considered a Weekly Abdominal Pain 30% Responder for that week.

- 6/12 Week Abdominal Pain Responder

A 6/12 Week Abdominal Pain Responder is a patient who meets the Weekly Abdominal Pain Responder criteria for at least 6 out of the 12 weeks of the Treatment Period. For each week in the Treatment Period, a Weekly Abdominal Pain Responder is a patient who has an improvement from baseline of at least 2 points (ie, a -2 change from baseline) in the respective weekly abdominal pain score. If a patient did not enter information into the eDiary on at least 4 days for a particular Treatment Period week, the patient will not be considered a Weekly Abdominal Pain Responder for that week.

- 6/12 Week Abdominal Discomfort Responder

A 6/12 Week Abdominal Discomfort Responder is a patient who meets the Weekly Abdominal Discomfort Responder criteria for at least 6 out of the 12 weeks of the Treatment Period. For each week in the Treatment Period, a Weekly Abdominal Discomfort Responder is a patient who has an improvement from baseline of at least 2 points (ie, a -2 change from baseline) in the respective weekly abdominal discomfort score. If a patient did not enter information into the eDiary on at least 4 days for a particular Treatment Period week, the patient will not be considered a Weekly Abdominal Discomfort Responder for that week.

- 6/12 Week Abdominal Bloating Responder

A 6/12 Week Abdominal Bloating Responder is a patient who meets the Weekly Abdominal Bloating Responder criteria for at least 6 out of the 12 weeks of the Treatment Period. For each week in the Treatment Period, a Weekly Abdominal Bloating Responder is a patient who has an improvement from baseline of at least 2 points (ie, a -2 change from baseline) in the respective weekly abdominal bloating score. If a patient did not enter information into the eDiary on at least 4 days for a particular Treatment Period week, the patient will not be considered a Weekly Abdominal Bloating Responder for that week.

- 6/12 Week CSBM Responder

A 6/12 Week CSBM Responder is a patient who meets the Weekly CSBM Responder criteria for at least 6 out of the 12 weeks of the Treatment Period. For each week in the Treatment Period, a Weekly CSBM Responder is a patient who has an increase from baseline of at least 1 in the respective CSBM weekly rate. If a patient did not enter information into the eDiary on at least 4 days for a particular Treatment Period week, the patient will not be considered a Weekly CSBM Responder for that week.

- Treatment Satisfaction

Treatment satisfaction is measured on a 5-point ordinal scale. Treatment satisfaction will be analyzed separately for each Treatment Period week.

- Adequate Relief

Assessment of adequate relief during the previous 7 days is measured on a binary scale (yes/no). Assessment of adequate relief will be analyzed separately for each Treatment Period week.

- 6/12 Week Adequate Relief Responder

A 6/12 Week Adequate Relief Responder is a patient who reports Adequate Relief for at least 6 out of the 12 weeks of the Treatment Period.

- Change from Baseline in Constipation Severity

Constipation severity is measured weekly using a 5-point ordinal scale. Change from baseline will be calculated at each week.

- Change from Baseline in IBS Symptom Severity

IBS symptom severity is measured weekly on a 5-point ordinal scale. Change from baseline will be calculated at each week.

7.9.3.1 Analyses of Additional Efficacy Endpoints

All categorical responder parameters (e.g., 6/12 Week CSBM Responder) and SBM within 24 Hours After First Dose, will be analyzed utilizing the same methods defined in Section 7.9.2.1.

All continuous change-from-baseline at each week endpoints and Treatment Satisfaction will be analyzed and summarized using the MMRM approach described in Section 7.9.1.1.

7.9.4 Randomized Withdrawal Period Endpoints

For the RW Period, statistical analyses will be presented by treatment sequence (treatment sequences defined in Section 7.1.4).

The following endpoints will be calculated for the RW Period following the methods described for the primary and additional endpoints in Sections 7.9.1 and 7.9.3:

- Change from Baseline in Abdominal Score at Each Week
- Change from Baseline in Abdominal Bloating at Each Week
- Change from Baseline in Abdominal Discomfort at Each Week
- Change from Baseline in Abdominal Pain at Each Week
- Change from Baseline in CSBM Frequency Rate at Each Week
- Change from Baseline in SBM Frequency Rate at Each Week
- Change from Baseline in BSFS (Stool Consistency) at Each Week
- Change from Baseline in Stool Consistency at Each Week
- Change from Baseline in Percent of Days with Use of Rescue Medicine over the RW Period

7.9.4.1 Randomized Withdrawal Period Analyses

All RW Period endpoints will be summarized for the RW Period only and for the Combined Treatment and RW Period using descriptive statistics and 95% CIs for each treatment sequence. No statistical inference will be performed.

7.10 POSITIVE CONTROL

Not applicable.

7.11 SAFETY ANALYSIS

For the Treatment Period, all safety analyses will be based on the Safety Population. For the RW Period and the combined 16-week Treatment-RW Period, the safety analyses will be performed using the RW Safety Population. The safety parameters will comprise adverse events (AEs), clinical laboratory parameters, and vital signs. For each safety parameter, the last nonmissing assessment made before randomization will be used as the baseline for all analyses of that safety parameter.

Treatment assignment for Safety summaries is based on the treatment the patient actually received. The 'treatment actually received' for patients who received treatment(s) other than their randomized treatment during the course of the trial will be defined as the treatment group in which the patient actually took the greatest number of doses.

Continuous variables will be summarized by number of patients and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients.

7.11.1 Adverse Events

Adverse events will be coded by system organ class and preferred term using the MedDRA dictionary, version 21.0.

An AE that occurs during the Treatment Period will be considered a treatment-emergent adverse event (TEAE) if it was not present prior to the date of the first dose of double-blind study drug or was present prior to the date of the first dose but increased in severity during the Treatment Period. If more than 1 AE was reported before the first dose of double-blind study drug and coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs occurring during the Treatment Period that were also coded to that preferred term.

An AE that occurs on or after the date of the first dose of the double-blind study drug for the RW Period will be considered a TEAE for the RW Period (RW TEAE) if it was not present prior to the date of the first dose of double-blind study drug of the Treatment Period or was present prior to the date of the first dose of double-blind study drug for the Treatment Period but increased in severity on or after the date of the first dose of the double-blind study drug for the RW Period. An AE that occurs more than 1 day after the last dose of study drug in the RW Period will not be considered a RW TEAE.

An AE that occurs on or after the date of the first dose of the double-blind study drug for the RW Period will be considered a newly emergent adverse event (NEAE) for the RW Period if it was not present prior to the date of the first dose of the double-blind study drug for the RW Period or was present prior but increased in severity after receiving RW period double-blind study drug. An AE that occurs more than 1 day after the last dose of double-blind study drug will not be counted as an NEAE.

