STATISTICAL ANALYSIS PLAN: MCP-103-204-SAP-01

Final Version 1.0, 04 October 2016

Study Title:	A Phase 2b, Randomized, Double-blind, Double-dummy, Placebo controlled, Parallel-group, Dose-range-finding Study of Two Delayed Release Formulations of Linaclotide Administered Orally for 12 Weeks to Patients with Irritable Bowel Syndrome with Constipation
Study Number:	MCP-103-204
Product Name:	linaclotide
Sponsor:	Ironwood Pharmaceuticals, Inc 301 Binney Street Cambridge, MA 02142
Final Date:	04 October 2016

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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
CIC	chronic idiopathic constipation
CMH	Cochran-Mantel-Haenszel
CSBM	complete spontaneous bowel movement
DR	delayed release
DR1	delayed release formulation 1 – targeted to release in ileal region
DR2	delayed release formulation 2 – targeted to release in the late ileum to ascending colon
eCRF	electronic case report form
eDiary	electronic diary
EOT	End-of-Treatment Period
EQ-5D-3L	EuroQol-5 Dimension
HEENT	head, ears, eyes, nose, throat
IBS-C	Irritable Bowel Syndrome with Constipation
IBS-SSS	Irritable Bowel Syndrome – Symptom Severity Scale
ICF	informed consent form
IPD	Important Protocol Deviations
IR	immediate release
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
SAE	serious adverse event
SAP	statistical analysis plan
SBM	spontaneous bowel movement
SD	standard deviation
SF-12-v2	Short Form-12 Health Survey Version 2
SF-MPQ-2	Short Form McGill Pain Questionnaire - 2
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. 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 amended protocol of Study MCP-103-204-P-03 (dated 09 October 2015). Specifications for the tables, figures, and data listings are contained in a separate document.

2. STUDY OBJECTIVES

The objectives of this study are to evaluate the safety, efficacy, and dose response of two different delayed release formulations of linaclotide (DR; DR formulation 1 is DR1; DR formulation 2 is DR2) administered orally to patients with irritable bowel syndrome with constipation (IBS-C). [redacted]

3. STUDY DESIGN

3.1 GENERAL DESCRIPTION

The MCP-103-204 study is a multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group, multiple-dose, 12-week study, consisting of 3 distinct periods (Screening, Pretreatment, and Treatment). The study will enroll patients who have IBS-C diagnosed using Rome III criteria. Approximately 520 eligible patients will be randomized in equal proportions to one of 8 treatments: 30 μg, 100 μg, or 300 μg of the linaclotide DR1 formulation; 30 μg, 100 μg, or 300 μg of the linaclotide DR2 formulation; 290 μg of the IR formulation of linaclotide (stated as linaclotide IR throughout); or placebo. [redacted]

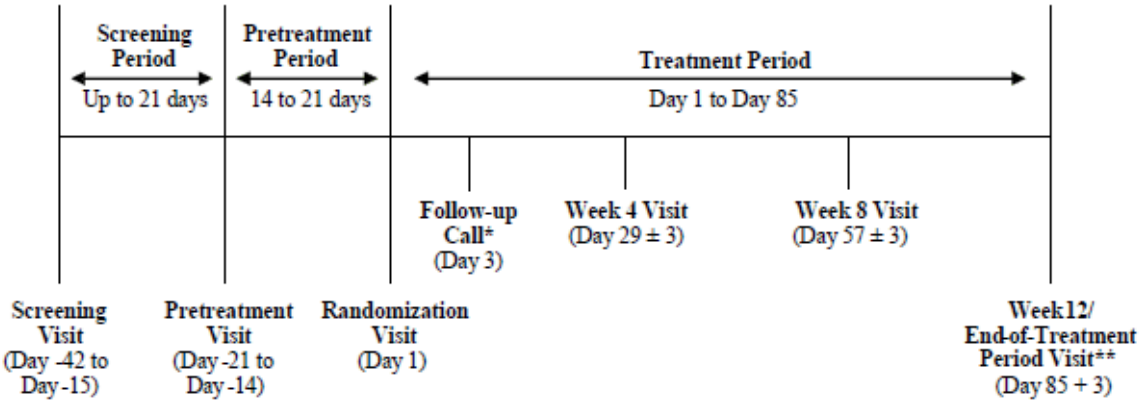
The length of this trial is 14-18 weeks, with 3 distinct periods, including up to 21 days of Screening, 14 to 21 days of Pretreatment, and 12 weeks of double-blind treatment. Signed informed consent from the patient or the patient's legally authorized representative will be obtained before any study-related procedures begin. 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.

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. Linaclotide IR at the 290 μg dose (the FDA-approved dose for IBS-C) is being included in the study as a positive control, against which the safety and efficacy of the various doses of the two test (DR) formulations can be compared; to maintain the blind (linaclotide IR is supplied as

a capsule and both linaclotide DR formulations are supplied as tablets), a double-dummy design was employed. 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 the active control, Linaclotide IR 290 ug (See Figure 1).

Figure 1. Overview of Study Design



Note: there is no Day 0.
*Applicable to a subset of patients
**This visit represents the end of the study

3.3 TREATMENTS ADMINISTERED

Patients will be instructed to take one tablet and one capsule in the morning at least 30 minutes before breakfast. Study drug in the form of oral tablets and oral capsules will be provided by Ironwood or designee. For the double-blind Treatment Period, study drug will be administered in a double dummy manner as described in Table 1:

Table 1. Treatments Administered

Treatment Group	Capsule	Tablet
30 µg linaclotide DR1	Placebo	30 µg linaclotide DR1
100 µg linaclotide DR1	Placebo	100 µg linaclotide DR1
300 µg linaclotide DR1	Placebo	300 µg linaclotide DR1
30 µg linaclotide DR2	Placebo	30 µg linaclotide DR2
100 µg linaclotide DR2	Placebo	100 µg linaclotide DR2
300 µg linaclotide DR2	Placebo	300 µg linaclotide DR2
290 µg linaclotide IR	290 µg linaclotide IR	Placebo
Placebo	Placebo	Placebo

Oral capsule and oral tablet both administered once daily in the morning at least 30 minutes before breakfast

3.4 METHODS OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

Patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized into the study at the Randomization Visit on Day 1. Approximately 520 patients will be randomized in equal proportions to one of eight treatments (described in Section 3.3). Randomization numbers will be assigned by interactive web response system (IWRS).

3.5 BLINDING

This study is a double-blind, double-dummy study.

4. DETERMINATION OF SAMPLE SIZE

The sample size per treatment group was determined based on a one-way design and includes 8 treatments: placebo; 30 µg, 100 µg, or 300 µg of the linaclotide DR1 formulation; 30 µg, 100 µg, or 300 µg of the linaclotide DR2 formulation; and the 290 µg dose of the linaclotide IR formulation (the FDA-approved dose for IBS-C). Previous trials with linaclotide IR demonstrated treatment differences with respect to Change from Baseline in 12-Week Abdominal Pain of 0.78 (-1.196 vs. -1.975 for placebo and linaclotide IR, respectively), and a standard deviation of 1.73 (based on the root mean squared error from an ANCOVA adjusting for baseline pain). Based on these historical values, it was estimated that, within each formulation, the highest two active treatment arms (DR1 100 µg and 300 µg; DR2 100 µg and 300 µg) would reflect the previously observed Change from Baseline (-1.975), the lowest active treatment arms within each formulation (DR1 30 µg; DR2 30 µg) would achieve a Change from Baseline of -1.586 reflecting 50% of the observed prior treatment difference (-0.39), and placebo would reflect the previously observed Change from Baseline (-1.196). Under these assumptions, a study with 65 patients per treatment arm (520 total patients) will have 81% power based on a 2-sided linear trends test within each formulation (linear contrast: -3 (placebo) -1 (30 µg) 1 (100 µg) 3 (300 µg); IR formulation not included) at an alpha level of 0.05. In addition, subsequent pairwise comparison between placebo and the active treatment groups reflecting the previously observed treatment difference will have 73% statistical power (two-sided, $\alpha = 0.05$).

