Clinical Study Protocol: MCP-103-204-P-03

Final Version, 09 October 2015

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
Study Phase:	2b
Product Name:	Linaclotide Delayed Release
Indication:	Irritable Bowel Syndrome with Constipation
Sponsor:	Ironwood Pharmaceuticals, Inc. 301 Binney Street Cambridge, MA 02142
Sponsor Contact:	Nick Omniewski, MPH Clinical Study Manager Ironwood Pharmaceuticals, Inc. Phone: (617) 621-8454 e-mail: nomniewski@ironwoodpharma.com

	Date
Original Protocol:	20 July 2015
Amendment #1:	17 August 2015
Amendment #2:	09 October 2015

SYNOPSIS

Study Number:

MCP-103-204

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 Centers:

Approximately 80 in the United States

Development Phase: 2b

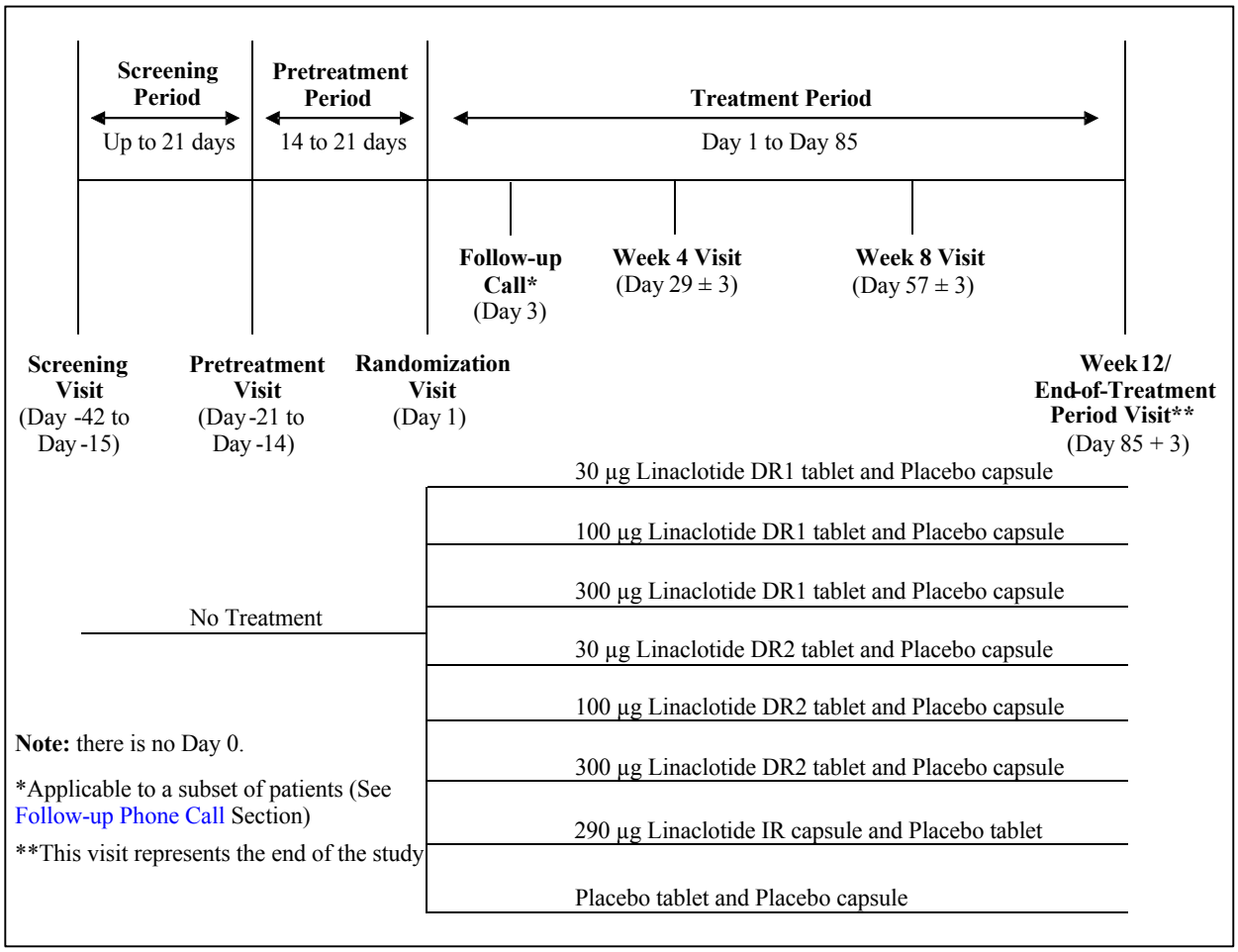
Objective(s):

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]

Methodology:

This is a multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, multiple-dose, 12-week study, consisting of 3 distinct periods, as illustrated in the figure below. The study will enroll patients who have IBS-C diagnosed using Rome III criteria. 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. Linaclotide IR is being included in the study as a positive control, against which the safety and efficacy of the various doses of the two test formulations can be compared. [redacted]

Overview of Study Design



Study Periods

1. Screening Period: The Screening Period starts with the signature of the informed consent form (ICF; Appendix I) and may last for up to 21 days. During this period, patient eligibility for entry into the Pretreatment Period will be determined. The end of the Screening Period coincides with the start of the Pretreatment Period.
2. Pretreatment Period: The Pretreatment Period is defined as the 14 to 21 calendar days immediately before the Randomization Visit. During this period, patients will provide the following information in a handheld electronic diary (eDiary):
   - Daily Bowel Movement (BM)-related Symptom-severity Assessments on an event-driven basis (meaning these are assessments made at the time the event occurs)
   - Daily Abdominal Symptom-severity Assessments in a daily evening report
   - Weekly Patient Assessment of Constipation Severity
   - Weekly Patient Assessment of IBS Symptom Severity
   - Weekly Patient Assessment of Adequate Relief

- Use of Per-protocol Rescue Medicine or Any Other Laxatives, Suppositories, or Enemas on an event-driven basis

Patients who satisfy all of the entry criteria will enter the Treatment Period.

3. Treatment Period: The Treatment Period begins with treatment assignment and lasts for 12 weeks. Patients will be randomly assigned to one of 8 treatments: 30 µg, 100 µg, or 300 µg of linaclotide DR1; 30 µg, 100 µg, or 300 µg of linaclotide DR2; 290 µg of linaclotide IR; or placebo. Study drug will be taken once daily in the morning at least 30 minutes before breakfast. Patients will continue to use the handheld eDiary to provide their daily assessments (Daily BM-related Symptom-severity Assessments on an event-driven basis, and Daily Abdominal Symptom-severity Assessments in a daily evening report), weekly assessments (Weekly Patient Assessment of Constipation Severity, Weekly Patient Assessment of IBS Symptom Severity, and Weekly Patient Assessment of Adequate Relief), and Use of Per-protocol Rescue Medicine or Any Other Laxatives, Suppositories, or Enemas on an event-driven basis. Quality-of-life and patient-outcome assessments will be performed at study visits throughout the Treatment Period. A list of these assessments and the visits when they will be performed is provided in the Study Procedures section below. Patients will complete a Week 4 Visit, Week 8 Visit, and Week 12/End of Treatment Visit during the Treatment Period. (See Schedule of Evaluations) 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. (See Follow-up Phone Call Section)

Study Procedures

During the Pretreatment and Treatment Periods, patients will enter information into the eDiary. Certain information will be entered by the patient on an event-driven basis, in a daily evening report, and on a weekly basis, as specified below.

Daily Assessments: The following information will be entered into the eDiary each day:

- Daily BM-related Symptom-severity Assessments
  - The following information will be entered by the patient for each BM on an event-driven basis:
    - BM day and time
    - Association with a sense of a complete evacuation
    - Stool consistency on the Bristol Stool Form Scale (BSFS)
    - Straining on a 5-point ordinal scale
    - Stool consistency on a 5-point ordinal scale

- Daily Abdominal Symptom-severity Assessments
  - The following information will be entered by the patient in a daily evening report:
    - Rating of abdominal pain at its worst during the previous 24 hours on a 0-to-10 point NRS
    - Rating of abdominal discomfort at its worst during the previous 24 hours on a 0-to-10 point NRS
    - Rating of abdominal bloating at its worst during the previous 24 hours on a 0-to-10 point numerical rating scale (NRS)
- Use of Per-protocol Rescue Medicine or Any Other Laxatives, Suppositories, or Enemas on an event-driven basis

Weekly Assessments: The following information will be entered by the patient into the eDiary each week at the same time as the daily evening report:

- Weekly Patient Assessment of Constipation Severity
- Weekly Patient Assessment of IBS Symptom Severity
- Weekly Patient Assessment of Adequate Relief

Study Visit Assessments: The following information will be captured on the eDiary at visits during the Treatment Period:

- Short Form-12 Health Survey version 2 (SF-12v2, captured at the Randomization Visit before the first dose of study drug and at all subsequent study visits)
- EuroQol-5 Dimension (EQ-5D, captured at the Randomization Visit before the first dose of study drug and all subsequent study visits)
- Short-Form McGill Pain Questionnaire-2 (SF-MPQ-2, captured at the Randomization Visit before the first dose of study drug and at all subsequent study visits)
- Irritable Bowel Syndrome-Symptom Severity Scale (IBS-SSS, captured at the Randomization Visit before the first dose of study drug and at the Week 4 Visit)
- Treatment Satisfaction Assessment (captured at the Week 4 Visit and all subsequent study visits)

Concomitant Medicine

- Rescue Medicine: During the Pretreatment and Treatment Periods, patients may use dispensed, protocol-permitted laxatives (bisacodyl tablets or suppositories) as Rescue Medicine when at least 72 hours have passed since their previous BM or when their

symptoms become intolerable. In order to qualify for randomization into the Treatment Period, patients must not have used Rescue Medicine on the calendar day before the Randomization Visit or on the day of the Randomization Visit up until the time of the clinic visit. Patients must agree to refrain from using Rescue Medicine from the time they arrive at the clinic for the Randomization Visit through the calendar day after randomization.

- Prohibited Medicine: Medicines that are not permitted during the Pretreatment and Treatment Periods are listed in Appendix II.

Number of Patients:

Approximately 520 IBS-C patients (65 patients per treatment group) will be randomized into the Treatment Period.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

To be eligible to participate in the study, patients must meet the following criteria:

1. Patient has signed an ICF.
2. Patient is ambulatory and community-dwelling (females must also be non-pregnant) and is aged 18 years or older at the Screening Visit. Lactating females must agree not to breastfeed.
3. Sexually active female patients of childbearing potential (i.e., women who are not postmenopausal or who have not had a bilateral oophorectomy, hysterectomy, or tubal ligation) must agree to use one of the following methods of birth control from the date they sign the ICF until 24 hours after their final dose of study drug:
   a. Hormonal contraception (i.e., oral contraceptive, contraceptive implant, or injectable hormonal contraceptive)
   b. Double-barrier birth control (e.g., condom plus intrauterine device, diaphragm plus spermicide, etc.)
   c. Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy
4. Females of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at the Randomization Visit prior to dosing.
5. Patient meets the colonoscopy requirements defined by the American Gastroenterological Association guidelines and described in Appendix III. (Note: Patients are eligible to enter the Pretreatment Period on the fifth calendar day after a colonoscopy.)
6. Patient has no clinically significant concurrent illness or findings on a physical examination and clinical laboratory tests (clinical chemistry panel, complete blood count [CBC], urine drug screen) after signing the ICF but before receiving the first dose of study drug. (Note:

The investigator will determine if a particular finding is clinically significant. In making this determination, the investigator will consider whether the particular finding could prevent the patient from performing any of the protocol-specified assessments, could represent a condition that would exclude the patient from the study, could represent a safety concern if the patient participates in the study, or could confound the study-specified assessments of safety or efficacy.)