The period in which a serious adverse event (SAE) occurred will follow the methods defined above for TEAEs, RW TEAEs, and NEAEs. Table 7.11-1 summarizes the classification of AEs.

Table 7.11-1 Adverse Event Classification

Type of AE	***Reference Period for Baseline***	***Starting Point of Period***	***Ending Point***
TEAE	Screening+ pretreatment	First dose during treatment period	Earlier of day after last dose of Trt period & day before first dose of RW period
RW TEAE	Screening+ pretreatment	First dose during RW period	Day after date of last dose of RW trt
NEAE	Screening+ pretreatment+ treatment	First dose during RW period	Day after date of last dose of RW trt

The number and percentage of patients in each treatment group who experience TEAEs will be summarized. For the Treatment Period, TEAEs will be summarized for each treatment group by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and relationship to study drug. The same summaries will be provided for each treatment sequence for the RW Period (RW TEAEs and NEAEs). For the Treatment-RW Period, TEAEs will be summarized for each treatment sequence by system organ class and preferred term only. If a patient has more than 1 AE coded to the same preferred term, the patient will be counted only once for that preferred term by identifying those TEAEs with the greatest severity and the closest relationship to study drug for the summarization by severity and by relationship to the study drug, respectively.

For the Treatment Period, the incidence of common (≥2% of patients in any treatment group) TEAEs, on-therapy serious adverse events (SAEs), and AEs leading to premature discontinuation of study drug will be summarized by preferred term and treatment group, sorted in decreasing frequency. The above summaries will also be provided for the RW Period by treatment sequence. In addition, the incidence of on-therapy SAEs that led to death will be summarized.

For the Screened Population, listings will be presented for patients who died, patients with SAEs, and patients with AEs leading to premature discontinuation, if any.

7.11.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in SI units) and changes from the baseline values at each assessment time point will be presented by treatment group for Treatment Period and by treatment sequence for the RW Period. The End of Treatment is the last non-missing postbaseline value in the Treatment Period; End of study is the last non-missing postbaseline value. The hematology and chemistry laboratory parameters listed in Section 5.4.5 will be summarized.

Clinical laboratory test values will be potentially clinically significant (PCS) if they meet either the low or high PCS criteria listed in Table 7.11-2. The number and percentage of patients with postbaseline PCS clinical laboratory values will be tabulated by treatment group for the Treatment Period and by treatment sequence for the RW and Treatment-RW Periods. The percentages will be calculated relative to the number of patients with non-PCS baseline values and at least 1 assessment in the corresponding postbaseline period. A supportive listing of patients with postbaseline PCS values will be provided, including the PID number, trial center, and baseline and postbaseline values. A listing of all AEs for patients with PCS clinical laboratory values will also be provided. The PCS flags will be derived flags (not from the clinically significant laboratory tests reported as AEs by trial centers).

Table 7.11-2 Criteria for Potentially Clinically Significant Laboratory Results

Parameter	*SI Unit*	*Lower Limit*	*Higher Limit*
CHEMISTRY			
Albumin	g/L	< 0.9 × LLN	> 1.1 × ULN
Alanine aminotransferase	U/L	—	≥ 3 × ULN
Alkaline phosphatase	U/L	—	≥ 3 × ULN
Aspartate aminotransferase	U/L	—	≥ 3 × ULN
Bicarbonate	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Bilirubin, total	µmol/L	—	> 1.5 × ULN
Calcium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Chloride	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Cholesterol, total	mmol/L	—	> 1.6 × ULN
Creatinine	µmol/L	—	> 1.3 × ULN
Glucose	mmol/L	< 0.8 × LLN	> 1.4 × ULN
Magnesium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Phosphate	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Potassium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Protein, total	g/L	< 0.9 × LLN	> 1.1 × ULN
Sodium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Urea nitrogen	mmol/L	—	> 1.2 × ULN
Uric acid	µmol/L	< 0.9 × LLN	> 1.1 × ULN

Parameter	*SI Unit*	*Lower Limit*	*Higher Limit*
HEMATOLOGY			
Basophils, absolute cell count	10^9/L	—	> 3 × ULN
Eosinophils, absolute cell count	10^9/L	—	> 3 × ULN
Hematocrit	Ratio	< 0.9 × LLN	> 1.1 × ULN
Hemoglobin	g/L	< 0.9 × LLN	> 1.1 × ULN
Lymphocytes, absolute cell count	10^9/L	< 0.8 × LLN	> 1.5 × ULN
Mean corpuscular hemoglobin	pg	—	> 3 × ULN
Mean corpuscular hemoglobin concentration	g/L	—	> 3 × ULN
Mean corpuscular volume	fL	< 0.9 × LLN	> 1.1 × ULN
Monocytes, absolute cell count	10^9/L	—	> 3 × ULN
Neutrophils, absolute cell count	10^9/L	< 0.8 × LLN	> 1.5 × ULN
Platelet count	10^9/L	< 0.5 × LLN	> 1.5 × ULN
Red blood cell count	10^{12}/L	< 0.9 × LLN	> 1.1 × ULN
White blood cell count	10^9/L	< 0.7 × LLN	> 1.5 × ULN

LLN = lower limit of normal value provided by the laboratory; SI = *Le Système International d'Unités* (International System of Units); ULN = upper limit of normal value provided by the laboratory.

7.11.3 Vital Signs

Descriptive statistics for body weight and vital signs (oral temperature, respiratory rate, systolic and diastolic blood pressure, and pulse rate) and changes from baseline values at each visit will be presented by treatment group for the Treatment Period and by treatment sequence for the Treatment-RW period. The End of Treatment is the last non-missing postbaseline value in the Treatment Period; End of study is the last non-missing postbaseline value.

Vital sign values will be considered PCS if they meet both the observed-value criteria and the change-from-baseline criteria listed in Table 7.11-3. The number and percentage of patients with postbaseline PCS vital signs will be tabulated by treatment group for the Treatment Period and by treatment sequence for the RW Period and the Treatment-RW Period. The percentages will be calculated relative to the number of patients with nonmissing baseline values and at least 1 assessment in the corresponding postbaseline period. A supportive listing of patients with postbaseline PCS values will be provided, including the PID number, trial center, and baseline and postbaseline values.

A listing of all AEs for patients with PCS vital sign values will also be provided.

Table 7.11-3 Criteria for Potentially Clinically Significant Vital Signs

Parameter	*Flag*	*Criteria*[a]	
		Observed Value	*Change From Baseline*
Sitting systolic blood pressure, mm Hg	High	≥ 180	Increase of ≥ 20
	Low	≤ 90	Decrease of ≥ 20
Sitting diastolic blood pressure, mm Hg	High	≥ 105	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Sitting pulse rate, bpm	High	≥ 120	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Weight, kg	High	—	Increase of ≥ 7%
	Low	—	Decrease of ≥ 7%

a A post-baseline value is considered potentially clinically significant if it meets both the observed-value and the change-from-baseline criteria.
bpm = beats per minute.