5. PHARMACOKINETICS, EFFICACY AND SAFETY ASSESSMENTS

5.1 STUDY SCHEMATIC AND SCHEDULE OF ASSESSMENT

The schedule of evaluations for Study MCP-103-204 is presented in Table 2. The double-blind treatment period starts with the first dose of double-blind study drug and ends with the last assessment.

Table 2. Schedule of Evaluations MCP-103-204

	Screening Period (Up to 21 days)	Pretreatment Period (14 to 21 days)	Treatment Period (12 weeks)				
Visit Days →	**Screening Visit (Day -42 through Day -15)**	**Pretreatment Visit (Day -21 to Day -14)**	**Randomization Visit (Day 1)**	**Follow-up Call (Day 3)**	**Week 4 Visit (Day 29±3)**	**Week 8 Visit (Day 57±3)**	**Week 12/End-of-Treatment Period Visit [o] (Day 85+3)**
Visit Numbers →	**Visit 1**	**Visit 2**	**Visit 3**		**Visit 4**	**Visit 5**	**Visit 6**
Study Procedure ↓							
Signature of ICF	X						
Inclusion and Exclusion Criteria Verification	X	X	X				
IWRS Registration [a]	X	X	X		X	X	X
Medical History	X						
Physical Examination [b]	X						X
Body Weight and Height [c]	X	X	X		X	X	X
Seated Vital Signs [d]	X	X	X		X	X	X
Prior and Concomitant Medicines [e]	X	X	X		X	X	X
Clinical Laboratory Tests [f]	X		X				X
Pregnancy Test [g]	X		X				X
Laxative/Suppository/Enema Washout Instructions [h]	X						
AE Evaluations [i]		X	X	X	X	X	X
eDiary Registration and Training [j]		X	X		X	X	X

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Visit Numbers →	**Visit 1**	**Visit 2**	**Visit 3**		**Visit 4**	**Visit 5**	**Visit 6**
Study Procedure ↓							
Daily and Weekly Assessments [k]		X	X		X	X	X
eDiary Compliance Verification and Reminder [l]			X		X	X	X
Rescue Medicine Dispensed [m]		X	X		X	X	
Patient eDiary Entry, in Clinic			X		X	X	X
Randomization			X				
SF-12v2			X		X	X	X
EQ-5D-3L			X		X	X	X
SF-MPQ-2			X		X	X	X
IBS-SSS			X		X		
Treatment Satisfaction Assessment					X	X	X
Study Drug Dispensed			X		X	X	
Study Drug Administration [n]			X				
Study Drug Accountability					X	X	X

AE = adverse event; BM = bowel movement; CIC = chronic idiopathic constipation; CBC = complete blood count; EQ-5D-3L = EuroQoL-5 Dimension; IBS-SSS = Irritable Bowel Syndrome – Symptom Severity Scale; ICF = informed consent form; SF-12-v2 = Short Form-12 Health Survey version 2; SF-MPQ-2 = Short Form McGill Pain Questionnaire-2

a. Site personnel will interact with IWRS to register the patient visit. Refer to the IWRS User Manual.
b. 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.
c. Height is measured only at the Screening Visit.
d. Vital signs must be obtained in the seated position and include oral temperature, respiratory rate, blood pressure, and pulse.
e. 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 history of using particular treatments for IBS-C and CIC.
f. Chemistry, CBC, and drug screen. The urine drug screen will be performed at the Screening Visit only.
g. To be eligible to continue in the study, a negative serum pregnancy test must be documented at the Screening Visit. A negative urine pregnancy test must be documented at the Randomization Visit (prior to dosing), and a negative serum pregnancy test must be documented at the Week 12/End-of-Treatment Period (EOT) Visit.
h. Study coordinator will instruct patients about the use of laxatives, suppositories, and enemas.
i. All AEs occurring after the patient signs the ICF will be captured. Appropriate site personnel will complete a follow-up phone call to patients within 48 hours following initial study drug administration to assess for developing AEs. The Sponsor will perform a blinded review of the safety information obtained from the first 40 follow-up phone calls, and determine whether follow-up phone calls to patients should continue or be discontinued.
j. 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.
k. An eDiary will be used for recording Daily BM-related Symptom Severity Assessments, Daily abdominal Symptom-severity Assessments, Weekly Assessments, EQ-5D-3L, Treatment Satisfaction Assessment, SF-MPQ-2, SF-12-v2, IBS-SSS, and any use of rescue medicine. Patients will enter BMs and rescue medicine in the eDiary on an event-driven basis, and will complete an evening entry each day to record daily assessments.
l. 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 EOT visit). (eDiary questions may be found in the eDiary User Manual.)
m. 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.
n. Study drug will be administered in the clinic at the Randomization Visit (study drug does not need to be taken in the morning before breakfast). 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.
o. Patients who are randomized but do not complete the Treatment Period (withdraw consent or are discontinued before they have completed 12 weeks of treatment), will be considered Treatment Period withdrawals and should complete the procedures required at the EOT Visit (even if out of window).

5.2 PHARMACOKINETIC ASSESSMENTS

There are no pharmacokinetic assessments planned for this study.

5.3 EFFICACY ASSESSMENTS

5.3.1 Key Efficacy Assessments

The key efficacy assessments that will be used to determine the key efficacy parameters are the eDiary questions that determine whether a bowel movement (BM) is a complete spontaneous BM (CSBM) and the daily patient assessment of Abdominal Pain at its Worst:

Complete Spontaneous Bowel Movement

- 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 Rescue Medicine Use. Patients will report rescue medicine use on an event-driven basis. An evening report will ask whether the patient entered all rescue medicine use for that day, and collect rescue medicine not previously entered for that day.

Each day of the Pretreatment and Treatment 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.) The patient will also complete eDiary entries on an event-driven basis to report use of Rescue Medicines (e.g., oral bisacodyl; bisacodyl suppository), laxatives, suppositories, or

enemas to treat their symptoms. Patients will complete a daily evening report to enter any BMs and Rescue Medicine usage not previously reported by the patient for that day.

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 numerical rating scale (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">

5.3.2 Other Efficacy Assessments

In addition to the key efficacy assessments, the following efficacy assessments are used in determining the other efficacy parameters.

Spontaneous Bowel Movement (SBM)

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

- BM day and time
- Day of any Rescue Medicine Use

Stool Consistency

Patient assessment of stool consistency will be collected using two questions by daily eDiary entry on an event-driven basis. For each BM, the patient assesses his/her stool using the Bristol Stool Form Scale (BSFS; Appendix I) which depicts the stool consistency characteristics along with descriptions for each of them. The patient assigns a corresponding score for each BM.

The 7-point ordinal BSFS scale is provided below:

"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)

Second, the patient assesses his/her stool using a 5-point ordinal scale:

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

- ❑ Very hard
- ❑ Hard
- ❑ Neither too hard nor too soft
- ❑ Loose but not watery
- ❑ Very loose and watery

Straining

Patient assessment of straining will be collected daily by eDiary entry. 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)

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">

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 the 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

Treatment Satisfaction Assessment

A treatment satisfaction assessment will be performed at the Week 4 Visit and all subsequent study visits by eDiary entry. 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

5.3.3 Health Outcomes Assessments

5.3.3.1 Short Form-12 Health Survey Version 2 (SF-12v2)

The SF-12v2 Health Survey (1) is a widely used generic measure of health status (Appendix II). The SF-12v2 measures eight concepts commonly represented in widely used surveys: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality (energy/fatigue), social functioning, role limitations due to emotional problems, and mental health (psychological distress and psychological well-being). These eight scales are aggregated into two summary measures: the Physical and Mental Component Summary Scores. The SF-12v2 will be self-administered at the Randomization Visit prior to the patient receiving study drug and at all subsequent study visits. Treatment Period withdrawals should complete the self-administration of the SF-12v2 at the EOT Visit (even if out of window).