7. Patient meets Rome III criteria for IBS (1): reports abdominal pain or discomfort at least 3 days/month during the 3 months before the diagnosis with the onset at least 6 months before the diagnosis, associated with two or more of the following features:
   a. Relieved with defecation
   b. Onset associated with a change in frequency of stool
   c. Onset associated with a change in form (appearance) of stool

   Note: the diagnosis can be made at the Screening Visit or can be based on symptoms that the patient had before starting chronic treatment with linaclotide or lubiprostone.
8. During the time when the Rome III criteria for IBS were met, the patient had hard or lumpy stools (Bristol Stool Form Scale [BSFS] scores of 1 or 2) with at least 25% of BMs and had loose (mushy) or watery stools (BSFS scores of 6 or 7) with less than 25% of BMs in the absence of antidiarrheal or laxative use.
9. Patient reports < 3 BMs (with each BM occurring in the absence of any laxative, suppository, or enema use during the preceding 24 hours) per week for at least 12 weeks, before the Screening Visit or before starting chronic treatment with linaclotide, lubiprostone, polyethylene glycol 3350, or any laxative.
10. Patient has an average score for abdominal pain at its worst of ≥ 3.0, as reported in the eDiary using an 11-point numerical rating scale (NRS) during the 14 calendar days before the Randomization Visit and the calendar day of Randomization up to the time when the data entry into the eDiary is made in clinic.
11. Patient reports ≤ 6 complete spontaneous BMs (CSBMs) and ≤ 10 spontaneous BMs (SBMs) in the eDiary over the 14 calendar days before the Randomization Visit and the calendar day of Randomization up to the time when the data entry into the eDiary is made in clinic. (Note: A CSBM is an SBM that is associated with a sense of complete evacuation. An SBM is a BM that occurs in the absence of laxative, suppository, or enema use on the calendar day of the BM or the calendar day before the BM as evidenced by the patient-reported concomitant medicine use via the eDiary.)
12. Patient is compliant (as defined in the study procedures section below) with eDiary completion by adequately responding to eDiary questions on 10 or more of the 14 calendar days before the Randomization Visit.

13. Patient is willing to discontinue any laxatives used before the Pretreatment Visit in favor of the protocol-defined Rescue Medicine (bisacodyl tablets or suppositories).
14. Patient is fluent in English or Spanish.
15. Patient is able to operate the eDiary adequately.
16. Patient agrees to refrain from making any new, major life-style changes that may affect IBS-C symptoms (e.g., starting a new diet or changing his or her exercise pattern) from the time of signature of the ICF to the last study visit.

Exclusion Criteria

Patients who meet any of the following criteria will not be eligible to participate in the study:

1. Patient reports loose (mushy) or watery stools (BSFS score of 6 or 7) in the absence of any laxative, suppository, enema, or prohibited medicine (as described in Appendix II) for > 25% of BMs during the 12 weeks before the Screening Visit.
2. Patient has a structural abnormality of the gastrointestinal (GI) tract or a disease or condition that can affect GI motility.
3. Patient has ever had a diagnosis or family history of familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, or any other form of familial colorectal cancer.
4. Patient has ever had a diagnosis of inflammatory bowel disease (IBD).
5. Patient currently has unexplained and clinically significant alarm symptoms (lower GI bleeding [rectal bleeding or heme-positive stool], iron-deficiency anemia, weight loss) or systemic signs of infection or colitis.
6. Patient currently has active peptic ulcer disease (i.e., disease that is not adequately treated or stable with therapy).
7. Patient has a history of diverticulitis or any chronic condition (e.g., chronic pancreatitis, polycystic kidney disease, ovarian cysts, endometriosis) that can be associated with abdominal pain or discomfort and could confound the assessments in this study, unless the patient is considered to have been cured of the condition.
8. Patient has a potential central nervous system cause of constipation (e.g., Parkinson's disease, spinal cord injury, and multiple sclerosis).
9. Patient has ever had any of the following diseases or conditions that can be associated with constipation: pseudo-obstruction, megacolon, megarectum, bowel obstruction, descending perineum syndrome, solitary rectal ulcer syndrome, systemic sclerosis.
10. Patient has ever had a fecal impaction that required hospitalization or emergency room treatment, or has a history of cathartic colon, laxative or enema abuse, ischemic colitis, or pelvic floor dysfunction (unless successful treatment has been documented by a normal balloon expulsion test).

11. Patient has had surgery that meets any of the following criteria:
    a. Bariatric surgery for treatment of obesity, or surgery to remove a segment of the GI tract at any time before the Screening Visit
    b. Surgery of the abdomen, pelvis, or retroperitoneal structures during the 6 months before the Screening Visit
    c. An appendectomy or cholecystectomy during the 60 days before the Screening Visit
    d. Other major surgery during the 30 days before the Screening Visit
12. Patient has a history of cancer other than treated basal cell or squamous cell carcinoma of the skin. (Note: Patients with a history of cancer are allowed provided that the malignancy has been in a complete remission for at least 5 years before the Randomization Visit. A complete remission is defined as the disappearance of all signs of cancer in response to treatment.)
13. Patient has a history of diabetic neuropathy.
14. Patient has untreated hypothyroidism or treated hypothyroidism for which the dose of thyroid hormone has not been stable for at least 6 weeks at the time of the Screening Visit.
15. Patient has a recent history (during the 12 months before the Randomization Visit) of drug or alcohol abuse. (Note: Patients with a history of drug or alcohol abuse that was diagnosed greater than 12 months before the Randomization Visit may be enrolled as long as they have exhibited no actual abuse during the 12 months before the Randomization Visit.)
16. Patient reports a BSFS score of 6 (loose, mushy stools) for > 1 SBM or a BSFS score of 7 (watery stools) with any SBM over the 14 calendar days before the Randomization Visit and the calendar day of Randomization up to the time when data is entered into the eDiary in the clinic.
17. Patient used Rescue Medicine (bisacodyl tablet or suppository) or any other laxative, suppository, or enema, on the calendar day before or the calendar day of the Randomization Visit.
18. Patient reported using a Prohibited Medicine (excluding laxatives, suppositories, and enemas) during the Pretreatment Period or is not willing or able to abide by the restrictions regarding use of Prohibited Medicines defined in Appendix II. (Note: The use of fiber, bulk laxatives, or stool softeners [such as docusate] is acceptable provided the patient has been on a stable dose during the 30 days before the Screening Visit and plans to continue on a stable dose throughout the study.)
19. Patient has been hospitalized for a psychiatric condition or has made a suicide attempt during the two years before the Randomization Visit.
20. Patient has taken commercially available linaclotide or participated in a linaclotide, plecanatide, or SP-333 clinical study during the 30 days before the Screening Visit.

21. Patient has received an investigational drug during the 30 days before the Screening Visit or is planning to receive an investigational drug (other than that administered during this study) or use an investigational device at any time during the study.
22. Patient has an acute or chronic condition that, in the investigator's opinion, would limit the patient's ability to complete or participate in this clinical study.
23. Patient has previously entered the Pretreatment Period of this study.
24. Patient is directly or indirectly involved in the conduct and administration of this study as an investigator, subinvestigator, study coordinator, other study staff member, or employee of Ironwood Pharmaceuticals, Forest Laboratories, Actavis, Inc., or Allergan, Inc.; or the patient is a first-degree family member, significant other, or relative residing with one of the above persons involved directly or indirectly in the study; or the patient is enrolled in this study at another clinical study site.

Test Products, Dosage, and Mode of Administration:

Test products will be administered in a double-dummy manner as follows:

- 30 µg linaclotide DR1 oral tablet and a placebo oral capsule (matching the 290 µg linaclotide IR oral capsule) administered once daily in the morning at least 30 minutes before breakfast
- 100 µg linaclotide DR1 oral tablet and a placebo oral capsule administered once daily in the morning at least 30 minutes before breakfast
- 300 µg linaclotide DR1 oral tablet and a placebo oral capsule administered once daily in the morning at least 30 minutes before breakfast
- 30 µg linaclotide DR2 oral tablet and a placebo oral capsule administered once daily in the morning at least 30 minutes before breakfast
- 100 µg linaclotide DR2 oral tablet and a placebo oral capsule administered once daily in the morning at least 30 minutes before breakfast
- 300 µg linaclotide DR2 oral tablet and a placebo oral capsule administered once daily in the morning at least 30 minutes before breakfast

Reference Therapy, Dosage, and Mode of Administration:

The reference therapy will be administered in a double-dummy manner as follows:

- 290 µg linaclotide IR oral capsule and a placebo oral tablet (matching the DR1 and DR2 oral tablet) administered once daily in the morning at least 30 minutes before breakfast
- Placebo oral capsule and a placebo oral tablet administered once daily in the morning at least 30 minutes before breakfast

Duration of Treatment:

The test product and reference therapy will be administered for 12 weeks. Total patient participation is expected to last for up to 130 days.

Criteria for Evaluation:

Key Efficacy Assessments

The following efficacy assessments based on the eDiary questions are used to determine the key efficacy parameters: number of BMs and whether the BM is an SBM or CSBM, and daily patient assessment of abdominal pain over the last 24 hours (11-point NRS).

Other Efficacy Assessments

Other efficacy assessments are based on stool consistency as measured by the BSFS scale and on a 5-point ordinal scale; straining as measured on a 5-point ordinal scale (1 = Not at all, 5 = An extreme amount); and daily patient assessments of abdominal discomfort and abdominal bloating, each on an 11-point NRS. In addition, the Weekly Patient Assessment of Constipation Severity, the Weekly Patient Assessment of IBS Symptom Severity, and the Weekly Patient Assessment of Adequate Relief will be evaluated.

Safety Measure(s):

AE recording (each visit), clinical laboratory measures (chemistry and hematology: Screening, Randomization, and End-of-Treatment Period Visits), vital sign parameters (each visit). Note: Urinalysis and electrocardiograms will not be obtained in this study.

Statistical Methods:

Analysis Populations

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

General Methods

Efficacy analyses will be performed on the ITT Population. Unless otherwise specified, all confidence intervals will be two-sided and with a confidence level of 95%. No adjustments will be made for multiplicity in the conduct of comparisons among the linaclotide DR doses for the key efficacy parameters, or in the testing of the other efficacy parameters.

For analysis of continuous parameters (e.g., change from baseline), descriptive statistics (n, mean, standard deviation, median, and range) will be calculated and presented for each treatment group. For categorical parameters (e.g., responder vs. non-responder), the number and percentage of each category will be calculated and presented for each treatment group.