7.11.4 Other Safety Parameters

7.11.4.1 Physical Examination

Any physical examination abnormality that the investigator considers to be potentially clinically significant and changed from the baseline will be reported as an AE. No separate analysis for Physical Examinations is planned.

7.12 HEALTH OUTCOMES ANALYSIS

Health outcome analyses will be performed on the ITT population for the Treatment Period and on the RW Population for the RW Period.

7.12.1 Irritable Bowel Syndrome–Quality of Life Assessment (IBS-QOL)

The IBS-QOL parameters consist of the overall average score and eight subscale scores (ie, dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual, and relationships). For the Week 12/ETP Visit and the Week 16/EOT Visit, change from baseline in the IBS-QOL overall average score and the subscale scores will be analyzed using an ANCOVA model with fixed effect terms for treatment group and geographic region and the corresponding baseline IBS-QOL score as a covariate.

Table 7.12-1 Irritable Bowel Syndrome–Quality of Life Questionnaire

Endpoint (Subscale)	*Items*	[redacted]	[redacted]
Dysphoria (DY)	1, 6, 7, 9, 10, 13, 16, 30	[redacted]	[redacted]
Interference with activity (IN)	3, 18, 19, 22, 27, 29, 31	[redacted]	[redacted]
Body image (BI)	5, 21, 25, 26	[redacted]	[redacted]
Health worry (HW)	4, 15, 32	[redacted]	[redacted]
Food avoidance (FA)	11, 23, 28	[redacted]	[redacted]
Social reaction (SR)	2, 14, 17, 34	[redacted]	[redacted]
Sexual (SX)	12, 20	[redacted]	[redacted]
Relationships (RL)	8, 24, 33	[redacted]	[redacted]
Overall (OV)	All items	[redacted]	[redacted]

Subscales are scored through simple summative scaling. All items are negatively framed (on a 1-5 point scale), with the highest response scale equaling the worst quality of life. When scored, all items are reversed so that, as IBS-QOL scores increase, quality of life increases. All final raw scores are transformed to a 0-to-100 scale using the following formula:

$$\text{Scale Score} = \frac{\text{Sum of the items} - \text{lowest possible score}}{\text{possible raw score range}} \times 100$$

This transformation converts the lowest and highest possible scores to 0 and 100, respectively. Scores between these values represent the percentage of the total possible score achieved.

If a patient is missing any item in the derivation of a subscale, that subscale is considered missing. If any item is missing, the total score is considered missing. However, the subscales with nonmissing items can still be calculated.

7.12.2 CDC Healthy Days Core Module (CDC HRQOL-4)

The CDC HRQOL-4 (the Healthy Days Core Module) consists of 4 questions. Self-rated general health, physically unhealthy days, mentally unhealthy days, and poor physical/mental days are collected. Unhealthy days is defined as:

Unhealthy days = minimum of (physically unhealthy days + mentally unhealthy days, or 30)

Descriptive summaries for the derived unhealthy days and the change from baseline will be summarized descriptively at each visit. For the Week 12/ETP Visit and the Week 16/EOT Visit, treatment difference between the change from baseline score will be performed using ANCOVA model with fixed effect terms for treatment group and geographic region and the corresponding baseline measure as a covariate.

8.0 CHANGES FROM ANALYSES PLANNED IN THE PROTOCOL

9.0 DATA HANDLING CONVENTIONS

9.1 VISIT TIME WINDOWS FOR SAFETY ANALYSIS

Table 9.1-1 below presents the visits assigned for the safety analysis corresponding to the range of trial days (window) during which an actual visit may have occurred.

Table 9.1-1 Visit Time Windows for Safety Analysis

Derived Visit	***Scheduled Test / Visit Day[a]***	***Window***
Baseline	Day 1	Days ≤ 1
Week 4 (Day 29) Visit	Day 29	Days [2, 43]
Week 8 (Day 57) Visit	Day 57	Days [44, 71]
Week 12 (Day 85) Visit	Day 85	Days ≥ 72 but prior to RW Day 1
End of Treatment Period[b]	End of Treatment Period Visit	
Week 16 (RW Day 29) Visit	RW Day 29	Days > RW Day 1
End of Trial	End of Trial Visit	

a Relative to the date of randomization or first RW dose; Day 1 = the day of randomization; RW Day 1 = the day of first RW dose.
b "End of Treatment Period/End of Trial" will be presented in analysis tables for safety parameters, including ECG, clinical laboratory, and vital signs.

Test/Visit Day will be calculated as follows: test/visit date – date of randomization or date of first RW dose + 1.

If there are multiple values available for the same Visit, the data with the latest date for that visit will be utilized for summary.

9.2 VISIT TIME WINDOWS FOR EFFICACY ANALYSIS

Table 9.2-1 presents the analysis weeks assigned for the efficacy analysis of the patient diary data related to BM characteristics. These analysis weeks will be used in the calculations for all week-based parameters (e.g., Abdominal Score, SBM weekly frequency rate, BSFS weekly scores).

Table 9.2-1 Analysis Time Windows for Efficacy Analysis

Period	*Analysis Week*	*Begins*[a]	*Ends*[a]
Pretreatment (Baseline[b])	Week –2	Day –14	Day –8
	Week –1	Day –7	Day 1 (time of randomization)
Treatment	Week 1	Day 1 (time of randomization)	Day 7
	Week 2	Day 8	Day 14
	Week 3	Day 15	Day 21
	Week 4	Day 22	Day 28
	Week 5	Day 29	Day 35
	Week 6	Day 36	Day 42
	Week 7	Day 43	Day 49
	Week 8	Day 50	Day 56
	Week 9	Day 57	Day 63
	Week 10	Day 64	Day 70
	Week 11	Day 71	Day 77
	Week 12	Day 78	Day of last treatment period dose day[c] (usually Day 85)
RW	Week 1	RW Day 1	RW Day 7
	Week 2	RW Day 8	RW Day14
	Week 3	RW Day15	RW Day 21
	Week 4	RW Day 22	Day of last RW dose (usually day 28)

Note: There is no Day 0 or Week 0. For eDiary assessments in which a patient is asked to report if an event occurred "yesterday" or "today" (e.g., a bowel movement or rescue medication use), these windows pertain to when the event occurred, not to when the event is reported. For example, if a patient reports in eDiary on Day 78 a bowel movement occurring "yesterday," that bowel movement (and subsequent stool consistency and straining scores) would be included in Analysis Week 11, not Analysis Week 12.

a Relative to the date of randomization or first RW dose; Day 1 = the day of randomization; RW Day 1 = the day of first RW dose. For the calculation of rates (eg, stool frequency rates) in which the duration of a week or the overall period is calculated to the nearest hour, a day begins and ends at midnight.

b Baseline values for efficacy parameters will be derived from the daily eDiary and eCRF data collected in the Pretreatment Period, specifically the period from 14 days before randomization up to the time of randomization.

c For patients who fail to provide the date of last dose at the last visit, the later date of the last known dose (drug dispense eCRF) or the last eDiary date will be used to impute the last dose date.