5.3.3.2 EuroQoL-5 Dimension (EQ-5D-3L)

The EQ-5D-3L is a generic measure of health status that is widely used in Europe (Appendix III)(2). The descriptive system consists of five questions assessing the following dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Responses to the five questions define a health state for which a utility index can be derived from published algorithms.(3) The second component of the EQ-5D-3L is a visual analogue scale, asking patients to rate their health from 0 to 100 (0 represents worst imaginable health state and 100 represents best imaginable health state). The EQ-5D-3L will be self-administered at the Randomization Visit prior to the patient receiving study drug and at all subsequent study visits. Treatment Period withdrawals should complete the self-administration of the EQ-5D at the EOT Visit (even if out of window).

5.3.3.3 Short Form McGill Pain Questionnaire-2 (SF-MPQ-2)

The SF-MPQ-2 is a measure that provides a comprehensive evaluation of both neuropathic and non-neuropathic pain through assessment of 22 words describing different qualities of pain and related symptoms (Appendix IV) (4). It will be self-administered at the Randomization Visit prior to the patient receiving study drug and at all subsequent study visits. Treatment Period withdrawals should complete the self-administration of the SF-MPQ-2 at the EOT Visit (even if out of window). The SF-MPQ-2 consists of a total pain score and four summary scales: (1) continuous descriptors, (2) intermittent descriptors, (3) neuropathic descriptors, and (4) affective descriptors.

5.3.3.4 Irritable Bowel Syndrome-Symptom Severity Scale (IBS-SSS)

The Irritable Bowel Syndrome-Symptom Severity Scale (IBS-SSS, Appendix V) (5) contains seven questions that ask patients to rate the severity and frequency of their abdominal pain, the severity of their abdominal distention, the dissatisfaction with their bowel habits, and how much abdominal pain or discomfort or altered bowel habits interfere with their life in general. The IBS-SSS will be self-administered at the Randomization Visit prior to the patient receiving study drug and at the Week 4 Visit.

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 form until 30 days after the patient's last study visit.

5.4.1.1 Causality Assessment

Causal relationship must be assessed according to the following scale:

- Related — An event where there is a reasonable possibility of a causal relationship between the event and the study drug
- Unrelated — Any other event

5.4.1.2 Severity Assessment

Severity will be assessed according to the following scale:

- Mild — The AE was an annoyance to the patient but did not further hinder baseline functioning
- Moderate — The AE caused the patient to experience some discomfort or some interference with normal activities but was not hazardous to health; prescription drug therapy may have been employed to treat the AE
- Severe — The AE caused the patient to experience severe discomfort or severely limited or prevented normal activities and represented a definite hazard to health; prescription drug therapy and/or hospitalization may have been employed to treat the AE

5.4.1.3 Serious Adverse Events

All adverse events will be categorized as Serious (as defined in the MCP-103-204 Protocol, Section 5.5.3.2) or Non-Serious.

5.4.2 Medical History

A complete medical history will be performed as defined in the Schedule of Assessments (Table 2).

5.4.3 Physical Examination

A complete physical examination will be performed as defined in the Schedule of Events (Table 2). 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 (if required).

5.4.4 Vital Signs

Vital sign measurements will be performed as defined in the Schedule of Events (Table 2). Vital sign measurements include oral temperature (°C), respiratory rate, systolic and diastolic blood pressure (BP), and pulse. Respiratory rate, 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 Events (Table 2). 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, and cholesterol
- **Other:** Urine drug screening (cocaine, barbiturates, amphetamines, opiates, benzodiazepine, alcohol, and cannabinoids) (screening 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 other visits specified in the Schedule of Evaluations. A negative urine pregnancy test must be documented at the Randomization 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 study.

6. STATISTICAL METHODS

6.1 GENERAL METHODS

All summaries will be presented by treatment unless specified otherwise. Descriptive statistics including the number of patients, mean, standard deviation (SD), median, minimum, and maximum 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 will be used, unless stated otherwise. There is no adjustment for multiplicity; p-values will be reported as nominal.

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 repeated measures (MMRM) or analysis of covariance (ANCOVA) when the absolute or change score are analyzed. Heterogeneity of slopes will be explored (e.g., review of residuals, inclusion of an interaction term, comparison of group differences at the 25^{th} and 75^{th} percentiles) and, if any changes to planned analyses are needed, the change will be documented in the clinical study report.

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 by center into the following 5 geographic regions (as listed in Table 7): Northeast, Southeast, Midwest, Southwest, and West.

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

6.6 MULTIPLE COMPARISONS/MULTIPLICITY

No multiple comparison adjustments are planned for this study.

6.7 USE OF AN EFFICACY SUBSET

Not applicable

6.8 ACTIVE CONTROL TO SHOW EQUIVALENCE

Not applicable

6.9 EXAMINATION OF SUBGROUPS

No subgroup analyses are planned for this study.

7. 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 Randomized Population

The Randomized Population consists of all patients in the Screened Population who were randomized to a treatment group in the study.

7.1.3 Safety Population

The Safety Population consists of all patients who received at least one dose of study drug, in which patients are evaluated according to the treatment they 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. All safety analyses will be based on the Safety population.

7.1.4 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population consists of all randomized patients who received at least one dose of study drug. 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.

7.2 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) performed by members of the Ironwood Clinical Trials team, including but not limited to the Clinical Medical Researcher and study Biostatistician. Deviations to be reviewed 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 Randomized, 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 overall only by study center within geographic region (See Section 9.3 for definition of geographic region).

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 randomly assigned to treatment), 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 randomized patients who are in the ITT population, 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 for the Randomized Population. 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.

7.4 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters (age; age group; race; ethnicity; sex; weight; height; and body mass index, calculated as weight [kg]/(height [m])^2) will be summarized descriptively by treatment group for the Safety and ITT populations. Baseline efficacy parameters (including SBM frequency, CSBM frequency, abdominal pain, abdominal bloating, abdominal discomfort, abdominal symptom composite score [consisting of abdominal pain, abdominal bloating, abdominal discomfort], stool consistency, and straining) will be summarized descriptively by treatment group for the ITT population. 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.

Abnormalities in patients' medical and surgical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 18.0. 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

Patients will take their initial dose of study drug at the trial center during the Randomization Visit (Visit 3). For all days in the Treatment Period, patients are instructed to take study drug

once daily in the morning at least 30 minutes before breakfast. The double-dummy dosing requires all patients to take one capsule and one tablet for each dose.

Dosing compliance for the Treatment Period is defined as the number of capsules and tablets (Total number of capsules + Total number of tablets) actually taken by a patient during the Treatment Period divided by the number of capsules and tablets that were expected to be taken during the Treatment Period multiplied by 100. The total number of capsules actually taken will be calculated as total number of capsules dispensed minus total number capsules returned minus total number of capsules lost. The same calculation will be applied for the calculation of total tablets taken. The total number of capsules and tablets expected to be taken during the Treatment Period is the number of days between the date of first dose taken and the date of last dose taken, inclusive, multiplied by 2. Patients will be included in the period summary only for the periods they were on study (i.e., the periods that are prior to or contain the last dose date). This information will be obtained from Study Drug Accountability Record of the patient's eCRF.

Descriptive statistics for study drug compliance will be presented for the Safety Population by treatment group for the Treatment Period as a whole and for each of the three consecutive drug dispensed/drug return periods (approximately 4-weeks) comprising the Treatment Period.

7.6 EXTENT OF EXPOSURE

Exposure to study drug for the Safety Population during the double-blind treatment period will be summarized by treatment group in terms of treatment duration and calculated as the number of days from the date of the first dose of double-blind study drug to the date of the last dose of double-blind study drug, inclusive. Overall treatment duration will also be categorized as 1 Day; >1 Day to ≤ 7 Days; >7 Days to ≤ 30 Days; >30 Day to ≤90 Days; and ≥90 Days.

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

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 medication is defined as any medication taken on or after the date of the first dose of double-blind study drug during the Treatment Period. Medications started after the date of the last dose of double-blind study drug will not be considered concomitant medications.

Both prior and concomitant medications will be coded by drug name and therapeutic class using WHO Drug Dictionary version B2 March 2015. 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 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 the eDiary and will be summarized as described in Section 7.9.2.

7.8 EDIARY COMPLIANCE

Patients are required to enter their evening diary assessments into the eDiary each evening during the pretreatment and treatment period. 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, and weekly. For each time period, eDiary percent compliance will be calculated as 100* the number of completed evening reports 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 eDairy entries each week; these will be presented by treatment group for the ITT Population. 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 key efficacy parameters.