Key Efficacy Parameters

- The Weekly Change from Baseline in Abdominal Pain
- The Weekly Change from Baseline CSBM Frequency
- 6/12 Week Abdominal Pain and Constipation (APC) +1 Responder

  A 6/12 Week APC +1 Responder is a patient who meets the Weekly APC +1 Responder criteria for at least 6 out of the 12 weeks of the Treatment Period. The Weekly APC +1

Responder criteria are defined below.

Key Efficacy Analysis

For each continuous weekly change-from-baseline measure defined above, inferential testing of the change from baseline will be evaluated employing a mixed model with repeated measures (MMRM) framework with week (categorical), treatment, and week-by-treatment fixed effects, patient as the random effect, and baseline value as a covariate. The initial covariance structure will be compound symmetry but exploratory analyses with unstructured and autoregressive (1) structures will also be considered, primarily for planning purposes.

Corresponding with the primary efficacy objective of the study, which is to study the dose response of a range of oral doses within the linaclotide DR1 and DR2 formulations, the efficacy analysis of weekly change from baseline will be conducted by employing an overall trend test (i.e., linear contrast) for each formulation to test for a monotonically increasing dose response. Within a formulation, if the overall trend test reaches statistical significance ($\alpha = 0.05$), then that linaclotide DR 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 efficacy analysis of 6/12 Week APC+1 Responder rate will be confirmatory of the above and conducted by employing an overall trend test (i.e., Cochran-Mantel-Haenszel [CMH] correlation statistic) for each formulation (excluding the Active Control [linaclotide IR]) to test for a monotonically increasing dose response within the formulation. If the overall CMH statistic reaches statistical significance ($\alpha = 0.05$), 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]

Other Efficacy Parameters

- **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. The Weekly CSBM +1 Responder criteria are defined below.
- **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. The Weekly Abdominal Pain Responder criteria are defined below.
- **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.

- **Weekly Abdominal Pain Responder**: For each week in the Treatment Period, a Weekly Abdominal Pain Responder is a patient who has a decrease from baseline of at least 30% in the mean abdominal pain score 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 Abdominal Pain Responder for that week.
- **Weekly APC +1 Responder**: For each week in 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.
- Change from Baseline in 12-week Abdominal Pain
- Change from Baseline in 12-week CSBM Frequency Rate
- Change from Baseline in 12-week SBM Frequency Rate
- Change from Baseline in 12-week Stool Consistency
- Change from Baseline in 12-week Straining
- Change from Baseline in 12-week Abdominal Discomfort
- Change from Baseline in 12-week Abdominal Bloating
- Change from Baseline in 12-week Constipation Severity
- Change from Baseline in 12-week Abdominal Symptom Score
- Change from Baseline in 12-week IBS Symptom Severity

Other Efficacy Analysis

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.

All continuous change-from-baseline in 12-week efficacy parameters will be evaluated by comparing each DR1 and DR2 dose with the placebo group using an analysis of covariance (ANCOVA) model with treatment group and geographic region as fixed-effect terms and baseline value as a covariate. Least-squares means for each treatment group, least-squares mean differences between each DR1 and DR2 dose and the placebo group and their corresponding confidence intervals, and p-values for the pairwise comparisons versus placebo will be presented. [redacted]

Safety Analysis

All safety parameters will be analyzed descriptively in accordance with the General Methods.

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 approved 290 µg dose of the linaclotide IR formulation. 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 deviations 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 groups (DR1 100 µg and 300 µg; DR2 100 µg and 300 µg) would reflect the previously observed treatment difference (-1.975), the lowest active treatment groups with each formulation (DR1 30 µg; DR2 30 µg) would reflect 50% of the observed treatment difference (-1.586), and placebo would reflect the previously observed difference (-1.196). Under these assumptions, a study with 65 patients per treatment group (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, $\alpha = 0.05$).

Date of Original Protocol: 20 July 2015

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
Daily and Weekly Assessments [k]		X	X		X	X	X

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	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 ↓							
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			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

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 (refer to Appendix III). 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 (see Section 5.4.7 Concomitant Medicines).
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 (refer to Appendix II).
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. (See Follow-up Phone Call Section)
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, 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).

STUDY IDENTIFICATION

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LIST OF ABBREVIATIONS

AE	adverse event/experience
ANCOVA	analysis of covariance
ANOVA	analysis of variance
APC	Abdominal Pain and Constipation
BM	bowel movement
BP	blood pressure
BSFS	Bristol Stool Form Scale
CIC	chronic idiopathic constipation
CBC	complete blood count
CFTR	cystic fibrosis transmembrane conductance regulator
cGMP	cyclic guanosine monophosphate
CMH	Cochran-Mantel-Haenszel
CRO	contract research organization
CSBM	complete spontaneous bowel movement
DHHS	Department of Health and Human Services
DR	delayed release
DR1	delayed release formulation 1
DR2	delayed release formulation 2
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EOT	End of Treatment Period
EQ-5D	EuroQol-5 Dimension
FDA	Food and Drug Administration
GC-C	guanylate cyclase-C
GCP	good clinical practice
GI	gastrointestinal
HEENT	head, ears, eyes, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act

HT	hydroxytryptophan
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome with constipation
IBS-D	irritable bowel syndrome with diarrhea
IBS-M	irritable bowel syndrome mixed
IBS-U	unclassified irritable bowel syndrome
IBS-SSS	irritable bowel syndrome – symptom severity scale
ICF	informed consent form
ICH	International Conference on Harmonisation
IR	immediate release
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	Interactive web response system
LAR	legally authorized representative
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model with repeated measures
NDA	New Drug Application
NRS	numerical rating scale
PCS	potentially clinically significant
PID	patient identification
QOL	quality of life
SAE	serious adverse event
SAP	statistical analysis plan
SBM	spontaneous bowel movement
SD	standard deviation
SF-12v2	Short Form-12 Health Survey version 2
SOC	system organ class
TEAE	treatment-emergent adverse event

1. ETHICAL CONSIDERATIONS

This clinical study is designed to comply with the International Conference on Harmonisation (ICH) Guidance on General Considerations for Clinical Trials (62 Code of Federal Regulations [CFR] 66113, December 17, 1997) and Good Clinical Practice (GCP): Consolidated Guidance (62 CFR 25692, May 9, 1997). The study will be conducted in full compliance with the US Food and Drug Administration (FDA) guidelines for GCP and in accordance with the ethical principles that have their origins in the Declaration of Helsinki and 21 CFR § 312.120.

1.1 INSTITUTIONAL REVIEW BOARD

Obtaining approval by the Institutional Review Board (IRB) prior to the start of the study will be the responsibility of the investigator. A copy of the approval letter will be transmitted to the Sponsor or designee. During the course of the study, the investigator will provide timely and accurate reports to the IRB on the progress of the study, and will notify the IRB of serious adverse events (SAEs) or other significant safety findings in a manner consistent with IRB policies and ICH and GCP requirements. The study protocol (and any amendments), Informed Consent Form (ICF; Appendix I), and associated documentation will be approved by the IRB prior to study initiation, in compliance with CFR, Title 21, Part 56.

1.2 PATIENT INFORMATION AND CONSENT

Before entry into the study, patients will be provided with a written explanation of the study describing the nature of the study, as well as its purpose, expected duration, and the benefits and risks involved in study participation. Patients will then be given the opportunity to ask questions and will be informed of their right to withdraw from the study without prejudice. After this explanation and before entering the study, the patient will voluntarily sign an ICF.

If new information becomes available that may be relevant to the patient's consent and willingness to participate in the study, the ICF will be revised. The revised consent form will be submitted to the IRB for review and approval prior to its use.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study will be performed at approximately 80 study centers in the US. The investigator at the study center will be responsible for ensuring that the study is conducted according to the signed Clinical Trial Agreement, the protocol, IRB requirements, and GCP guidelines.

The investigator will be responsible for the oversight of the site's conduct of the study, which will consist of completing all protocol assessments, maintaining the study file and the patient records, drug accountability, corresponding with the IRB, and completing the electronic case report forms (eCRFs).

3. INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal (GI) disorder characterized by recurrent symptoms of abdominal pain and/or discomfort, accompanied by altered bowel function and a feeling of bloating.(2-6) In moderate to severe cases of IBS, an overall deterioration in quality of life (QOL) is often present.(7) IBS is one of the most frequently seen disorders in the United States; data suggest the prevalence of IBS is 11-14% of the adult population.(7) IBS is subtyped as IBS with diarrhea (IBS-D) or IBS with constipation (IBS-C), based on Rome III guidelines. Patients who meet criteria for both diarrhea and constipation are subtyped as IBS mixed (IBS-M); patients who do not fit into any of these three subtypes are classified as having unclassified IBS (IBS-U).(8)

Patients with IBS have increased visceral hypersensitivity and disregulated intestinal peristalsis. Abdominal pain in IBS is most often reported as lower left quadrant pain.(8) Patients with IBS have also demonstrated increased rectal hypersensitivity to balloon distension.(9) Therefore, it is hypothesized that abdominal pain in IBS patients originates, at least in part, in the colon and rectum.

Linaclotide (LINZESS®) is an orally-administered, minimally-absorbed 14-amino acid synthetic peptide agonist of guanylate cyclase C (GC-C) approved by FDA in 2012 for the treatment of IBS-C and chronic idiopathic constipation (CIC) in adults. It is the first approved GC-C agonist. As a GC-C agonist, linaclotide and its active metabolite improve bowel symptoms and abdominal pain via localized effects of cyclic guanosine monophosphate (cGMP) on the intestinal mucosa. Linaclotide induces fluid secretion in two ways: 1) by increasing intracellular cGMP leading to cystic fibrosis transmembrane conductance regulator (CFTR) channels and chloride secretion that results in net sodium and water movement into the intestinal lumen;(10) and 2) by inhibiting sodium reabsorption in the colon.(11) These effects on fluid dynamics within the GI tract are believed to play a role in accelerating intestinal transit and increasing stool water, which in turn results in softer stools. Orally administered linaclotide has also been shown to reduce visceral pain in animal models and in patients with IBS-C.(12) Linaclotide is believed to reduce abdominal pain by acting locally in the intestinal mucosa to reduce firing of mechanosensitive afferent nerve fibers.

The FDA-approved linaclotide immediate release (IR) formulation (LINZESS®) is a rapidly dissolving capsule, and dissolution tests suggest that it is released primarily in the stomach. Although GC-C is found throughout the GI tract, LINZESS® IR and its active metabolite likely have their greatest activity in the proximal region of the small intestine, as experiments conducted with rodent intestinal fluid have shown that both linaclotide and its metabolite are degraded into smaller peptide fragments and amino acids in the reducing environment of the small intestine.(13) Some linaclotide or its active metabolite can traverse the entire GI tract; in a Phase 1 clinical study with LINZESS®, up to 5% of the oral dose was recovered in the feces of healthy volunteers, in the form of the active metabolite. However, the amount of linaclotide and/or its metabolite reaching different regions of the GI tract following oral administration of LINZESS® is not known. A delayed release (DR) formulation that could avoid being degraded in the proximal small intestine may allow linaclotide to be delivered directly to the lower intestine, bypassing the GC-C receptors higher up in the GI tract.