For the Treatment Period or RW Period, diary day is calculated as diary date – date of randomization or date of first RW dose + 1. For the Pretreatment Period, diary day is calculated as diary date - date of randomization. However, the day of randomization is always trial Day 1. Patients will complete their diary entries once a day, with the exception of Day 1 of entry into the Treatment Period, during which 2 diary data sets will be collected. On Day 1, daily questions will be entered before and after the randomization, whereas weekly questions will be entered before but not after randomization.

If a patient withdraws during the Treatment Period or RW Period, the patient's Treatment Period or RW Period shall end on the day of the last dose. The affected Treatment Period or RW Period week shall be shortened to the end of the withdrawn patient's Treatment Period or RW Period, and all subsequent Treatment Period or RW Period weeks will be missing for that patient.

Table 9.2-2 presents the analysis weeks assigned for the efficacy analysis of the patient diary data related to Weekly Questions (e.g., Weekly Patient Assessment of Constipation Severity, Weekly Patient Assessment of IBS Symptom Severity, Weekly Patient and Assessment of Adequate Relief, and Weekly Patient Assessment of Treatment Satisfaction).

Table 9.2-2 Analysis Time Windows for Efficacy Analysis – Weekly Assessments

Period	***Analysis Week***	***Begins***	***Ends***
Pretreatment (Baseline[b])	Week –2	Day –11	Day –5
	Week –1	Day –4	Day 1 (time of randomization)
Treatment	Week 1	Day 7	Day 10
	Week 2	Day 11	Day 17
	Week 3	Day 18	Day 24
	Week 4	Day 25	Day 31
	Week 5	Day 32	Day 38
	Week 6	Day 39	Day 45
	Week 7	Day 46	Day 52
	Week 8	Day 53	Day 59
	Week 9	Day 60	Day 65
	Week 10	Day 66	Day 72
	Week 11	Day 73	Day 79
	Week 12	Day 80	Day of last treatment period weekly dose day (usually Day 84)*
RW	Week 1	RW Day 7	RW Day 10
	Week 2	RW Day 11	RW Day17
	Week 3	RW Day18	RW Day 24
	Week 4	RW Day 25	Day of last RW dose (28+3 Days)

*For patients completing the treatment period, but not entering the RW period, Day 87 defines the End study day for Week 12 assignment.

In general, weekly questions will be assigned only to the analysis week for which the question covers at least 4 days of that week.

If a weekly question covers days from different study phases, the answers will be discarded. For example, a weekly question answered on study day 2 would cover part of 1 day from the treatment phase & 6 days from the pre-treatment phase, so these data would be discarded.

If patients answer the weekly questions multiple times for a week, for each question, the average of the respective answers will be assigned as the weekly value.

For time periods covering more than a week, the value will be calculated as the average of the weekly values. Thus, for pre-treatment, the value will be calculated as the average of week -2 and week -1.

9.3 POOLING OF TRIAL CENTERS

Because of the potential of many trial centers to have a small number of patients, the centers will be pooled by the following 5 geographic regions (as listed in Table 9.3-1): Northeast, Southeast, Midwest, Southwest, and West. All analyses using trial center will use this 5-category center variable.

Table 9.3-1 Definition of Geographic Regions

Northeast	*Southeast*	*Midwest*	*Southwest*	*West*
CT	AL	IA	AZ	CA
DE	AR	IL	NM	CO
MA	FL	IN	OK	ID
MD	GA	KS	TX	MT
ME	KY	MI		NV
NH	LA	MN		OR
NJ	MS	MO		UT
NY	NC	ND		WA
PA	SC	NE		WY
RI	TN	OH		
VT	VA	SD		
	WV	WI		

9.4 DERIVED EFFICACY VARIABLES

9.4.1 Patient Recall for eDiary Data

Bowel Habits

The eDiary is designed to allow patients to enter Daily Bowel Habits through a spontaneous report or the evening report.

The spontaneous report allows the patient to report BMs, occurring between evening reports, at any time. If the previous evening report was not completed, then the patient can report BM information occurring between 7:00 PM of the previous night and the current spontaneous report.

These BM information reporting rules were put into place to reduce recall bias.

Rescue Medicine (RM)

The spontaneous report allows the patient to report RM information, occurring between evening reports, at any time. If the previous evening report was not completed, then the patient can report RM information between 7:00 PM of the previous night and the current spontaneous report.

These RM information reporting rules were put into place to reduce recall bias.

Abdominal Symptom Severity

During the Evening Diary Report, the eDiary will capture separately the rating of abdominal pain, abdominal bloating, and abdominal discomfort experienced by the patient during the past 24 hours.

9.4.2 Handling of Missing eDiary Data

In the eDiary, for each BM and rescue medicine use reported, the patient will be asked whether the BM or rescue medicine use occurred "today" or "yesterday." The following conventions will be followed in the event of missing data:

Gaps in the eDiary Data

If a patient does not complete either a spontaneous or evening report every day, there will be gaps in the data.

There will be no adjustments for these gaps in the eDiary data for the efficacy data analyses using an OC approach. Effectively, this means that analyses will assume that no rescue medicine use or BMs occurred during these gaps.

Missing "Today" or "Yesterday" Information for Rescue Medicine

When a patient uses rescue medicine and the exact date of use is known, there will be a 2-day window during which any BMs will not be assessed as SBMs: (1) the day when the rescue medicine was administered and (2) the day after. If, in the daily diary, a patient has reported taking a rescue medicine but the corresponding date is missing, the rescue medicine use must have occurred either on the day of the diary entry or on the day before the diary entry. The rescue medicine window in this missing-date scenario will be 3 days, covering the day before the eDiary report, the day of the eDiary report, and the day after the eDiary report. This window will be used to determine if a BM should be considered an SBM.

For the analysis of rescue medicines, the missing date will be imputed as the date in which the rescue medicine was reported.

Missing "Today" or "Yesterday" Information for Bowel Movements

If a patient reports having had a BM but does not provide the exact date, the BM must have occurred either on the day of the report or on the day before the report. For determining whether a BM is an SBM, this 2-day BM window will be used in conjunction with the rescue medicine window. If there is any overlap between the 2-day BM window and the patient's rescue medicine window (which could be either 2-day window or 3-day window), the BM will not be considered an SBM.