Daily eDiary assessments collect information on BMs, including whether a BM is an SBM. SBM is defined as a BM that occurs in the absence of a 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.

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 the day of randomization up to the time of randomization. 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.

Baseline values for patient symptom severity parameters (e.g., abdominal discomfort, abdominal bloating, abdominal pain, abdominal symptom score [details provided in Section 7.9.2], and constipation severity) will be the average of the non-missing severity scores reported during this period.

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 7.9.2). All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

7.9.1 Key Efficacy Parameter(s)

There are 3 key efficacy parameters: 1) Weekly Change from Baseline in Abdominal Pain, 2) Weekly Change from Baseline in CSBM Frequency, and 3) 6/12 Week Abdominal Pain and Constipation (APC) +1 Responder. The criteria for each of the 3 primary efficacy parameters are provided below:

Weekly Change from Baseline in Abdominal Pain

Abdominal pain is measured daily using an 11-point NRS. A patient's weekly abdominal pain score is the average of the nonmissing abdominal pain scores reported by the patient during each week.

Weekly Change from Baseline in CSBM Frequency

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

6/12 Week 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.

- A Weekly APC +1 Responder is a patient who meets the criteria to be a Weekly CSBM +1 Responder and a Weekly Abdominal Pain Responder. 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 APC +1 Responder for that week.

- A Weekly CSBM +1 Responder is a patient who has an increase from baseline of at least 1 in the CSBM weekly rate for that week. 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 +1 Responder for that week.
- A Weekly Abdominal Pain Responder is a patient who has a decrease in the weekly average of the abdominal pain score of at least 30% compared with the baseline average. 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.

7.9.1.1 Analyses of the Key Efficacy Parameters

All analyses of the key primary efficacy endpoints will be performed on the ITT Population.

For each continuous weekly change-from-baseline measure defined above, inferential testing of the change from baseline will be evaluated employing a MMRM framework with week (categorical), treatment, geographical region, and week-by-treatment fixed effects, and baseline value as a covariate. A compound symmetry covariance structure will be used to model the covariance of within-patient results. Exploratory analyses with unstructured and autoregressive (1) covariance structures will also be considered for planning purposes.

The overall dose response within each DR formulation will be conducted by employing an overall trend test (i.e., linear contrast, see Appendix VI) for each formulation to test for a monotonically increasing dose response within the MMRM. Overall treatment effect pairwise comparisons will be performed between each linaclotide treatment and placebo. [redacted]

Pairwise treatment comparisons with placebo will be performed at each week utilizing the same MMRM models.

The efficacy analysis of 6/12 Week APC+1 Responder rate will be performed by using a CMH test controlling for geographic region for each DR formulation (i.e., 1. DR1 and Placebo; 2. DR2 and Placebo). The overall trend test will be assessed via the CMH correlation statistics to test for

a monotonically increasing dose response within the formulation. Pairwise comparisons between each linaclotide dose and placebo will be performed.

7.9.1.2 Sensitivity Analyses of the Key Efficacy Parameters

If warranted, for selected efficacy endpoints, the potential impact of missing data on the estimates of treatment effect will be assessed using alternative statistical methods. The following sensitivity analysis approach based on multiple imputations (MI) will be utilized.

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 Intent-to-treat (ITT) Population for each week of the Treatment Period (Please refer to Section 7.8 for additional details).

Weekly data for a patient with less than 4 complete evening diaries will be classified as missing for that week. A pattern-mixture model using a placebo-based multiple imputation method (6) will be used as sensitivity analyses to explore the effects of missing data on the key efficacy endpoints and select other endpoints for the ITT Population.

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 Control-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 ;
Run;
```

c. Set Mono_rest1 and reg_imp1 Call this dataset IMP1.

d. Repeat Steps 2a-2c for weeks 2 – 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);
Run;
```

3. Analyze each of the 1000 imputed complete datasets.
   a. For continuous endpoints, perform same statistical analyses (MMRM or ANCOVA) as described for observed case.
   b. For responder endpoint:
      a. Using the CSBM and Abdominal Pain data imputed above, recalculate the responder
      b. For each imputed dataset, perform Cochran-Mantel-Haenszel (CMH) analyses as described above.

4. Estimation and Inference of the MI datasets will be performed using Rubin's combination rules (7) as implemented through the MIANALYZE procedure in SAS.

7.9.2 Other Efficacy parameter(s)

The other efficacy parameters are as follows:

- **Weekly CSBM +1 Responder:** For each week in the Treatment Period, a Weekly CSBM +1 Responder is a patient who has an increase from baseline of at least 1 in the CSBM weekly rate for that week. 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 +1 Responder for that week.

- **6/12 Week CSBM +1 Responder:** A 6/12 Week CSBM +1 Responder is a patient who meets the Weekly CSBM +1 Responder criteria for at least 6 out of the 12 weeks of the Treatment Period.
- **9/12 Week CSBM +1 Responder:** A 9/12 Week CSBM +1 Responder is a patient who meets the Weekly CSBM +1 Responder criteria for at least 9 out of the 12 weeks of the Treatment Period.
- **CSBM (SBM) within 24 Hours of Receiving the First Dose of Study Drug:** Date and time of first dose and date and time of first CSBM (SBM) is used to determine whether a CSBM (SBM) is occurred within 24 hours after the patient took the first dose of study drug.
- **Change from Baseline in 12-week CSBM Frequency Rate:** A patient's 12-week CSBM frequency rate will be the CSBM rate (CSBMs/week) calculated over the 12 weeks of the Treatment Period.
- **Weekly Abdominal Pain Responder:** A Weekly Abdominal Pain Responder is a patient who has a decrease in the weekly average of the abdominal pain score of at least 30% compared with the baseline average. 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 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.
- **9/12 Week Abdominal Pain Responder:** A 9/12 Week Abdominal Pain Responder is a patient who meets the Weekly Abdominal Pain Responder criteria for at least 9 out of the 12 weeks of the Treatment Period.
- **Weekly Abdominal Symptom Score Responder:** A Weekly Abdominal Symptom Score Responder is a patient who has a decrease in the weekly average of the Abdominal Symptom Score of at least 30% compared with the baseline average. 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 Symptom Score Responder for that week.
- **6/12 Week Abdominal Symptom Score Responder:** A 6/12 Week Abdominal Symptom Score Responder is a patient who meets the Weekly Abdominal Symptom Score Responder criteria for at least 6 out of the 12 weeks of the Treatment Period.

- **9/12 Week Abdominal Symptom Score Responder:** A 9/12 Week Abdominal Symptom Score Responder is a patient who meets the Weekly Abdominal Symptom Score Responder criteria for at least 9 out of the 12 weeks of the Treatment Period.
- **Change from Baseline in 12-week Abdominal Pain:** Abdominal pain is measured daily using an 11-point NRS. The patient's abdominal pain score for the Treatment Period is the average of the non-missing daily worst abdominal pain scores reported by the patient during the 12-week Treatment Period.
- **Percent Change from Baseline in 12-week Abdominal Pain:** Percent change will be calculated as the 100 * the Change from Baseline in Abdominal Pain divided by the baseline Abdominal Pain score.
- **Change from Baseline in 12-week SBM Frequency Rate:** A patient's 12-week SBM frequency rate will be the SBM rate (SBMs/week) calculated over the 12 weeks of the Treatment Period.
- **Change from Baseline in 12-week Stool Consistency:** Stool consistency is measured using the 7-point BSFS. The patient's BSFS score for the Treatment Period is the average of the non-missing BSFS scores from the SBMs reported by the patient during the 12-week Treatment Period.
- **Change from Baseline in 12-week Straining:** Straining is measured using a 5-point ordinal scale. The patient's straining score for the Treatment Period is the average of the non-missing straining scores from the SBMs reported by the patient during the 12-week Treatment Period.
- **Change from Baseline in 12-week Abdominal Discomfort:** Abdominal discomfort is measured daily using an 11-point NRS. The patient's abdominal discomfort score for the Treatment Period is the average of the non-missing daily abdominal discomfort scores reported by the patient during the 12-week Treatment Period.
- **Change from Baseline in 12-week Abdominal Bloating:** Abdominal bloating is measured daily using an 11-point NRS. The patient's abdominal bloating score for the Treatment Period is the average of the non-missing daily abdominal bloating scores reported by the patient during the 12-week Treatment Period.
- **Change from Baseline in 12-Week Abdominal Symptom Score:** The patient's abdominal symptom score for the Treatment Period is the average of the non-missing daily abdominal symptom scores reported by the patient during the 12-week Treatment Period. A patient's daily abdominal symptom score is calculated as the average of the daily abdominal pain, abdominal bloating, and abdominal discomfort. If two or more of the individual daily abdominal symptoms are missing, then the Abdominal Symptom Score for that day will be missing.