Ironwood Pharmaceuticals and Forest Laboratories, LLC (an affiliate of Actavis, Inc.) are developing a DR formulation of linaclotide for patients who have IBS-C or CIC with the hypothesis that delivery of linaclotide to these regions will limit fluid secretion while preserving the inhibition of fluid reabsorption in the colon and enhancing the nociceptive effects of the drug by enabling higher concentrations of linaclotide to interact with GC-C in the colon. Two different DR tablet formulations have been developed:

- DR1 [redacted]
- DR2 [redacted]

[redacted] It is anticipated that delivery of linaclotide to the lower intestine will limit CFTR-mediated fluid secretion while preserving the inhibition of fluid reabsorption in the colon,

and will enable the delivery of higher concentrations of linaclotide directly to interact with GC-C in the proximal region of the small intestine, the hypothesized source of pain in IBS-C.

This is the first clinical study of linaclotide using a delayed release formulation. The clinical development program for LINZESS® that culminated in FDA approval for use in adult patients with IBS-C included two large double-blind, placebo-controlled registration trials.(14,15) These trials evaluated the safety and efficacy of linaclotide IR at a dose of 290 µg, administered as an oral capsule. One trial had a 26-week Treatment Period and one trial had a 12-week Treatment Period followed by a 4-week Randomized Withdrawal Period; however, the overall design of both Phase 3 trials was identical through the first 12 weeks of the Treatment Period. Both trials met all of their pre-specified primary and secondary efficacy endpoints. For each of the four primary efficacy parameters, the linaclotide dose group in both trials had statistically significantly higher proportions of responders compared with placebo (controlling for multiplicity). For all secondary efficacy change-from-baseline parameters (including complete spontaneous bowel movement [CSBM] frequency rate, spontaneous bowel movement [SBM] frequency rate, stool consistency, straining, bloating, abdominal discomfort, abdominal pain, and abdominal pain-free days) and responder parameters (6/12 Week CSBM +1 Responder and 6/12 Week Abdominal Pain Responder), the linaclotide group demonstrated statistically significant improvement compared with the placebo group ($p < 0.01$ for all secondary parameters controlling for multiplicity) in both trials.

Linaclotide was well-tolerated in these trials. (14,15) There were no deaths. One patient died during the Screening Period but never received either linaclotide or placebo. There were a total of 15 SAEs in the two trials. There were 9 (1.1%) SAEs in placebo-treated patients and 6 (0.7%) SAEs in linaclotide-treated patients. Overall, there was no obvious pattern in the types of SAEs experienced in either the placebo or linaclotide group. There were no SAEs of diarrhea. Treatment-emergent AEs (TEAEs) occurred in 54.9% of placebo-treated and 60.8% of linaclotide-treated patients. Diarrhea was the most frequent TEAE and was reported in 3.0% of patients treated with placebo and 19.8% of patients treated with linaclotide. Diarrhea was generally mild to moderate in severity. Diarrhea resulted in the discontinuation of 0.4% of patients treated with placebo and 5.3% treated with linaclotide. Human studies have not been conducted with the DR formulations of linaclotide. As the IR and DR formulations have the

same active ingredient, similar gastrointestinal side effects (diarrhea, abdominal pain, abdominal distension, and flatulence) may be expected. However, the frequency and severity of these effects remain to be determined.

Refer to the Investigator's Brochure for a more detailed description of the chemistry, pharmacology, efficacy, and safety of linaclotide, based on studies conducted in animals, healthy volunteers, and in patients with IBS-C and CIC and its relevance to the delayed release formulations.

4. STUDY OBJECTIVES

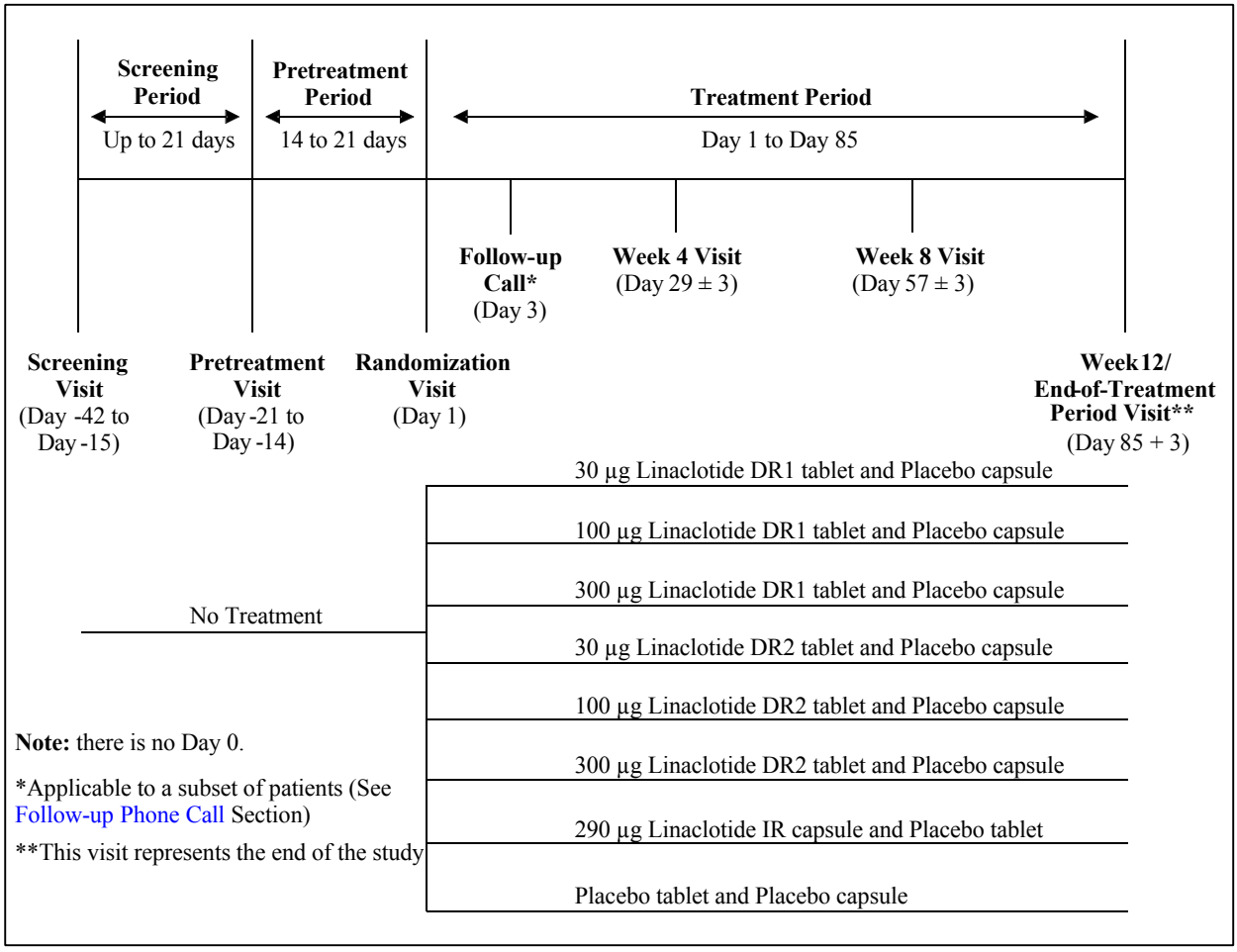
The objectives of this study are to evaluate the safety, efficacy, and dose response of two different delayed release formulations of linaclotide (DR; DR formulation 1 is DR1; DR formulation 2 is DR2) administered orally to patients with irritable bowel syndrome with constipation (IBS-C). [redacted]

5. INVESTIGATIONAL PLAN

5.1 OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

This is a multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, multiple-dose, 12-week study, consisting of 3 distinct periods, as illustrated in Figure 1 below. The study will enroll patients who have IBS-C diagnosed using Rome III criteria. 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 (the approved dose) of the linaclotide IR formulation; or placebo. Linaclotide IR is being included in the study as a positive control, against which the safety and efficacy of the various doses of the two test formulations can be compared. [redacted]

Figure 1. Overview of Study Design



The study will consist of up to 21 days of screening, 14 to 21 days of pretreatment, and 12 weeks of double-blind treatment. At the end of the Pretreatment Period, during which patients will provide qualifying Bowel Movement (BM)-related and Abdominal Symptom-severity Assessments, and Rescue Medicine information, patients meeting the entry criteria for this study will be randomized in equal proportions to one of the 8 double-blind treatment groups.

5.1.1 Study Periods

5.1.1.1 Screening Period

The Screening Period starts with signature of the ICF and may last for up to 21 days. During this period, patient eligibility for entry into the Pretreatment Period will be determined. The end of the Screening Period coincides with the start of the Pretreatment Period. Any over-the-counter or prescription laxatives, suppositories, or enemas used to treat IBS-C must not be taken during the calendar day before the Pretreatment Visit through the end of the Treatment period; whereas other prohibited medicines must not be taken during the 14 calendar days before the Pretreatment Visit through the end of the Treatment period (refer to Appendix II).

5.1.1.2 Pretreatment Period

The Pretreatment Period is defined as the 14 to 21 calendar days immediately before the Randomization Visit. During this period, patients will provide the following information in a handheld electronic diary (eDiary):

- Daily BM-related Symptom-severity Assessments on an event-driven basis
- Daily Abdominal Symptom-severity Assessments in a daily evening report
- Weekly Patient Assessment of Constipation Severity
- Weekly Patient Assessment of IBS Symptom Severity
- Weekly Patient Assessment of Adequate Relief
- Use of Per-protocol Rescue Medicine or any other Laxatives, Suppositories, or Enemas on an event-driven basis

Patients who satisfy all of the entry criteria will enter the Treatment Period.

5.1.1.3 Treatment Period

The Treatment Period begins with treatment assignment and lasts for 12 weeks. Patients will be randomly assigned to one of 8 treatments: 30 µg, 100 µg, or 300 µg of linaclotide DR1; 30 µg, 100 µg, or 300 µg of linaclotide DR2; 290 µg of linaclotide IR; or placebo. Study drug will be taken once daily in the morning at least 30 minutes before breakfast. (Note: Patients will take their initial dose of study drug at the clinic during the Randomization Visit.) At the Randomization Visit, patients must have fasted for at least 2 hours prior to arriving at the clinic for their visit. Patients will continue to use the handheld eDiary to provide their daily assessments (Daily BM-related Symptom-severity Assessments on an event-driven basis, and Daily Abdominal Symptom-severity Assessments in a daily evening report), weekly assessments (Weekly Patient Assessment of Constipation Severity, Weekly Patient Assessment of IBS Symptom Severity, and Weekly Patient Assessment of Adequate Relief), and the use of per-protocol Rescue Medicine and any other Laxatives, Suppositories, or Enemas on an event-driven basis. Quality-of-life and patient-outcome assessments will be performed at study visits throughout the Treatment Period. A list of these assessments and the visits when they are performed is provided in the Schedule of Evaluations (Table 1). Patients will complete a Week 4 Visit, Week 8 Visit, and Week 12/End of Treatment Visit during the Treatment Period. (See Schedule of Evaluations) 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. In doing this, patients will be asked the same nonleading question that is asked at the study visits. (See Section 5.5.3.2.1)

5.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE 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., eDiary), and a 12-week Treatment Period to compare the test treatment to the placebo control and active control.