Many analyses require specific dates for each BM. If a BM date is missing, it will be imputed as the date/time stamp of the eDiary report in which the BM was reported. However, the following exception applies to this imputation rule:

When the first day of the BM window is the last day of a rescue medicine window and the second day of the BM window is not also a day of a rescue medicine window, the missing BM date will be imputed as the first day of the BM window (i.e., the day before the eDiary report in which the BM was recorded). This rule of exception is designed to minimize the risk of mischaracterizing a non-spontaneous BM as an SBM.

Missing Stool Consistency Questions

No imputation will be performed for a missing BSFS score or the stool consistency 5-point ordinal measure.

Missing Completeness of Evacuation Response

If the completeness of evacuation response (Question #12) is missing, an SBM will not be considered complete.

Missing Daily Abdominal Symptoms

No imputation will be performed for missing daily abdominal symptoms (Abdominal Pain, Abdominal Discomfort, Abdominal Bloating).

9.4.3 Weekly Stool Frequency Rates

The components for calculating a patient's stool frequency rates (BM, SBM, and CSBM weekly rates) for a given analysis week are as follows:

- The number of BMs that occurred during that analysis week
- The number of those BMs that were SBMs
- The number of those SBMs that were CSBMs
- The length of time of the analysis week

The determination of the length of time of an analysis week is provided in Section 9.4.3.1.

9.4.3.1 Length of an Analysis Week

With respect to a patient's scheduled analysis weeks, the term *duration* is used. In regard to the *duration* of a week, it is expected that 1 or more of a patient's "weeks" may not be exactly 7×24 hours in duration (e.g., a patient may withdraw or discontinue early from the trial). Deviations from the 7×24–hour norm are structural in nature; and, as such, the calculations of the weekly rates of SBMs or CSBMs will incorporate the actual duration of the week.

Following an observed-cases approach, no adjustment to the duration of a week will be made for missing eDiary data absent because of missed reports.

9.4.3.2 Weekly Stool Frequency Rate Calculations

The weekly frequency rate for SBMs (CSBMs) will be based on the number of SBMs (CSBMs) occurring during that week, adjusting for differences in the duration of the week versus the 7×24–hour norm. A description of the corresponding formula is provided below.

Weekly stool frequency rates for each analysis week will be calculated as follows:

$$\textit{Weekly Frequency Rate (Analysis Week}_i\textit{)} = (7 \times 24) \times C_i/D_i$$

Where:

i is an indicator of analysis week number (e.g., $i = -2, -1, 1, \ldots, 12$),

C_i is the number of events (SBMs or CSBMs) reported during analysis week i, and

D_i is the duration (in hours) of analysis week i, from beginning to end (Table 9.2-1).

9.4.3.3 Overall Weekly Stool Frequency Rate Calculations for Each Analysis Period

For each of the analysis periods (Pretreatment [Baseline] and Treatment Period), the overall weekly stool frequency rates will be calculated in a manner similar to that for an individual week. The corresponding formulas are provided below.

Overall weekly stool frequency rates for each analysis period will be calculated as follows:

$$\textit{Weekly Frequency Rate (Analysis Period}_j\textit{)} = (7 \times 24) \times C_j/D_j$$

Where:

j is an indicator of analysis period number (e.g., $j = 1$ [pretreatment], 2 [treatment]),

C_j is the number of events (SBMs or CSBMs) reported during analysis period j, and

D_j is the duration (in hours) of analysis period j, from beginning to end (Table 9.2-1).

9.4.4 Other Weekly Scores Derivation

For the abdominal score, first the daily average of Abdominal Pain, Abdominal Bloating and Abdominal Discomfort will be calculated. If more than 1 of the symptom scores is missing on a day, that daily abdominal score will be missing. Weekly scores will be based on the average of the non-missing daily abdominal scores.

For Abdominal Score, Pain, Bloating, and Discomfort, the patient's weekly average will be the average of the non-missing daily scores reported by the patient during each week.

For stool consistency questions, the patient's weekly score will be the average of the non-missing daily scores from the SBMs reported by the patient during each week.

For straining, the patient's weekly straining score will be the average of the non-missing daily straining scores from the SBMs reported by the patient during each week.

9.5 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If a patient has repeated assessments prior to the start of double-blind study drug, then the results from the final non-missing assessment made prior to the start of the double-blind study drug will be used as baseline. If end-of-trial assessments are repeated or if unscheduled visits occur, the last non-missing post baseline assessment will be used as the end-of-trial assessment for generating summary statistics. However, all post-baseline assessments will be used for PCS value determination as described above and all assessments will be presented in the data listings.

9.6 MISSING DATE OF THE LAST DOSE OF STUDY DRUG

When the date of the last dose of double-blind study drug is missing for a patient in the Safety Population, all efforts should be made to obtain the date from the Investigator. If after all efforts are made it is still missing, the latest date reported from eDiary entry or from the Study Drug Dispensation eCRF question 'Date of most recent dose' will be used as the last dose date.

9.7 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE that started prior to the first double-blind study drug, all efforts should be made to obtain the severity from the investigator. If it is still missing after all efforts, then a severity of "Mild" will be assigned. If the severity is missing for an AE that started on or after the date of the first dose of double-blind study drug, then a severity of "Severe" will be assigned. The imputed values for the missing severity assessment will be used for the incidence summary, while the actual missing values will be presented in data listings.

9.8 MISSING RELATIONSHIP TO STUDY DRUG FOR ADVERSE EVENTS

If the relationship to study drug is missing for an AE started on or after the date of the first dose of double-blind study drug, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, a causality of "Related" will be assigned in the corresponding analysis derived data set. The imputed values for the missing relationship to double-blind study drug will be used only for incidence summary, while the actual missing values will be presented in data listings.

9.9 MISSING DATE INFORMATION FOR ADVERSE EVENTS

The following imputation rules apply to cases in which the start date is incomplete for adverse events.

a. If AEs occurred during the Screening or Pretreatment Period (i.e., the Screening or Pretreatment Period is identified AE eCRF)

Missing day, month and year

- If the entire AE start date is missing, then the start date of the Period identified on the AE eCRF page will be assigned to the missing fields.

Missing day and month

- If the year is the same as the year of the date of informed consent, then the day and month of the date of informed consent will be assigned to the missing fields.

- If the year is prior to the year of the date of informed consent, then December 31 will be assigned to the missing fields.

- If the year is after the year of the date of informed consent, then January 1 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 are the same as the month and year of the date of informed consent, then the date of informed consent will be assigned to the missing day.

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

If the stop date is complete and it is before the date of randomization and the imputed start date as above is after the stop date, the start date will be imputed by the stop date. If the stop date is complete and it is on or after the date of randomization and the imputed start date as above is after the stop date, the start date will be imputed by the date immediately before the date of randomization.