- **Change from Baseline in 12-Week Constipation Severity:** Constipation severity is measured weekly using a 5-point ordinal scale. The patient's constipation severity score for the Treatment Period is the average of the non-missing weekly constipation severity scores reported by the patient during the 12-week Treatment Period.
- **Change from Baseline in 12-week IBS Symptom Severity:** IBS symptom severity is measured weekly on a 5-point ordinal scale. The patient's IBS symptom severity score for the Treatment Period is the average of the non-missing weekly IBS symptom severity scores reported by the patient during the 12-week Treatment Period.
- **Change from Baseline in 12-Week Percent of Days with Use of Rescue Medicine:** The percent of days using per-protocol rescue medicine or any other laxative, suppository, or enema during the Treatment Period will be calculated as 100 * the number of days rescue medicine was used during the Treatment Period divided by the total number of days on treatment.
- **Treatment Satisfaction:** Treatment satisfaction is measured on a 5-point ordinal scale. Treatment satisfaction will be analyzed separately at each post-dose visit.
- **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 at each post-dose visit.
- **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.
- **9/12 Week Adequate Relief Responder**: A 9/12 Week Adequate Relief Responder is a patient who reports Adequate Relief for at least 9 out of the 12 weeks of the Treatment Period.

7.9.2.1 Sustained Responders

Select 9/12 Week and 6/12 Week responder parameter will also be assessed for as sustained response to determine if the treatment effect is maintained during weeks 9 to 12 of the treatment period. A 9/12 Week Sustained Responders is a patient meeting the 9/12 Week Responder definition, plus are weekly responders for 3 of the last 4 weeks (weeks 9-12) of the treatment period. A 6/12 Week Sustained Responders is a patient meeting the 6/12 Week Responder definition, plus are weekly responders for 2 of the last 4 weeks (weeks 9-12) of the treatment period. The Sustained Responder definition will be applied to the following response endpoints:

- APC+1 Responder
- CSBM+1 Responder
- Abdominal Pain Responder

7.9.2.2 Analyses of Other Efficacy Parameters

All categorical responder parameters (e.g., Weekly CSBM +1 Responder) and CSBM (SBM) with 24-hours of first dose, will be analyzed utilizing the same methods defined above for the key efficacy measure 6/12 Week APC +1 Responder.

All continuous change-from-baseline in 12-week efficacy parameters will be evaluated using an ANCOVA model with treatment group and geographic region as fixed-effect terms and baseline value as a covariate. Least-squares (LS) means for each treatment group, LS mean differences between each linaclotide dose and placebo and their corresponding confidence intervals, and p-values for the pairwise comparisons versus placebo will be presented. [redacted]

For Treatment Satisfaction, inferential testing will be evaluated employing a MMRM framework with week (categorical), treatment, and week-by-treatment fixed effects, and patient as the random effect. The covariance structure will be unstructured. Pairwise comparisons between each treatment group and placebo will be performed overall and at each visit. Associated LSMeans, LSMeans differences and confidence intervals will be presented.

For Change from Baseline in 12-Week CSBM, SBM, Stool Consistency (BSFS and 5 point ordinal score), Abdominal Pain, Abdominal Discomfort, Abdominal Bloating, and the Abdominal Symptom Composite Score, sensitivity analyses will be performed by applying the same ANCOVA model to the rank-transformed data. Change and baseline values will be ranked based on the normalization method of Blom with ties set to the mean. If the results of the sensitivity analysis show consistency with those obtained from the original analysis, only results from the original ANCOVA will be reported.

For Change from Baseline in weekly SBM, Stool Consistency (BSFS and 5 point ordinal score), Abdominal Discomfort, Abdominal Bloating, and the Abdominal Symptom Composite Score, an ANCOVA with treatment and geographic region as fixed effects and baseline as a covariate will be fit. All pairwise comparisons performed for the 12-week analyses will be performed for each week.

7.10 POSITIVE CONTROL

The 290 µg linaclotide dose is FDA-approved for the treatment of IBS-C (Linzess®) and is included in the current trial to evaluate assay sensitivity and to provide comparative data for the patient population treated with 290 µg linaclotide within the linaclotide program. Linaclotide 290 µg will be compared to placebo utilizing the same method described for pairwise comparison described in Section 7.9.

7.11 SAFETY ANALYSIS

The safety analysis will be performed using the Safety Population. The safety parameters will include AEs, clinical laboratory and vital sign parameters, and physical examination. For each of the clinical laboratory and vital sign parameters, the last non-missing safety assessment before the first dose of double-blind drug will be used as the baseline for all analyses of that safety parameter.

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 18.

An AE that occurs during the Treatment Period will be considered a treatment-emergent adverse event (TEAE) if it started after the first dose of double-blind study drug or was present prior to the date of the first dose of double-blind study drug but increased in severity after the first dose of double-blind study drug. 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. An AE that occurs more than one day after the date of the last dose of double-blind study drug will not be considered as a TEAE.

The number and percentage of patients reporting TEAEs in each treatment group will be tabulated by system organ class (SOC) and preferred term and further categorized by severity and relationship to the study drug. 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 using the highest severity and closest relationship to study drug for the summarization by severity and relationship to study drug, respectively.

The incidence of common (≥ 2% of patients in any treatment group) TEAEs will be summarized by preferred term and treatment group for the Treatment Period.

A serious adverse event (SAE) that occurred between the date of the first dose of double-blind study drug and 30 days after the date of the last dose of double-blind study drug, inclusive, will be considered an on-therapy SAE. The number and percentage of patients who have on-therapy SAEs will be summarized by preferred term and treatment group. In addition, the incidence of on-therapy SAEs that led to death will be summarized separately by preferred term for each treatment group.

The number and percentage of patients in the Safety Population who have AEs leading to premature discontinuation of the study drug will be summarized by preferred term and treatment.

For patients experiencing a TEAE coded as diarrhea, the number of days from first dose of study drug for the Treatment Period to the onset date of the first occurrence of treatment-emergent diarrhea during the Treatment Period will be summarized by treatment group using descriptive

statistics. In addition, the incidence of treatment-emergent diarrhea by time of first onset for the Treatment Period will be calculated for each treatment group.

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 the following laboratory parameters:

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, and cholesterol

Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in Table 3. The number and percentage of patients who have PCS post-baseline clinical laboratory values will be tabulated by treatment group for the Treatment Period. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 assessment in the corresponding post-baseline period. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS value in the corresponding post-baseline period. A supportive listing of patients with PCS post-baseline values will be provided, including the PID number, trial center, baseline and all post-baseline (including non-PCS) values. A listing of all AEs for patients with post-baseline PCS laboratory values will also be provided.

Table 3. 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
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	10^9/L	—	> 3 × ULN

Table 3. Criteria for Potentially Clinically Significant Laboratory Results

Parameter	SI Unit	Lower Limit	Higher Limit
count			
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 vital signs (systolic and diastolic blood pressures, pulse rate, respiratory rate, temperature, and weight) and changes from baseline values at each visit and at the end of study will be presented by treatment group for the Treatment Period.