5.3 SELECTION OF STUDY POPULATION

5.3.1 Inclusion Criteria

To be eligible to participate in the study, patients must meet the following criteria:

1. Patient has signed an ICF.
2. Patient is ambulatory and community-dwelling (females must also be non-pregnant) and is aged 18 years or older at the Screening Visit. Lactating females must agree not to breastfeed.
3. Sexually active female patients of childbearing potential (i.e., women who are not postmenopausal or who have not had a bilateral oophorectomy, hysterectomy, or tubal ligation) must agree to use one of the following methods of birth control from the date they sign the ICF until 24 hours after their final dose of study drug:
   a. Hormonal contraception (i.e., oral contraceptive, contraceptive implant, or injectable hormonal contraceptive)
   b. Double-barrier birth control (e.g., condom plus intrauterine device, diaphragm plus spermicide, etc.)
   c. Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy
4. Females of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at the Randomization Visit prior to dosing.
5. Patient meets the colonoscopy requirements defined by the American Gastroenterological Association guidelines and described in Appendix III. (Note: Patients are eligible to enter the Pretreatment Period on the fifth calendar day after a colonoscopy.)
6. Patient has no clinically significant concurrent illness or findings on a physical examination and clinical laboratory tests (clinical chemistry panel, complete blood count [CBC], urine drug screen) after signing the ICF but before receiving the first dose of study drug. (Note: The investigator will determine if a particular finding is clinically significant. In making this determination, the investigator will consider whether the particular finding could prevent the patient from performing any of the protocol-specified assessments, could represent a condition that would exclude the patient from the study,

could represent a safety concern if the patient participates in the study, or could confound the study-specified assessments of safety or efficacy.)

7. Patient meets Rome III criteria for IBS (1): reports abdominal pain or discomfort at least 3 days/month during the 3 months before the diagnosis with the onset at least 6 months before the diagnosis, associated with two or more of the following features:
   a. Relieved with defecation
   b. Onset associated with a change in frequency of stool
   c. Onset associated with a change in form (appearance) of stool

   Note: the diagnosis can be made at the Screening Visit or can be based on symptoms that the patient had before starting chronic treatment with linaclotide or lubiprostone.
8. During the time when the Rome III criteria for IBS were met, the patient had hard or lumpy stools (Bristol Stool Form Scale [BSFS] scores of 1 or 2) with at least 25% of BMs and had loose (mushy) or watery stools (BSFS scores of 6 or 7) with less than 25% of BMs in the absence of antidiarrheal or laxative use.
9. Patient reports < 3 BMs (with each BM occurring in the absence of any laxative, suppository, or enema use during the preceding 24 hours) per week for at least 12 weeks, before the Screening Visit or before starting chronic treatment with linaclotide, lubiprostone, polyethylene glycol 3350, or any laxative.
10. Patient has an average score for abdominal pain at its worst of ≥ 3.0, as reported in the eDiary using an 11-point numerical rating scale (NRS) during the 14 calendar days before the Randomization Visit and the calendar day of Randomization up to the time when the data entry into the eDiary is made in clinic.
11. Patient reports ≤ 6 complete spontaneous BMs (CSBMs) and ≤ 10 spontaneous BMs (SBMs) in the eDiary over the 14 calendar days before the Randomization Visit and the calendar day of Randomization up to the time when the data entry into the eDiary is made in clinic. (Note: A CSBM is an SBM that is associated with a sense of complete evacuation. An SBM is a BM that occurs in the absence of laxative, suppository, or enema use on the calendar day of the BM or the calendar day before the BM as evidenced by the patient-reported concomitant medicine use via the eDiary.)
12. Patient is compliant (as defined in the study procedures section below) with eDiary completion by adequately responding to eDiary questions on 10 or more of the 14 calendar days before the Randomization Visit.
13. Patient is willing to discontinue any laxatives used before the Pretreatment Visit in favor of the protocol-defined Rescue Medicine (bisacodyl tablets or suppositories).
14. Patient is fluent in English or Spanish.
15. Patient is able to operate the eDiary adequately.

16. Patient agrees to refrain from making any new, major life-style changes that may affect IBS-C symptoms (e.g., starting a new diet or changing his or her exercise pattern) from the time of signature of the ICF to the last study visit.

5.3.2 Exclusion Criteria

Patients who meet any of the following criteria will not be eligible to participate in the study:

1. Patient reports loose (mushy) or watery stools (BSFS score of 6 or 7) in the absence of any laxative, suppository, enema, or prohibited medicine (as described in Appendix II) for > 25% of BMs during the 12 weeks before the Screening Visit.
2. Patient has a structural abnormality of the gastrointestinal (GI) tract or a disease or condition that can affect GI motility.
3. Patient has ever had a diagnosis or family history of familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, or any other form of familial colorectal cancer.
4. Patient has ever had a diagnosis of inflammatory bowel disease (IBD).
5. Patient currently has unexplained and clinically significant alarm symptoms (lower GI bleeding [rectal bleeding or heme-positive stool], iron-deficiency anemia, weight loss) or systemic signs of infection or colitis.
6. Patient currently has active peptic ulcer disease (i.e., disease that is not adequately treated or stable with therapy).
7. Patient has a history of diverticulitis or any chronic condition (e.g., chronic pancreatitis, polycystic kidney disease, ovarian cysts, endometriosis) that can be associated with abdominal pain or discomfort and could confound the assessments in this study, unless the patient is considered to have been cured of the condition.
8. Patient has a potential central nervous system cause of constipation (e.g., Parkinson's disease, spinal cord injury, and multiple sclerosis).
9. Patient has ever had any of the following diseases or conditions that can be associated with constipation: pseudo-obstruction, megacolon, megarectum, bowel obstruction, descending perineum syndrome, solitary rectal ulcer syndrome, systemic sclerosis.
10. Patient has ever had a fecal impaction that required hospitalization or emergency room treatment, or has a history of cathartic colon, laxative or enema abuse, ischemic colitis, or pelvic floor dysfunction (unless successful treatment has been documented by a normal balloon expulsion test).
11. Patient has had surgery that meets any of the following criteria:

a. Bariatric surgery for treatment of obesity, or surgery to remove a segment of the GI tract at any time before the Screening Visit
b. Surgery of the abdomen, pelvis, or retroperitoneal structures during the 6 months before the Screening Visit
c. An appendectomy or cholecystectomy during the 60 days before the Screening Visit
d. Other major surgery during the 30 days before the Screening Visit

12. Patient has a history of cancer other than treated basal cell or squamous cell carcinoma of the skin. (Note: Patients with a history of cancer are allowed provided that the malignancy has been in a complete remission for at least 5 years before the Randomization Visit. A complete remission is defined as the disappearance of all signs of cancer in response to treatment.)
13. Patient has a history of diabetic neuropathy.
14. Patient has untreated hypothyroidism or treated hypothyroidism for which the dose of thyroid hormone has not been stable for at least 6 weeks at the time of the Screening Visit.
15. Patient has a recent history (during the 12 months before the Randomization Visit) of drug or alcohol abuse. (Note: Patients with a history of drug or alcohol abuse that was diagnosed greater than 12 months before the Randomization Visit may be enrolled as long as they have exhibited no actual abuse during the 12 months before the Randomization Visit.)
16. Patient reports a BSFS score of 6 (loose, mushy stools) for > 1 SBM or a BSFS score of 7 (watery stools) with any SBM over the 14 calendar days before the Randomization Visit and the calendar day of Randomization up to the time when data is entered into the eDiary in the clinic.
17. Patient used Rescue Medicine (bisacodyl tablet or suppository) or any other laxative, suppository, or enema, on the calendar day before or the calendar day of the start of the Randomization Visit.
18. Patient reported using a Prohibited Medicine (excluding laxatives, suppositories, and enemas) during the Pretreatment Period or is not willing or able to abide by the restrictions regarding use of Prohibited Medicines defined in Appendix II. (Note: The use of fiber, bulk laxatives, or stool softeners [such as docusate] is acceptable provided the patient has been on a stable dose during the 30 days before the Screening Visit and plans to continue on a stable dose throughout the study.)
19. Patient has been hospitalized for a psychiatric condition or has made a suicide attempt during the two years before the Randomization Visit.
20. Patient has taken commercially available linaclotide or participated in a linaclotide, plecanatide, or SP-333 clinical study during the 30 days before the Screening Visit.

21. Patient has received an investigational drug during the 30 days before the Screening Visit or is planning to receive an investigational drug (other than that administered during this study) or use an investigational device at any time during the study.
22. Patient has an acute or chronic condition that, in the investigator's opinion, would limit the patient's ability to complete or participate in this clinical study.
23. Patient has previously entered the Pretreatment Period of this study.
24. Patient is directly or indirectly involved in the conduct and administration of this study as an investigator, subinvestigator, study coordinator, other study staff member, or employee of Ironwood Pharmaceuticals, Forest Laboratories, Actavis, Inc., or Allergan, Inc.; or the patient is a first-degree family member, significant other, or relative residing with one of the above persons involved directly or indirectly in the study; or the patient is enrolled in this study at another clinical study site.

5.3.3 Removal of Patients From Therapy or Assessment

A premature discontinuation will occur when a patient who signed the ICF ceases participation in the study, regardless of circumstances, before the completion of the protocol. Patients can prematurely discontinue or be prematurely discontinued by the investigator or sponsor from the study at any time for any reason including the following:

- Failure to meet Inclusion/Exclusion Criteria (Screen Failure)
- Adverse event (AE)
- Lack of efficacy
- Protocol violation
- Non-compliance with study drug
- Withdrawal of consent
- Lost to follow-up (every effort must be made to contact the patient; a certified letter must be sent)
- Study termination by Sponsor
- Pregnancy
- Other, such as administrative reasons

Patients who are randomized but do not complete the Treatment Period (withdraw consent or are discontinued before they have completed visits up to and including the Week 12/ End-of-Treatment Period (EOT) Visit, will be considered Treatment Period withdrawals and should complete the procedures required at the EOT Visit (even if out of window) at the time of their discontinuation. The reasons for premature discontinuation from the study will be documented on the study termination form of the eCRF. All data on the patient prior to discontinuation will be made available to Ironwood (or designee). Any patient who withdraws because of an AE will be followed until the AE resolves, stabilizes, or can be explained as being unrelated to study drug. The study centers should make a reasonable effort to follow pregnant patients until delivery or end of the pregnancy.

If a patient does not return for a scheduled termination visit (EOT Visit), the study center should contact the patient. Every effort is to be made to contact the patient, including sending a certified letter. In every case, the patient outcome, including lost to follow-up information, will be documented.

The investigator may allow a patient to stop taking study drug for up to three days should an intolerable AE occur. If the investigator believes that the patient is unable to resume dosing or requires a suspension of dosing on more than one occasion, the investigator should contact the Medical Monitor to discuss the patient's continued participation in the study.

5.3.4 Replacement Procedures

Patients in this study who prematurely discontinue treatment will not be replaced.