If the start date is completely missing, then the date of informed consent will be used to impute the start date.

b. If AEs occurred during the Treatment Period (i.e., the Treatment Period is identified on the AE eCRF)

Missing day, month and year

- If the entire AE start date is missing, then the start date of the Period identified on the AE eCRF page will be assigned to the missing fields

Missing day and month

- If the year is the same as the year of the date of the first dose of double-blind study drug, then the day and month of the date of the first dose of double-blind study drug will be assigned to the missing fields.

- If the year is prior to the year of the date of the first dose of double-blind study drug, then December 31 will be assigned to the missing fields.

- If the year is after the year of the date of the first dose of double-blind study drug, then January 1 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 are the same as the month and year of the date of the first dose of double-blind study drug, then the date of the first dose of double-blind study drug will be assigned to the missing day.

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

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, then the following algorithm is used to impute the start date:

- If the stop date is after the date of the first dose of double-blind study drug, the date of the first dose of double-blind study drug will be assigned to the missing start date.

- If the stop date is before the date of the first dose of double-blind study drug, the stop date will be assigned to the missing start date.

c. If AEs occurred during the RW Period (ie, the RW Period is checked on the AE eCRF)

Missing day, month and year

- If the entire AE start date is missing, then the start date of the Period identified on the AE eCRF page will be assigned to the missing fields.

Missing day and month

- If the year is the same as the year of the date of the first dose of double-blind study drug in the RW Period, the day and month of the date of the first dose of double-blind study drug in the RW Period will be assigned to the missing fields.

- If the year is prior to the year of the date of the first dose of double-blind study drug in the RW Period, December 31 will be assigned to the missing fields.

- If the year is after the year of the date of the first dose of double-blind study drug in the RW Period, January 1 will be assigned to the missing fields.

9.10 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 patient, impute the start date first.

9.10.1 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, month and year

- If the start date is completely missing, then the date of the screening visit will be assigned to the missing field.

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 double-blind study drug, then the day and month of the date of the first dose will be assigned to the missing fields.

- If the year of the incomplete start date is prior to the year of the date of the first dose of double-blind study drug, then December 31 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 double-blind study drug, then the day of the date of the first dose will be assigned to the missing day.

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

9.10.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of double-blind study drug is missing, replace it with the last diary call date. 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, month and year

- If the stop date is completely missing, then the end of trial date will be assigned.

Missing day and month

- If the year of the incomplete stop date is prior to the year of the date of the last dose of double-blind study drug, then December 31 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 either the year is before the year of the date of the last dose of double-blind study drug or if both years are the same but the month is before the month of the date of the last dose of double-blind study drug, then the last day of the month will be assigned to the missing day.

9.11 CHARACTER VALUES OF CLINICAL LABORATORY PARAMETERS

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table, for example, due to it being a character string rather than a numerical type, a coded value needs to be appropriately determined and used in the statistical analyses. However, the actual values as reported in the database will be presented in data listings.

Table 9.11-1 shows examples of how some possible laboratory results should be coded for the analysis.

Table 9.11-1 Examples of Coding Special Character Values for Clinical Laboratory Parameters

Laboratory Test, SI Unit	*Possible Laboratory Results*	*Coded Value for Analysis*
CHEMISTRY		
ALT, U/L	< 5	0
AST, U/L	< 5	0
Bilirubin, total, µmol/L	< 2	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SI = *Le Système International d'Unités* (International System of Units).

10.0 REFERENCES

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APPENDIX 1: BRISTOL STOOL FORM SCALE

Type 1 - Separate hard lumps like nuts (difficult to pass)

Type 2 - Like a sausage but lumpy

Type 3 - Like a sausage but with cracks on the surface

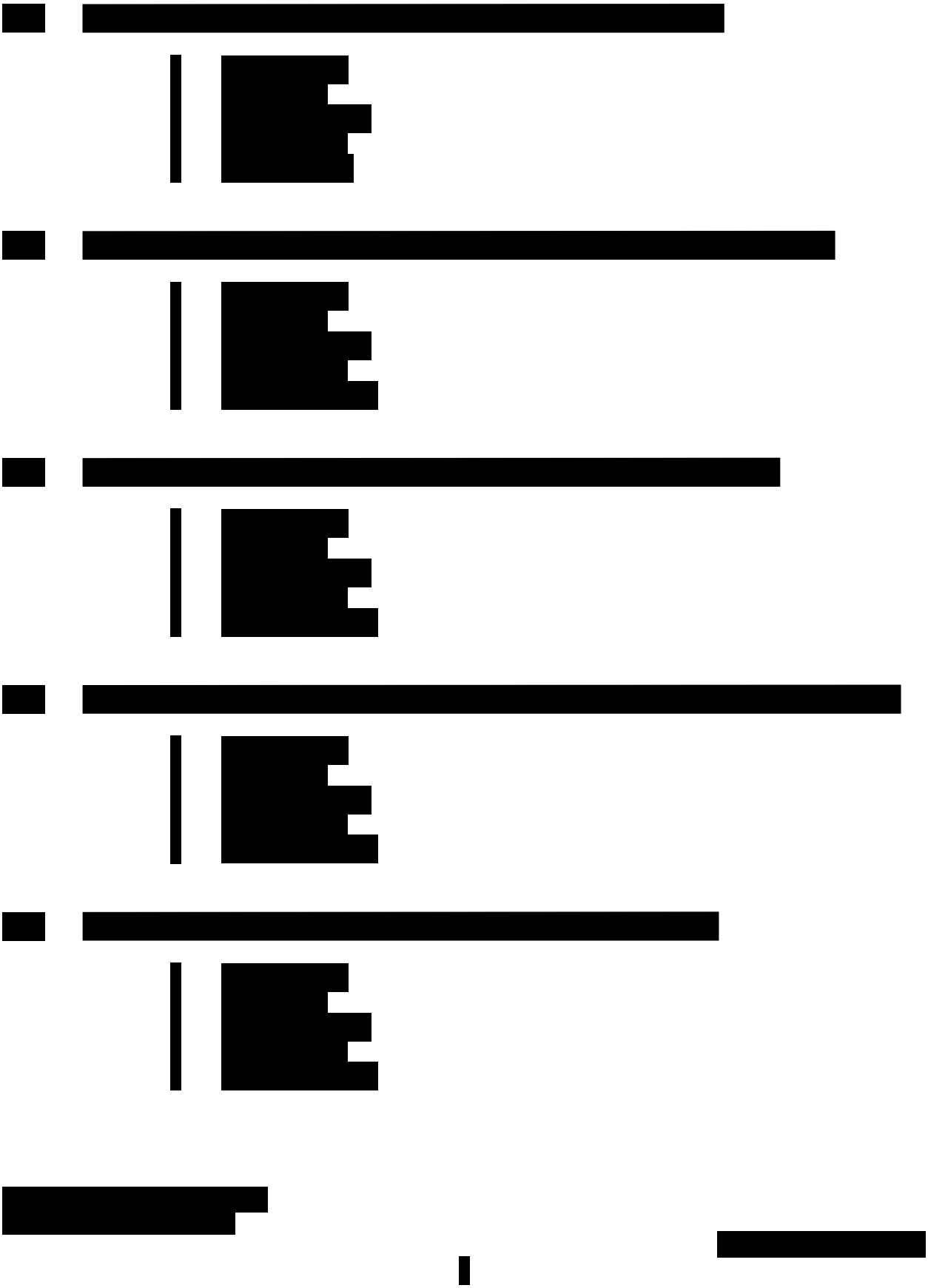
Type 4 - Like a sausage or snake, smooth and soft