Vital sign values will be considered PCS if they meet both the observed-value criteria and the change-from-baseline criteria listed in Table 4. The number and percentage of patients with PCS post-baseline values will be tabulated by treatment group for the Treatment Period. The percentages will be calculated relative to the number of patients with baseline values and at least 1 post-baseline assessment for the Treatment Period. The numerator will be the total number of patients with available baseline values and at least 1 PCS post-baseline value for the Treatment Period. A supportive listing of patients with PCS post-baseline values will be provided, including the PID number, trial center, baseline and all post-baseline (including non-PCS) values.

In addition, a listing of all AEs that occurred in patients who had PCS post-baseline vital sign values will be provided.

Table 4. 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.

7.12.1 Short Form-12 Health Survey Version 2

The higher-order norm-based scores, Physical Component Summary (PCS-12) and Mental Component Summary (MCS-12), will be computed at Randomization, Week 4, Week 8, and EOT. Descriptive statistics (n, mean, SD, median, minimum, and maximum) will be presented for the absolute and change-from-baseline by visit. Treatment differences for the change from baseline at each post-dose visit will be analyzed using an ANCOVA with treatment and

geographic region as fixed effects and baseline summary score as a covariate. (See Section 9.12.1 for scale scoring)

7.12.2 EuroQol-5 Dimension (EQ-5D-3L)

Patient responses to the descriptive system (i.e., health state) will be converted to the corresponding utility score and the descriptive statistics (n, mean, SD, median, minimum and maximum) will be presented for utility score by treatment group. The same statistics will be calculated for the analog scale reflecting the patient's preference for their health state. Results will be presented at baseline and at each post-baseline week using both observed case (OC) and last observation carried forward (LOCF) approaches to missing post-baseline data. (See Section 9.12.2 for scale scoring)

7.12.3 Short Form McGill Pain Questionnaire - 2 (SF-MPQ-2)

At each assessment of the SF-MPQ-2, total pain score and the 4 subscales (Continuous pain, Intermittent pain, Neuropathic pain, and Affective pain) will be calculated. Descriptive statistics and the change from baseline will be presented for each score. Treatment differences with respect to change from baseline will be assessed using an ANCOVA with treatment and geographic region as fixed effects and baseline value as a covariate. (See Section 9.12.3 for scale scoring)

7.12.4 Irritable Bowel Syndrome-Symptom Severity Scale (IBS-SSS)

At each assessment of the IBS-SSS, the IBS-SSS Total score will be calculated. Descriptive statistics will be presented for the IBS-SSS Total score and each severity score. (See Section 9.12.4 for scale scoring)

8. CHANGES FROM ANALYSES PLANNED IN THE PROTOCOL

a. For the key efficacy parameters Weekly Change from Baseline in Abdominal Pain and Weekly Change from Baseline in CSBM Frequency, the protocol states:

Additional exploratory comparisons between the linaclotide doses (DR1, DR2) and linaclotide IR, [redacted] All other comparisons between linaclotide dose (DR1, DR2, and IR) will be performed descriptively.

b. For 6/12 Week APC+1 Responder rate, the protocol states:

If the overall CMH statistic reaches statistical significance (α = 0.05), the tested formulation will be considered efficacious and the nature of the dose response will be explored among the individual linaclotide DR doses within the formulation. [redacted]

The SAP clarifies statistical inference compares Placebo to each DR1 and DR2 doses only, regardless of the overall trend significance. All other treatment comparisons will be descriptive in nature.

c. For each 6/12 Week and 9/12 Week responder endpoint defined in the protocol, a corresponding "Sustained Responder" was added. Each new 'Sustained Responder' parameter will be presented and analyzed as described in Sections 7.9.1.1 and 7.9.1.2

d. For the analyses of the 12-week Change from baseline, the protocol states:

[redacted] All other comparisons between linaclotide dose (DR1, DR2, and IR) will be performed descriptively.

e. For all responders in the "Other Efficacy Endpoint" section, the protocol states:

All categorical responder parameters (e.g., Weekly CSBM +1 Responder) will be analyzed utilizing the same methods defined above for the key efficacy measure 6/12 Week APC +1 Responder.

The SAP clarifies statistical inference compares Placebo to each DR1 and DR2 doses only. All other treatment comparisons will be descriptive in nature.

f. For patients experiencing a TEAE coded as diarrhea, analyses of the number of days from first dose of study drug for the Treatment Period to the onset date of the first occurrence of treatment-emergent diarrhea during the Treatment Period listed in the SAP were not identified in the protocol.

g. The endpoints and analyses of 6/12 and 9/12 Week Adequate Relief were not specified in the protocol.

9. DATA HANDLING CONVENTIONS

9.1 VISIT TIME WINDOWS FOR SAFETY ANALYSIS

Table 5 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 5. Visit Time Windows for Safety Analysis

Derived Visit	Scheduled Test / Visit Day[a]	Window
Baseline	Day 1	Days ≤ 1
Day 29 Visit	Day 29	Days [2, 43]
Day 57 Visit	Day 57	Days [44, 71]
Day 85 Visit	Day 85	Days [72, 99]
End of Trial[b]	Final or termination visit	

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

Test/Visit Day will be calculated as follows: test/visit date – date of randomization.

9.2 VISIT TIME WINDOWS FOR EFFICACY ANALYSIS

Table 6 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., SBM weekly frequency rate, BSFS weekly scores).

Table 6. 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	last dose day[c] (usually Day 85)

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; Day 1 = the day of randomization. For the calculation of rates (e.g., 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 last eDiary date will be used to impute the last dose date.

For the Treatment Period, diary day is calculated as diary date – date of randomization + 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, the patient's Treatment Period shall end on the day of the last dose. The affected Treatment Period week shall be shortened to the end of the

withdrawn patient's Treatment Period, and all subsequent Treatment Period weeks will be missing for that patient.

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 7): Northeast, Southeast, Midwest, Southwest, and West. All analyses using trial center will use this 5-category center variable.

Table 7. 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.

The evening report allows the patient to report BM information between the time of the previous evening report and the current evening report (~24-hour recall). If the previous evening report was not completed, then the patient can report BM information within the evening report occurring between 7:00 PM of the previous night and the current evening 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.

The evening report allows the patient to report RM information between the time of the previous evening report and the current evening report (~24-hour recall). If the previous evening report was not completed, then the patient can report RM information within the evening report occurring between 7:00 PM of the previous night and the current evening 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, bloating, and 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 window will be used in conjunction with the rescue medicine window. If there is any overlap between the BM window and the patient's rescue medicine 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 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:

$$Weekly\ Frequency\ Rate\ (Analysis\ Week_i) = (7 \times 24) \times C_i/D_i$$

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 6).

9.4.3.3 Overall Weekly Stool Frequency Rate Calculations for Each Analysis Period

For each of the 2 analysis periods (Pretreatment and Treatment), 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:

$$Weekly\ Frequency\ Rate\ (Analysis\ Period_j) = (7 \times 24) \times C_j/D_j$$

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 6).

9.4.4 Other Weekly Scores Derivation

For Abdominal 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.

For the abdominal symptom composite 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 symptom composite score will be missing. Weekly scores will be based on the average of the non-missing abdominal symptom composite scores.

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-study assessments are repeated or if unscheduled visits occur, the last non-missing post baseline assessment will be used as the end-of-study 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 last eDiary entry will be used as the last dose date.

9.7 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE 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 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 (i.e., partial missing) for adverse events.

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

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 checked on the AE eCRF)**

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.

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 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 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 due, for example, 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 8 shows examples of how some possible laboratory results should be coded for the analysis.

Table 8. 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).

9.12 HEALTH OUTCOME PARAMETERS

9.12.1 Short Form 12 Health Survey Version 2

The SF-12 is a multipurpose, short-form health survey consisting of 12 questions designed for use in clinical practice and research, health policy evaluations, and general population surveys. The SF-12, Version 2.0, contains 12 items that, when scored, yield an 8-scale profile of functional health and well-being, as well as physical and mental summary measures.

The 8 scales (also known as domains) are as follows: Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE), and Mental Health (MH). A norm-based score will be computed for each of the 8 scales using standard scoring rules. These rules generate a standardized score (with a mean of 50 and an SD of 10 in the general U.S. Population) for each of the scales such that higher scores represent better health condition.