5.4 TREATMENTS

5.4.1 Treatments Administered

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 follows:

- 30 µg linaclotide DR1 oral tablet and a placebo oral capsule (matching the 290 µg linaclotide IR oral capsule) administered once daily in the morning at least 30 minutes before breakfast

- 100 μg linaclotide DR1 oral tablet and a placebo oral capsule administered once daily in the morning at least 30 minutes before breakfast
- 300 μg linaclotide DR1 oral tablet and a placebo oral capsule administered once daily in the morning at least 30 minutes before breakfast
- 30 μg linaclotide DR2 oral tablet and a placebo oral capsule administered once daily in the morning at least 30 minutes before breakfast
- 100 μg linaclotide DR2 oral tablet and a placebo oral capsule administered once daily in the morning at least 30 minutes before breakfast
- 300 μg linaclotide DR2 oral tablet and a placebo oral capsule administered once daily in the morning at least 30 minutes before breakfast
- 290 μg linaclotide IR oral capsule and a placebo oral tablet (matching the DR1 and DR2 oral tablet) administered once daily in the morning at least 30 minutes before breakfast
- Placebo oral capsule and a placebo oral tablet administered once daily in the morning at least 30 minutes before breakfast

5.4.2 Identity of Investigational Product

All study drug will be supplied in bottles containing thirty five (35) tablets of linaclotide DR1 (30 μg, 100 μg, or 300 μg), linaclotide DR2 (30 μg, 100 μg, or 300 μg), or matching placebo tablets; or thirty five (35) capsules of linaclotide IR (290 μg) or matching placebo capsules. Bottles will be uniquely numbered and labeled in a double-blind fashion that conforms to regulatory requirements.

All study drug will be provided by Ironwood or designee. Linaclotide IR (290 μg) and matching placebo capsules will be stored at the study center in an appropriate secure, temperature controlled area at 77°F (25°C), excursions permitted to 59-86°F (15-30°C). Linaclotide DR1 (30 μg, 100 μg, or 300 μg), linaclotide DR2 (30 μg, 100 μg, or 300 μg), and matching placebo tablets will be stored refrigerated at the study center in an appropriate secure, temperature controlled area at 36-46°F (2-8°C). Any deviations from the storage conditions must be reported to Ironwood and use of the study medication suspended until authorization for its continued use has been provided by Ironwood.

The investigator must ensure that the receipt and use of all study drug supplied is recorded and supervise the storage and allocation of these supplies. All study medication supplies must be retained in a locked room that may only be accessed by the investigator, or other duly designated persons. Study medication must not be used outside the context of this protocol and under no circumstances should the investigator or study center personnel allow the supplies to be used other than as directed by this protocol without prior authorization from Ironwood. All unused study drug must be returned to Ironwood's designee. Whenever study drug is returned (excluding Sponsor-supplied per-protocol Rescue Medicine), unit counts must be performed by study center staff and verified by a site monitor to ensure reliable drug accountability. Drug unit counts are documented on the appropriate eCRF form. Prior to the end of the study, instructions for the return of all unused tablets/capsules and study drug bottles will be provided.

5.4.3 Method of Assigning Patients to Treatment Groups

The patient identification (PID) number will consist of seven digits; the first three digits represent the study center number, followed by a one-digit study indicator ('4') and a three-digit patient number assigned in an ascending sequential order, beginning with 001, 002, etc. The patient will retain the same PID number (which is also the Screening Number) throughout the Treatment Period.

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 (as described in Section 5.4.1). Randomization numbers will be assigned by interactive web response system (IWRS).

5.4.4 Selection of Dosage in the Study

This protocol is intended to evaluate the safety, efficacy, and dose response of the DR1 and DR2 formulations of linaclotide, compared with each other and with the linaclotide IR formulation. The linaclotide IR formulation has been included as a positive control at the dose level (290 µg) approved by FDA for the treatment of IBS-C in adults. As this is a dose-range-finding study, three dose levels of each DR formulation will be evaluated; in order to facilitate comparison of the DR1 and DR2 formulations, the same doses (30 µg, 100 µg, and 300 µg) will be used for each. The 300 µg dose approximates the 290 µg dose of linaclotide IR (the FDA-approved dose for IBS-C), allowing for direct comparison of the DR formulations with the IR formulation. The 30 µg dose represents approximately 1/10 of the 290 µg dose of linaclotide IR. In a Phase 1 food-effect study (MCP-103-103) in patients administered the FDA-approved IR formulation, active peptide recovery in stool samples from fed and fasted subjects following once-daily administration of linaclotide IR 290 µg for 7 days averaged 3-5%; therefore, the 30 µg dose is approximately 2-fold greater than the amount of linaclotide entering the large intestine with the IR formulation. The 100 µg dose was selected because it represents a ½ log difference from the 30 µg dose and the 300 µg dose.

5.4.5 Selection and Timing of Dose for Each Patient

All study drug will be administered orally once daily. Patients who meet all eligibility criteria at the Screening and Pretreatment Visits will be randomized to treatment at the Randomization Visit (randomization number assigned by IWRS) and dispensed two bottles, one containing 35 tablets and one containing 35 capsules. Additional bottles will be dispensed at subsequent visits per the Schedule of Evaluations (Table 1). Patients will be instructed to take one tablet and one capsule in the morning at least 30 minutes before breakfast. Patients will take their initial dose of study drug (one tablet and one capsule, as described in Section 5.4.1) at the study center during the Randomization Visit. Patients must have fasted for at least 2 hours prior to arriving at the clinic for this visit. Patients will be instructed to return all unused study drug and bottles to the study center at the visits defined in the Schedule of Evaluations (Table 1).

5.4.6 Blinding

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

A list of patient randomization codes will be generated by Actavis, and implemented by the IWRS vendor (an electronic version will be stored on a secure server). This list will identify each patient by randomization number and include the patient's corresponding treatment assignment. The medication code list will be supplied by Almac Clinical Services to the IWRS contract research organization.

In case of an emergency, the IWRS will be accessed to obtain the study drug assignment of a patient. Accessing the IWRS for emergency unblinding should be done only in an emergency that necessitates identifying the study drug for the welfare of the patient, and only after unsuccessfully attempting to contact the Medical Monitor or designee. If the blind is broken, the study center will notify the Ironwood contact (see the Study Identification information in the Synopsis) immediately. An explanation for breaking the blind will be recorded on the relevant eCRF. Breaking the code at the study center will disqualify the patient from further participation in the study.

5.4.7 Concomitant Medicines

A complete list of drugs that are conditionally allowed and drugs that are not allowed as concomitant medicines for either episodic or chronic use or as Rescue Medicine is provided in Appendix II. During the Pretreatment and Treatment Periods, patients may use dispensed, protocol-permitted laxatives (bisacodyl tablets or suppositories) as Rescue Medicine when at least 72 hours have passed since their previous BM or when their symptoms become intolerable. In order to qualify for randomization into the Treatment Period, patients must not have used Rescue Medicine on the calendar day before the Randomization Visit and on the day of the Randomization Visit up until the time of the clinic visit. Patients must agree to refrain from using Rescue Medicine from the time they arrive at the clinic for the Randomization Visit through the calendar day after randomization.

At the Screening Visit, all ongoing medicines or investigational products taken by the patient, and past use of certain IBS-C or CIC (approved or unapproved) prescription medications

(including tegaserod [Zelnorm®], prucalopride, plecanatide, linaclotide [Linzess®] and lubiprostone [Amitiza®]), even if not ongoing at the time of the Screening Visit, will be recorded. Any over-the-counter or prescription laxatives, suppositories, or enemas used to treat IBS-C may not be used during the Pretreatment and Treatment Periods and may not be used on the calendar day before the Pretreatment Visit. Other prohibited medicines may not be used during the Pretreatment and Treatment Periods and may not be used during the 14 calendar days before the Pretreatment Visit (refer to Appendix II). Thereafter, any changes in concomitant medicines or new medicines added will be recorded on the eCRF. Concomitant medicines will be recorded at study visits throughout the entire study. Rescue Medicine will be documented by the patient via eDiary.

5.4.8 Treatment Compliance

Study drug will be administered to the patient by study center staff at the Randomization Visit. For all other days in the Treatment Period, study drug will be taken by the patient once daily in the morning at least 30 minutes before breakfast. Study drug compliance by the patient will be closely monitored during the Treatment Period by counting the number of tablets/capsules returned and recording that information on the eCRF. Every effort will be made to collect all unused study drug.

5.5 EFFICACY AND SAFETY VARIABLES

5.5.1 Schedule of Evaluations

The schedule of study procedures and assessments is presented by visit in the Schedule of Evaluations in Table 1. The descriptions of the procedures to be performed at each visit are provided below. Following randomization, all visits should adhere to a window of ± 3 days during the Treatment Period, except for the EOT Visit, which cannot occur before Day 85.

Table 1. Schedule of Evaluations

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

Table 1. Schedule of Evaluations

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 ↓							
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			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

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 (refer to Appendix III). 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 (see Section 5.4.7 Concomitant Medicines).
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 (refer to Appendix II).
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. (See Follow-up Phone Call Section)
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, 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).

Screening Visit (Visit 1)

At the Screening Visit, a review of Inclusion and Exclusion Criteria will be conducted to determine the patient's eligibility for progression to the Pretreatment Period. Overall eligibility should be determined by the investigator or an appropriately trained health professional listed on Form FDA 1572. Study procedures will be reviewed with the patient, the caregiver, and the patient's legally authorized representative (LAR: if different from the caregiver); and documentation of informed consent will be obtained. After the patient signs the ICF, the study coordinator will access IWRS to register the patient's Screening Visit, and the patient will then be assigned a unique PID number in sequential order. The following procedures will be performed thereafter:

- Medical history
- Physical examination
  - A physical examination should include all assessments (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 in all patients who do not require a colonoscopy (refer to Appendix III). After the Screening Period, the rectal examination is optional and may be performed at the discretion of the investigator.
  - The breast and genitourinary examinations are optional at the discretion of the investigator.
- Body weight and height
- Seated vital signs
- Documentation of prior and concomitant medicines, including investigational products and past use of tegaserod (Zelnorm®), prucalopride, plecanatide, linaclotide (Linzess®), and lubiprostone (Amitiza®)
- Collection of blood and urine samples for clinical laboratory determinations
  - Clinical chemistry
  - Complete blood count (CBC)
  - Urine drug screen
- Serum pregnancy test (result must be confirmed as negative in order to qualify for study participation)

- Instructions given for patients to discontinue the use of all laxatives, suppositories and/or enemas at least one calendar day before the first day of the Pretreatment Period, and all other prohibited medicines (as defined in Appendix II) at least 14 calendar days before the first day of the Pretreatment Period.
- Patient reminder (schedule patient's next visit and remind the patient to refrain from using prohibited medicines as described in Appendix II)

Pretreatment Visit (Visit 2)

The Pretreatment Period will occur between 14 and 21 days immediately before the Randomization Visit. The purposes of this period are to collect Pretreatment Period data to determine whether the patient is eligible to continue into the Treatment Period of the study, to provide the patient with experience using the data collection methods employed during the study (i.e., eDiary), and for comparison with data collected during the Treatment Period.