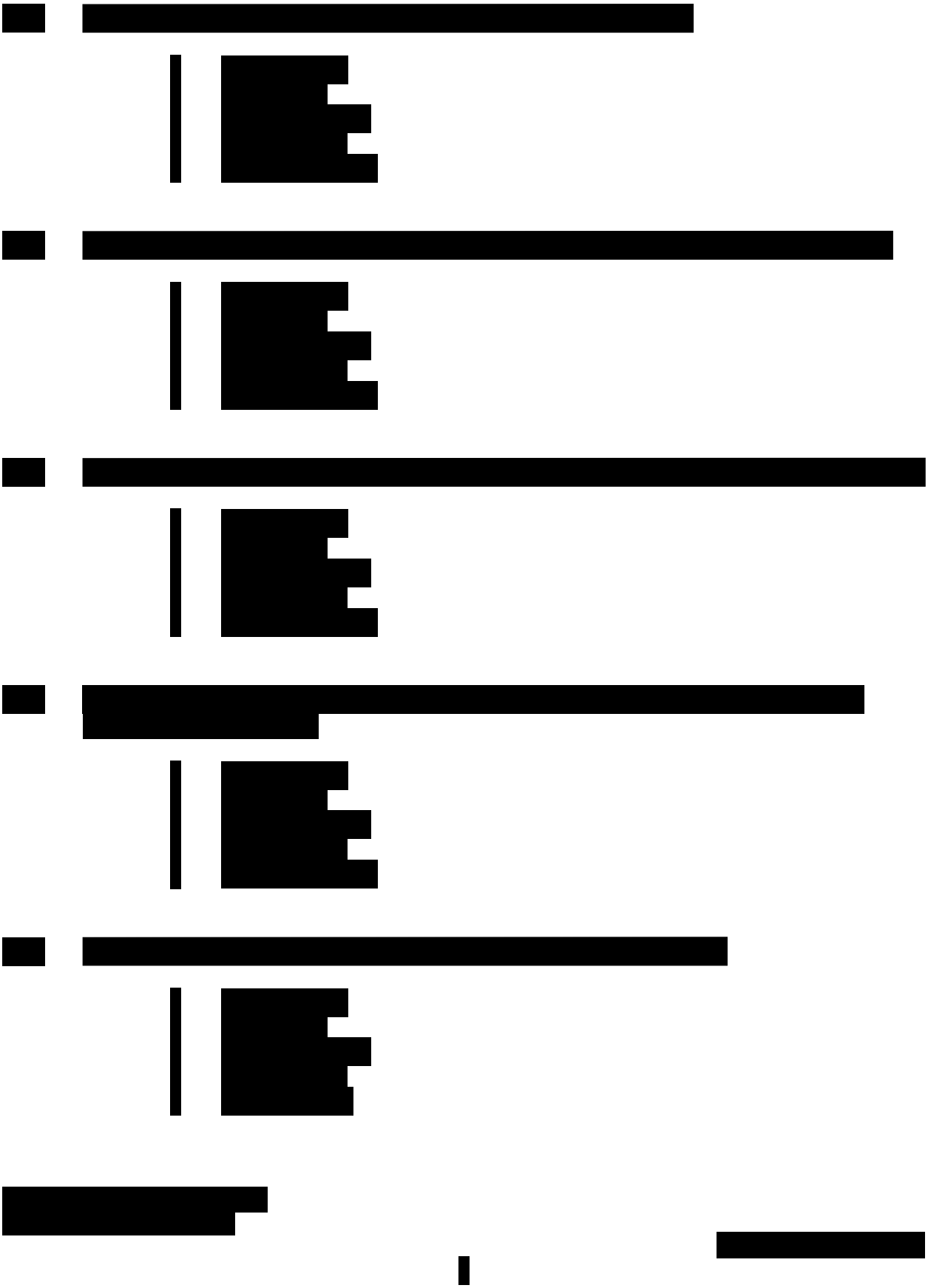
Type 5 - Soft pieces with clear-cut edges (easy to pass)

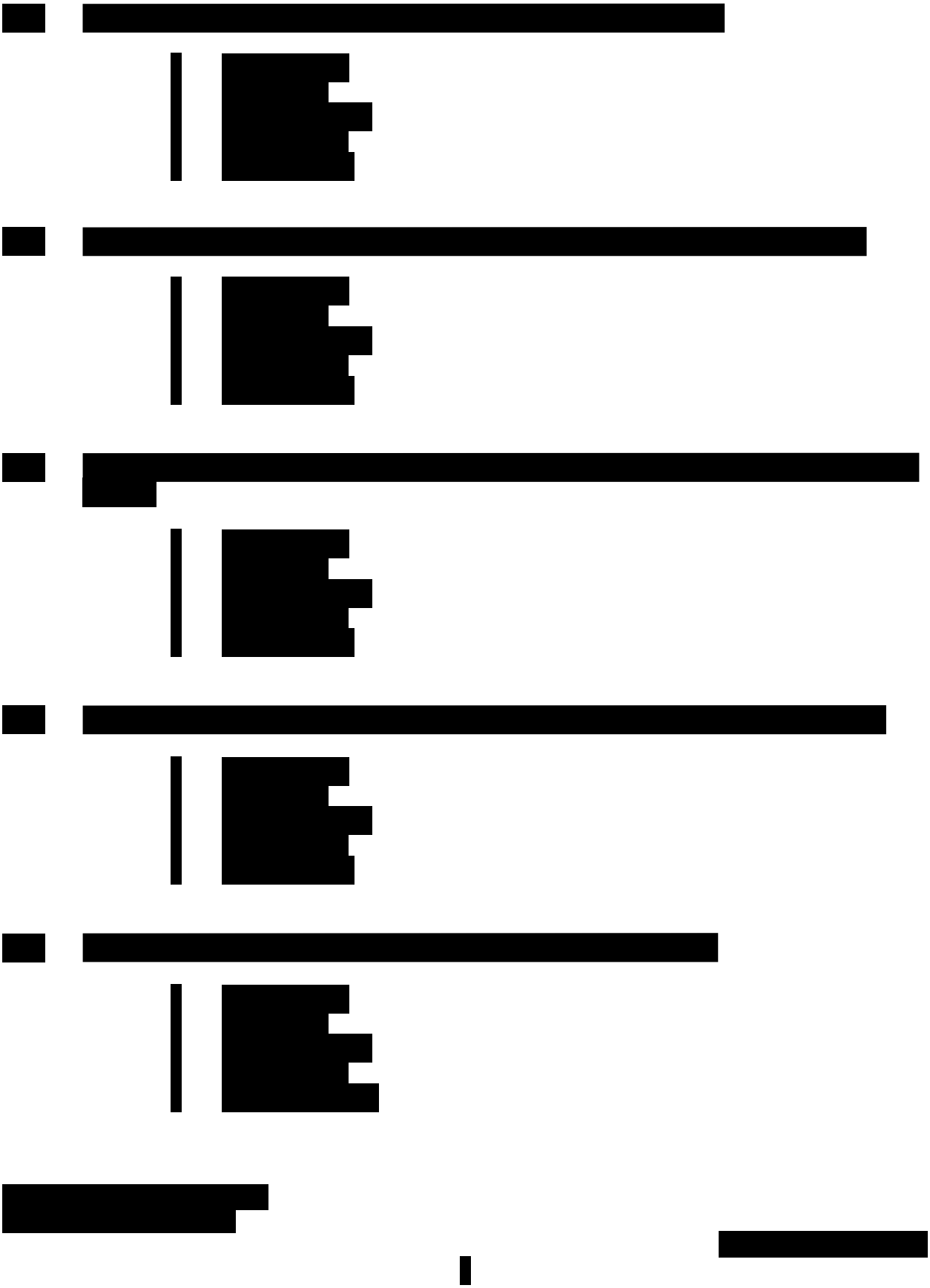
Type 6 - Fluffy pieces with ragged edges, a mushy stool