In addition, scores from these 8 scales will be aggregated in 2 distinct, higher-order summary norm-based scores: Physical Component Summary (PCS-12) and Mental Component Summary (MCS-12) scores. These 2 summary scores will also be standardized to have a mean of 50 and an SD of 10 in the general US Population.

The steps involved in scoring SF-12 can be found at Ware et al (1995) (1); they are briefly described as follows:

Item Recoding

Reverse score items 1, 5, 6a, and 6b so that, for all scales, higher scores indicate better health condition. The scores 1, 2, 3, 4, and 5 of items 5, 6a, and 6b will be reversed to 5, 4, 3, 2, and 1. For item 1, the scores 1, 2, 3, 4, and 5 will be reversed to 5, 4.4, 3.4, 2.0, and 1.0.

Aggregate and Transform Scale Scores

A transformed scale score for each scale will be computed by subtracting the lowest possible derived score from the actual derived score, dividing the difference by the corresponding possible derived score range, and multiplying the ratio by 100. Table 9 summarizes the process.

Table 9. Summary of Formulas for Scoring and Transforming Scales

Scale	Sum Final Item Values (After Recoding)	Lowest and Highest Possible Derived Scores	Possible Derived Score Range
Physical Functioning (PF)	2a + 2b	2, 6	4
Role-Physical (RP)	3a + 3b	2, 10	8
Bodily Pain (BP)	5	1, 5	4
General Health (GH)	1	1, 5	4
Vitality (VT)	6b	1, 5	4
Social Functioning (SF)	7	1, 5	4
Role-Emotional (RE)	4a + 4b	2, 10	8
Mental Health (MH)	6a + 6c	2, 10	8

Compute Standardized Values (z-Scores) for the Short Form-12 Health Survey, Version 2.0, Scales

A z-score for each scale is computed by subtracting the 1998 general US population mean for each SF-12 scale and dividing the difference by the corresponding scale SD from the 1998 general US population (Table 10).

Table 10. 1998 General US Population Means and Standard Deviations Used to Derive Short Form-12 Health Survey, Version 2.0, z-Scores—Acute Form

SF-12 Scale	Mean[a]	SD[a]
Physical Functioning (PF)	80.64733	29.71224
Role-Physical (RP)	80.61635	27.84366
Bodily Pain (BP)	83.42495	24.34172
General Health (GH)	71.96134	23.53406
Vitality (VT)	55.11847	25.63085
Social Functioning (SF)	84.58234	25.21668
Role-Emotional (RE)	86.79996	22.64927
Mental Health (MH)	71.38235	20.54864

a. The means and SDs for each scale of the Short Form-12 Health Survey, Version 2.0, are based on the 0-100 scoring.

Compute Aggregate Summary Scores

An aggregate physical and mental summary score will be computed by multiplying the z-score of each SF-12 scale by its respective factor score coefficient (Table 11) and summing the 8 products for each summary score.

Table 11. 1990 Factor Score Coefficients Used to Derive Physical Component Summary and Mental Component Summary Scale Scores—Standard and Acute Forms

SF-12 Scale	Standard and Acute Form Factor Score Coefficients	
	PCS	MCS
Physical Functioning (PF)	0.42402	-0.22999
Role-Physical (RP)	0.35119	-0.12329
Bodily Pain (BP)	0.31754	-0.09731
General Health (GH)	0.24954	-0.01571
Vitality (VT)	0.02877	0.23534
Social Functioning (SF)	–0.00753	0.26876
Role-Emotional (RE)	–0.19206	0.43407
Mental Health (MH)	–0.22069	0.48581

MCS = Mental Component Summary; PCS = Physical Component Summary; SF-12 = Short Form-12 Health Survey.

Compute Norm-Based Summary Scores

This step involves transforming the aggregate physical and mental summary scores to the norm-based (50, 10) scoring (mean = 50 and SD = 10 in the general 1998 US population) by multiplying the respective aggregate summary score by 10 and adding 50. See Ware et al (1) for details of the standard scoring rules.

If any item is missing in SF-12, then the PCS-12 and MCS-12 scores will not be calculated and will be set to missing.

9.12.2 EuroQol-5 dimension (EQ-5D-3L)

The 5-item responses of the EQ-5D-3L define a health state that can be converted into a single summary utility index that assigns weights (ie, value) to each level. Different weights are available. For this study, the US TTO (time trade-off) weights will be used (3).

The EQ-5D-3L index is computed according to the following equation as:

$$EQ_{index} = 1 - \{0.146016 \times m_1 + 0.557685 \times m_2 + 0.1753425 \times s_1 + 0.4711896 \times s_2 + 0.1397295 \times u_1 + 0.3742594 \times u_2 + 0.1728907 \times p_1 + 0.5371011 \times p_2 + 0.156223 \times a_1 + 0.4501876 \times a_2 + -0.1395949 \times d_1 + 0.0106868 \times^* i_{22} + -0.1215579 \times i_3 + -0.0147963 \times i_{32}\}$$

where the variables m_1, s_1, u_1, p_1, a_1, m_2, s_2, u_2, p_2, a_2 , i_2, i_{22}, i_3, i_{32} and d_1 are given in Table 12.

Table 12. EuroQol Quality-of-Life Questionnaire Utility Index

EuroQoL	Level 2	Level 3	
Mobility	m_1 = 1 if Level 2 selected 0 otherwise	m_2 = 1 if Level 3 selected 0 otherwise	m_0 = 1 if m_1 = 0 & m_2 = 0 0 otherwise
Self-care	s_1 = 1 if Level 2 selected 0 otherwise	s_2 = 1 if Level 3 selected 0 otherwise	s_0 = 1 if s_1 = 0 & s_2 = 0 0 otherwise
Usual activity	u_1 = 1 if Level 2 selected 0 otherwise	u_2 = 1 if Level 3 selected 0 otherwise	u_0 = 1 if u_1 = 0 & u_2 = 0 0 otherwise
Pain/discomfort	p_1 = 1 if Level 2 selected 0 otherwise	p_2 = 1 if Level 3 selected 0 otherwise	p_0 = 1 if p_1 = 0 & p_2 = 0 0 otherwise
Anxiety/depression	a_1 = 1 if Level 2 selected 0 otherwise	a_2 = 1 if Level 3 selected 0 otherwise	a_0 = 1 if a_1 = 0 & a_2 = 0 0 otherwise
Interaction terms	$i_2 = \max\{0, (m_1 + s_1 + u_1 + p_1 + a_1) - 1\}$		
	$i_{22} = i_2 \times i_2$		
	$i_3 = \max\{0, (m_2 + s_2 + u_2 + p_2 + a_2) - 1\}$		
	$i_{32} = i_3 \times i_3$		
	$d_1 = \max\{0, 4 - (m_0 + s_0 + u_0 + p_0 + a_0)\}$		

If any dimension is missing in the EQ-5D-3L, the EQ-5D-3L index will not be calculated and will be set to missing.

9.12.3 Short Form McGill Pain Questionnaire - 2 (SF-MPQ-2)

The SF-MPQ-2 is composed of 22 items investigating 4 dimensions.

Dimension of Pain (Subscales)	Number of items	Cluster of items	Direction of Score
Continuous	6	1, 5-6, 8-10	Lower score = Lower pain
Intermittent	6	2-4, 11, 16, 18	
Neuropathic	6	7, 17, 19-22	
Affective Descriptor	4	12-15	

Subscale score: For each of the scales, scores are calculated by taking the mean of the item ratings included in the scale.

Total score: mean of all SF-MPQ-2 item ratings

Interpretation and Analysis of missing data: - No correction is necessary for missing data if the subject has omitted a few items. Mean scores should be calculated on the available items.

9.12.4 Irritable Bowel Syndrome-Symptom Severity Scale (IBS-SSS)

The IBS-SSS has 2 severity questions each with a 0-10 point rating scale where a higher score represents greater severity or poorer quality of life (see Appendix V), one frequency of pain (0-10) over the last 10 days question, one dissatisfaction score with a 0-10 point rating where a higher score represents greater dissatisfaction, and one indication of how much pain, discomfort or altered bowel interfere with general life score with a 0-10 scale where a higher score representing greater interference. The IBS-SSS total score will be the average of the 5 non-missing scores described above.