The study coordinator will access IWRS to register the patient's Pretreatment Visit. At the Pretreatment Visit, which will occur between Day -21 and Day -14 (inclusive), the Inclusion and Exclusion Criteria will again be reviewed, study procedures will be explained to the patient, and the following will be performed:

- Verification that Inclusion and Exclusion Criteria continue to be met
- Body weight
- Seated vital signs
- Documentation of concomitant medicines
- Review of AEs, from the signing of the ICF to Visit 2
- Register visit in eDiary
- eDiary training (patients will be instructed on the use of eDiary) and the assessments that will be collected as listed below:
  - Daily BM-related Symptom-severity Assessments on an event-driven basis (frequency, consistency, straining and completeness)
  - Daily Abdominal Symptom-severity Assessments in a daily evening report (abdominal bloating, abdominal discomfort, and abdominal pain)

- Use of Per-protocol Rescue Medicine or any other Laxatives, Suppositories, and Enemas on an event-driven basis
- Weekly Patient Assessment of Constipation Severity
- Weekly Patient Assessment of IBS Symptom Severity
- Weekly Patient Assessment of Adequate Relief

- Dispensing of Rescue Medicine; review with patient how Rescue Medicine should be used
- Patient reminder (schedule patient's next visit and remind the patient to refrain from using prohibited medicines and to refrain from using Rescue Medicine the calendar day before and day of the Randomization Visit)

Randomization Visit (Visit 3)

At the Randomization Visit, the Inclusion and Exclusion Criteria will again be reviewed to confirm the patient's eligibility. At this visit, the study coordinator will register the Randomization Visit on the patient's eDiary, and the patient will respond to the required assessments on the eDiary in the clinic. After the patient completes the eDiary entry, the study coordinator will access the eDiary website to confirm the patient's eligibility. If the patient's eligibility is confirmed in the eDiary website and all Inclusion and Exclusion criteria are met (reference below bulleted procedures to be completed prior to randomization), the study coordinator will confirm on the eDiary that the patient is randomized. The study coordinator will then register the Randomization Visit in IWRS, and the IWRS will assign a randomization number. Once the necessary procedures are completed (reference below bulleted procedures to be completed after randomization but prior to first dose), each eligible patient will be administered study drug (initial doses) in the clinic. The patient will be dispensed two bottles containing double-blind study drug (one bottle containing tablets and one bottle containing capsules) for the first four weeks of the Treatment Period. The study coordinator will perform the appropriate procedures after study drug administration, including review of the study procedures with the patient and instruct the patient to continue to complete the eDiary daily.

The following procedures will be performed before randomization and administration of the first dose of study drug at the study center:

- Verification that Inclusion and Exclusion Criteria continue to be met

- Body weight
- Seated vital signs
- Documentation of concomitant medicines
- Collection of blood for clinical laboratory determinations
  - Clinical chemistry
  - CBC
- Urine pregnancy test (result must be confirmed as negative before randomization and the administration of the first dose of study drug)
- Review of AEs
- eDiary compliance verification (study coordinator will verify the patient's compliance with the daily entry requirement) and eDiary entry in the clinic, including the following assessments:
  - Daily BM-related Symptom-severity Assessments on an event-driven basis
  - Daily Abdominal Symptom-severity Assessments in a daily evening report
  - Use of Per-protocol Rescue Medicine or any other Laxatives, Suppositories, and Enemas on an event-driven basis
  - Weekly Patient Assessment of Constipation Severity
  - Weekly Patient Assessment of IBS Symptom Severity
  - Weekly Patient Assessment of Adequate Relief

In addition, the study coordinator will verify the patient's compliance with the eDiary entry requirement during the Pretreatment Period and remind the patient to complete his or her eDiary entry each day.

The following procedures will be performed after randomization (prior to first dose):

- SF-12v2 (Short Form-12 Health Survey version 2 [self-administered by the patient; Appendix VII])
- EQ-5D (EuroQoL-5 Dimension [self-administered by the patient; Appendix VIII])
- SF-MPQ-2 (Short-Form McGill Pain Questionnaire-2 [self-administered by the patient; Appendix IX])
- IBS-SSS (Irritable Bowel Syndrome-Symptom Severity Scale [self-administered by the patient; Appendix X])

- Study drug (initial doses) administered in the clinic

The following procedures will be performed after study drug administration:

- Dispensing of study drug - one bottle containing 34 tablets (one bottle = 35 tablets less the initial dose) and one bottle containing 34 capsules (one bottle = 35 capsules less the initial dose)
- eDiary entry reminder (patients will be instructed to complete eDiary throughout the day of the Randomization Visit and reminded to complete eDiary entry each day thereafter)
- Dispensing of Rescue Medicine, as needed; review with patient how Rescue Medicine should be used
- Patient reminders (schedule patient's next visit and remind the patient to refrain from using prohibited medicines and to refrain from using Rescue Medicine for the remainder of the day of randomization and for the calendar day after randomization)

Follow-up Phone Call (Day 3)

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. In doing this, patients will be asked the same nonleading question that is asked at the study visits. (See Section 5.5.3.2.1) Any AE reported during the phone call will be captured on the eCRF. Patients who report AEs during the follow-up phone call will be provided with instructions on the appropriate follow-up care. The Sponsor will perform a blinded review of the safety information obtained from the first 40 follow-up phone calls. If the safety information from the phone calls is consistent with the known safety profile of the IR formulation of linaclotide (LINZESS® 290 µg in IBS-C), then no further follow-up phone calls will be made to patients. The Sponsor will communicate accordingly to the clinical sites to indicate whether follow-up phone calls to patients should continue or be discontinued.

Week 4 Visit (Visit 4)

The following procedures will be performed:

- Register visit in IWRS
- Body weight

- Seated vital signs
- Documentation of concomitant medicines
- Review of AEs
- Register visit in eDiary and eDiary compliance verification (study coordinator will verify the patient's compliance with the daily entry requirement); after determining the patient's compliance, the study coordinator will remind the patient to complete eDiary entry to provide the following information:
  - Daily BM-related Symptom-severity Assessments on an event-driven basis
  - Daily Abdominal Symptom-severity Assessments in a daily evening report
  - Use of Per-protocol Rescue Medicine or any other Laxatives, Suppositories, and Enemas on an event-driven basis
  - Weekly Patient Assessment of Constipation Severity
  - Weekly Patient Assessment of IBS Symptom Severity
  - Weekly Patient Assessment of Adequate Relief
- Dispensing of Rescue Medicine, as needed; review with patient how Rescue Medicine should be used
- SF-12v2 (self-administered by the patient; Appendix VII)
- EQ-5D (self-administered by the patient; Appendix VIII)
- SF-MPQ-2 (self-administered by the patient; Appendix IX)
- IBS-SSS (Irritable Bowel Syndrome-Symptom Severity Scale [self-administered by the patient; Appendix X])
- Treatment Satisfaction Assessment (self-administered by the patient)
- Dispensing of study drug (one bottle containing 35 tablets and one bottle containing 35 capsules)
- Study drug accountability
- Patient reminders (schedule patient's next visit and remind the patient to refrain from using prohibited medicines and to return any unused study drug at the next visit)

Week 8 Visit (Visit 5)

The following procedures will be performed:

- Register visit in IWRS
- Body weight
- Seated vital signs
- Documentation of concomitant medicines
- Review of AEs
- Register visit in eDiary and eDiary compliance verification (study coordinator will verify the patient's compliance with the daily entry requirement); after determining the patient's compliance, the study coordinator will remind the patient to complete eDiary entry to provide the following information:
  - Daily BM-related Symptom-severity Assessments on an event-driven basis
  - Daily Abdominal Symptom-severity Assessments in a daily evening report
  - Use of Per-protocol Rescue Medicine or any other Laxatives, Suppositories, and Enemas on an event-driven basis
  - Weekly Patient Assessment of Constipation Severity
  - Weekly Patient Assessment of IBS Symptom Severity
  - Weekly Patient Assessment of Adequate Relief
- Dispensing of Rescue Medicine, as needed; review with patient how Rescue Medicine should be used
- SF-12v2 (self-administered by the patient; Appendix VII)
- EQ-5D (self-administered by the patient; Appendix VIII)
- SF-MPQ-2 (self-administered by the patient; Appendix IX)
- Treatment Satisfaction Assessment (self-administered by the patient)
- Dispensing of study drug (one bottle containing 35 tablets and one bottle containing 35 capsules)
- Study drug accountability
- Patient reminders (schedule patient's next visit and remind the patient to refrain from using prohibited medicines and to return any unused study drug at the next visit)

Week 12/End-of-Treatment Period Visit (Visit 6)

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). Any clinical findings obtained during the final examination or at premature discontinuation for any reason, including clinically significant laboratory abnormalities, will be followed until the condition returns to screening status, has resolved or stabilized, or can be explained as being unrelated to study drug.

The following procedures will be performed:

- Register visit in IWRS
- Physical examination (rectal, breast, and genitourinary examinations are optional at the discretion of the investigator)
- Body weight
- Seated vital signs
- Documentation of concomitant medicines
- Collection of blood for clinical laboratory determinations:
  - Clinical chemistry
  - CBC
- Serum pregnancy test
- Review of AEs
- Register visit in eDiary and eDiary compliance verification (study coordinator will verify the patient's compliance with the daily entry requirement); eDiary entry in the clinic, including the following assessments:
  - Daily BM-related Symptom-severity Assessments on an event-driven basis
  - Daily Abdominal Symptom-severity Assessments in a daily evening report
  - Use of Per-protocol Rescue Medicine or any other Laxatives, Suppositories, and Enemas on an event-driven basis
  - Weekly Patient Assessment of Constipation Severity
  - Weekly Patient Assessment of IBS Symptom Severity

- Weekly Patient Assessment of Adequate Relief

- SF-12v2 (self-administered by the patient; Appendix VII)
- EQ-5D (self-administered by the patient; Appendix VIII)
- SF-MPQ-2 (self-administered by the patient; Appendix IX)
- Treatment Satisfaction Assessment (self-administered by the patient)
- Study drug accountability
- Register visit in IWRS (study coordinator will confirm in IWRS that the patient has completed participation in the study)

5.5.2 Efficacy Measurements

5.5.2.1 Key Efficacy Assessments

The key efficacy assessments that will be used to determine the key efficacy parameters (Section 5.7.7.1) are the eDiary questions that determine whether a BM is a 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, which are described in Section 5.5.2.2.) The patient will also complete eDiary entries on an event-driven basis to report use of Rescue Medicines (e.g., oral bisacodyl; bisacodyl suppository) 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 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">

5.5.2.2 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

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

Refer to Section 5.5.2.1 for the questions.

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 BSFS (Appendix IV) which depicts the stool consistency characteristics along with descriptions for each of them. The patient assigns a corresponding score for each BM. The BSFS is a well-accepted and widely-used measurement of stool consistency.(16) 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">

Abdominal Symptom Score Scale

A patient's Abdominal Symtom Score Scale will be a composite measure based on combined scores from the Daily Patient Assessment of Abdominal Pain at its Worst, Daily Patient Assessment of Abdominal Discomfort at its Worst, and Patient Assessment of Abdominal Bloating at its Worst.

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

5.5.2.3 Health Outcomes Assessments

SF-12v2

The SF-12v2 Health Survey is a widely used generic measure of health status (Appendix VII)(17). 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).