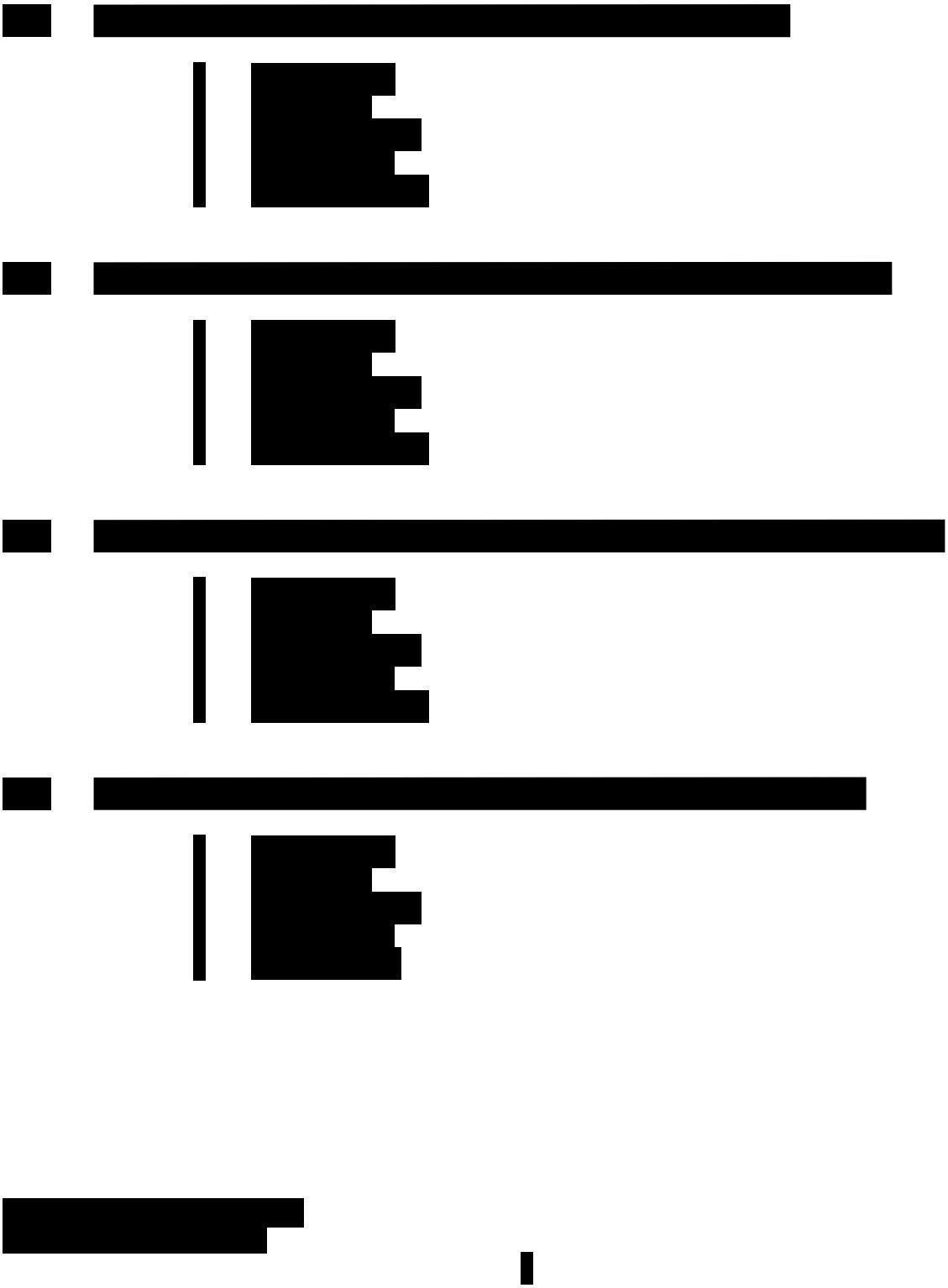
Type 7 - Watery, no solid pieces (entirely liquid)

APPENDIX 2: IBS-QOL









APPENDIX 3: CDC HRQOL-4

Healthy Days Core Module (CDC HRQOL– 4)

1. Would you say that in general your health is

Please Read

a. Excellent 1
b. Very good 2
c. Good 3
d. Fair 4

or

e. Poor 5

Do not read these responses

Don't know/Not sure 7
Refused 9

2. Now thinking about your physical health, which includes physical illness and injury, for how many days during the past 30 days was your physical health not good?

a. Number of Days _ _
b. None 8 8

Don't know/Not sure 7 7
Refused 9 9

3. Now thinking about your mental health, which includes stress, depression, and problems with emotions, for how many days during the past 30 days was your mental health not good?

a. Number of Days _ _
b. None 8 8 If both Q2 AND Q3 = "None," skip next question

Don't know/Not sure 7 7
Refused 9 9

4. During the past 30 days, for about how many days did poor physical or mental health keep you from doing your usual activities, such as self-care, work, or recreation?

a. Number of Days _ _
b. None 8 8

Don't know/Not sure 7 7
Refused 9 9