10. REFERENCES

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APPENDIX I. 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 II. SF-12V2

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
b Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3

3. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

APPENDIX III. EQ-5D-3L QUESTIONNAIRE

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ☐
I have some problems in walking about ☐
I am confined to bed ☐

Self-Care

I have no problems with self-care ☐
I have some problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

Usual Activities (e.g., work, study, housework, family, or leisure activities)

I have no problems with performing my usual activities ☐
I have some problems with performing my usual activities ☐
I am unable to perform my usual activities ☐

Pain/Discomfort

I have no pain or discomfort ☐
I have moderate pain or discomfort ☐
I have extreme pain or discomfort ☐

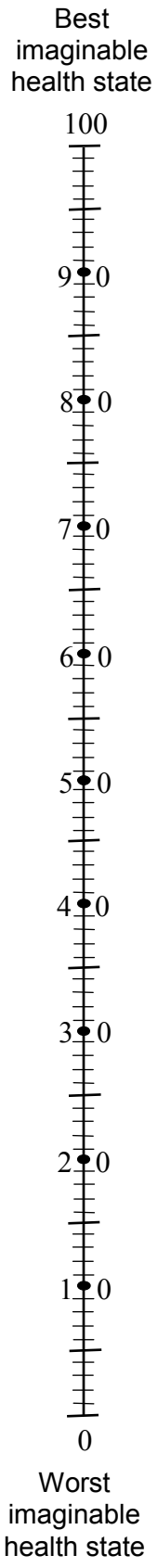
Anxiety/Depression

I am not anxious or depressed ☐
I am moderately anxious or depressed ☐
I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



APPENDIX IV. SHORT-FORM MCGILL PAIN QUESTIONNAIRE-2

Short-Form McGill Pain Questionnaire-2 (SF-MPQ-2)

This questionnaire provides you with a list of words that describe some of the different qualities of pain and related symptoms. Please put an **X** through the numbers that best describe the intensity of each of the pain and related symptoms you felt during the past week. Use 0 if the word does not describe your pain or related symptoms.

1. Throbbing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
2. Shooting pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
3. Stabbing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
4. Sharp pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
5. Cramping pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
6. Gnawing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
7. Hot-burning pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
8. Aching pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
9. Heavy pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
10. Tender	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
11. Splitting pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
12. Tiring-exhausting	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
13. Sickening	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
14. Fearful	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
15. Punishing-cruel	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
16. Electric-shock pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
17. Cold-freezing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
18. Piercing	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
19. Pain caused by light touch	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
20. Itching	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
21. Tingling or 'pins and needles'	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
22. Numbness	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*

APPENDIX V. IRRITABLE BOWEL SYNDROME-SYMPTOM SEVERITY SCALE

IBS-SSS Questionnaire

1. A. Do you currently (in the last month) suffer from abdominal (tummy) pain?

☐ Yes

☐ No

B. If yes, how severe is your abdominal (tummy) pain? Please indicate a number from 0 to 10, with 0 meaning " no pain" and 10 meaning "very severe."

no pain 0 1 2 3 4 5 6 7 8 9 10 very severe

C. Please enter the number of times that you get the pain every 10 days. For example, if you choose 4 it means that you get pain 4 out of 10 days. If you get pain every day enter 10.

no days with pain 0 1 2 3 4 5 6 7 8 9 10 10 days with pain

2. A. Do you currently suffer from abdominal distention* (bloating, swollen or tight tummy)? *Women, please ignore distention related to your period.

☐ Yes

☐ No

B. If yes, how severe is your abdominal distention/tightness? Please indicate a number from 0 to 10, with 0 meaning "no distention" and 10 meaning "very severe."

no distention 0 1 2 3 4 5 6 7 8 9 10 very severe

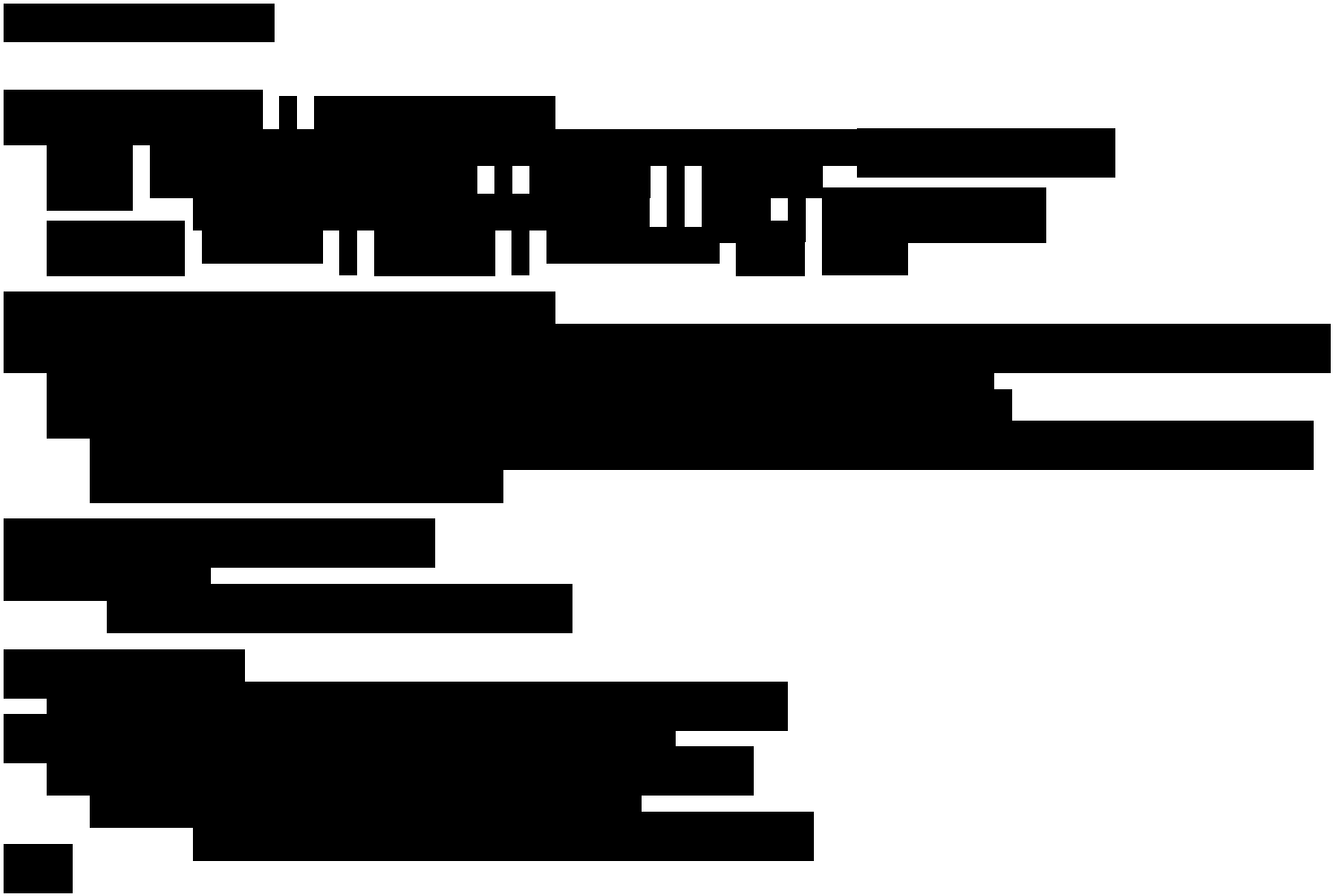
3. How dissatisfied are you with your bowel habits? Please indicate a number from 0 to 10, with 0 meaning "very happy" and 10 meaning "very unhappy."

very happy 0 1 2 3 4 5 6 7 8 9 10 very unhappy

4. Please indicate how much abdominal pain or discomfort or altered bowel habits are affecting or interfering with your life in general. Please indicate a number from 0 to 10, with o meaning “not at all” and 10 meaning “completely.”

not at all 0 1 2 3 4 5 6 7 8 9 10 completely

[redacted]



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