EQ-5D

The EQ-5D is a generic measure of health status that is widely used in Europe (Appendix VIII)(18). 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.(19) The second component of the EQ-5D 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 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).

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 IX) (20). 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.

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

The Irritable Bowel Syndrome-Symptom Severity Scale (IBS-SSS) (21) contains seven questions that ask patients to rate the severity and frequency of their abdominal pain and distention, dissatisfaction with bowel habits, and the extent to which the patient's bowel habits interfere with life in general. The IBS-SSS (Appendix X) also includes queries related to stool passage and bowel functioning which are not included in the IBS-SSS total score (e.g., stool consistency, BM frequency, urgency, straining, incomplete evacuation, and passing mucus or blood in the stool). The IBS-SSS will be self-administered at the Randomization Visit prior to the patient receiving study drug and at the Week 4 Visit.

5.5.3 Safety Assessments

Patients must be seen by a physician or an appropriately trained health professional listed on Form FDA 1572 at every visit, and the AE evaluation must be documented. The procedures in this section will be performed at the designated visits.

5.5.3.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH, E2A).

An AE, therefore, can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH, E2A). An AE includes, but is not limited to, the following:

- Any unfavorable changes in general condition
- Any clinically significant worsening of a preexisting condition
- Any intercurrent diseases and accidents

Note: A procedure is not an AE, but the reason for a procedure may be an AE.

Laboratory abnormalities, changes in vital signs, and physical examination findings should be considered AEs and reported on the AE reporting form of the patient's eCRF if they are deemed to be clinically significant, necessitate intervention and/or the investigator considers them to be AEs.

5.5.3.1.1 Causality Assessment

For all AEs, the investigator must provide an assessment of causal relationship to study drug. The causality assessment must be recorded on the appropriate AE reporting form of the patient's eCRF. Causal relationship must be assessed according to the following:

Related: An event where there is a reasonable possibility of a causal relationship between the event and the study drug

Unrelated: Any other event

5.5.3.1.2 Severity Assessment

The investigator will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting form of the patient's eCRF. Severity, which is a description of the intensity of manifestation of the AE, is distinct from seriousness, which implies a patient outcome or AE-required treatment measure associated with a threat to life or functionality. 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; the AE may have been intermittent or continuous.

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.

5.5.3.2 Serious Adverse Events

According to ICH guidelines, an SAE is any AE occurring at any dose that meets one or more of the following criteria/outcomes:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of an existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- Is another important medical event that may not result in death, be life-threatening, or require hospitalization; such an event may be considered serious when, based on appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening, other serious [medically important] event).

5.5.3.2.1 Reporting Adverse Events and Serious Adverse Events

General Reporting Requirements

It is Ironwood policy to collect and record all AEs (i.e., any untoward medical occurrences or unfavorable and unintended signs, symptoms, or diseases) that occur in patients after the time the patients sign the ICF for the study.

At each visit following the first visit and at the follow-up phone call within 48 hours following initial study drug administration (when applicable), patients are to be queried regarding any AEs that have occurred since the previous visit. Patients will be asked to volunteer information concerning AEs with a nonleading question such as, "How have you been since your last visit?" Study center personnel will then record all pertinent information verbatim (as reported by the patient) in the patient's source documentation and subsequently into the eCRF.

Patients who report AEs during the follow-up phone call will be provided with instructions on the appropriate follow-up care. The Sponsor will perform a blinded review of the safety information obtained from the first 40 follow-up phone calls. If the safety information from the phone calls is consistent with the known safety profile of the IR formulation of linaclotide (LINZESS® 290 µg in IBS-C), then no further follow-up phone calls will be made to patients. The Sponsor will communicate accordingly to the clinical sites to indicate whether follow-up phone calls to patients should continue or be discontinued.

All AEs must be recorded in the patient's source documentation and subsequently on the appropriate AE reporting page of the patient's eCRF whether or not they are considered causally related to study drug.

For every AE, the investigator must:

- Provide instructions to the patient on the appropriate follow-up care, if necessary;
- Provide an assessment of the severity, causal relationship to study drug, and seriousness of the event;
- Document all actions taken with regard to study drug (i.e., no action taken, treatment temporarily interrupted or treatment discontinued). The investigator may allow a patient to temporarily interrupt study drug for up to three days should an AE occur. If the investigator

believes that the patient is unable to resume dosing or requires a suspension of dosing on more than one occasion, then the investigator should contact the Medical Monitor to discuss the patient's continued participation in the study; and

- Detail any other treatment measures taken for the AE

SPECIAL SITUATION: *EXPOSURE* TO STUDY DRUG DURING PREGNANCY

1. A patient who reports pregnancy prior to study drug randomization must be withdrawn from the study. The pregnancy is recorded as a reason for screen failure. Since there has been no exposure to study drug, there is no need to notify Ironwood Drug Safety of the pregnancy.

2. A patient who reports pregnancy after randomization, must discontinue study drug at once. The site must notify Ironwood Drug Safety of the pregnancy (within 24 hours), using the standard *Pregnancy Notification Form*. The site makes reasonable efforts to follow the pregnancy to term and notifies Ironwood Drug Safety of the pregnancy outcome (within 24 hours of being informed), using the standard *Pregnancy Outcome Form*.

Adverse Event Reporting Period

At each study visit following the first visit, at the follow-up phone call within 48 hours following initial study drug administration (when applicable), and during any communication with a patient or patient representative occurring outside a defined study visit, all AEs reported by the patient or patient representative or observed or otherwise identified by the investigator or other study personnel must be documented. For all AEs, the reporting period begins at the signature of the ICF and continues until the patient is lost to follow-up or until completion of study participation (e.g., early termination or EOT Visit.)

Serious Adverse Event Reporting Period

Upon learning of an AE considered serious as described in Section 5.5.3.2, the investigator or other study personnel must inform Ironwood or designee of the event as soon as possible (not later than 24 hours from learning of the event). Reporting will not be delayed pending a

resolution or an outcome of the event. If an outcome of an SAE is not available at the time of the initial report, Ironwood expects follow-up to proceed until such time as an outcome is known. The starting point for the collection of SAEs will be from the time the patient signs the ICF. An SAE will be defined as an on-therapy SAE if it occurred on or after the date of the first dose of double-blind study drug and within 30 days of the date of the last dose of double-blind study drug.

5.5.3.2.2 Follow-Up Procedures for Serious Adverse Events

Ironwood or designee will promptly investigate all safety information received. Follow-up information to a safety report will be submitted as soon as the relevant information is available (21 CFR § 312.32 [d]).

Relevant information such as discharge summaries, autopsy reports, and medical consultations will be reviewed in detail by the investigator. The investigator will comment on any event, abnormal laboratory result, or any other finding, noting whether it will be considered adverse or part of the patient's natural disease history and, if adverse, whether it will be considered a serious or nonserious AE. In addition, the investigator will report on an SAE form all subsequent events or other findings determined to be relevant and will state for each event or finding whether it is related to study drug. All events determined to be nonserious will be reported on the relevant eCRF form.

5.5.3.3 Clinical Laboratory Determinations

Blood and urine samples will be collected for clinical laboratory tests (according to the study specific manual) at the Screening Visit and other visits defined in the Schedule of Evaluations (Table 1). At the Screening Visit, the investigator will assess the clinical significance of any values outside the reference ranges provided by the central laboratory, and patients with abnormalities judged to be clinically significant will be excluded from the study.

Clinical laboratory tests will be performed according to directives in the Schedule of Evaluations (Table 1).

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 (Table 1). 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.

A central laboratory will be used to evaluate all urine and blood samples (except for the urine pregnancy test), which will be collected, processed, and stored according to the instructions provided by the laboratory.

5.5.3.4 Vital Signs

At every study visit, vital sign measurements will be performed (with the patients in the seated position) and documented. The parameters are oral temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure (BP). Pulse and BP readings will be taken after the patient has been sitting for five minutes.

5.5.3.5 Other Safety Assessments

5.5.3.5.1 Physical Examination

A complete physical examination will be performed at the Screening Visit and EOT Visit, as defined in the Schedule of Evaluations (Table 1), by the investigator or a licensed health professional listed on Form FDA 1572. Any physical examination abnormality that the investigator considers to be potentially clinically significant and changed from the baseline will be reported as an AE. A rectal examination should be performed during the Screening Period in all patients who do not require a colonoscopy (refer to Appendix III). After the Screening Period, the rectal examination is optional and may be performed at the discretion of the investigator. For all physical examinations, the breast and genitourinary examinations are optional and may be performed at the discretion of the investigator.

5.5.3.5.2 Medical History

A complete medical history will be provided by the patient at the Screening Visit.

5.6 DATA QUALITY ASSURANCE

5.6.1 Data Monitoring

Before any patient enters the study, a representative of Ironwood or its authorized designee will meet with the investigator and his/her staff to review the procedures to be followed while conducting the study and to train them on recording the data on the eCRFs using the electronic data capture (EDC) system. After the first patient signs the ICF, the Ironwood representative, a site monitor, will periodically monitor the progress of the study by conducting monitoring visits. This site monitor will also be able to review the status of data queries remotely, possibly warranting more frequent communication with the investigator and his/her staff. The investigator will make available to the site monitor the computer that accesses the eCRFs during monitoring visits. The investigator and his/her staff will be responsible for reviewing eCRFs, resolving data queries generated by the site monitor via the system, providing missing or corrected data, approving all changes performed on his/her data, and endorsing the patient data within the EDC system. This approval method will include applying an electronic signature, which is a uniquely assigned username and password that together will represent a traditional handwritten signature.

5.6.2 Data Recording and Documentation

All data collected in the context of this study will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (e.g., essential documents [commonly called regulatory documents], correspondence) will be retained at the study center, along with adequate source documentation, according to FDA and ICH requirements. All study records must be available for inspection by Ironwood, its authorized designee, and the FDA.

Data collection will involve the use of the Medidata RAVE EDC system, to which only authorized personnel will have access. In addition to periodic monitoring occurring within the system by Sponsor site monitors, programmatic edit checks and manual review procedures will be used to review the data for completeness, logic, and adherence to the study protocol. As a result of this monitoring and these checks, data queries may be electronically issued to the clinical study centers and electronically closed by those centers. The identifying information (assigned username, date, and time) for both the originator of the query (if created during the monitoring process) and the originator of the data change (if applicable), as well as the investigator's approval of all changes performed on his/her patients' data, will be collected.

5.7 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

5.7.1 Analysis Populations

5.7.1.1 ITT 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.

5.7.1.2 Safety Population

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

5.7.2 General Methods

Descriptive statistics (n, mean, standard deviation [SD], minimum, median, and maximum) will be calculated to summarize continuous variables. Frequency and percentage of patients in each category will be calculated to summarize categorical variables.

Unless otherwise specified, all confidence intervals will be two-sided with a confidence level of 95%. No adjustments will be made for multiplicity in the conduct of comparisons among the linaclotide DR dose for the key efficacy parameters, or in the testing of the other efficacy parameters.

Statistical analyses will be performed using Version 9.3 (or newer) of SAS for Windows.

5.7.3 Patient Disposition

The number of screen failures (i.e., patients who entered the Screening Period but not the Pretreatment Period) and the number of pretreatment failures (i.e., patients who entered the Pretreatment Period but were not randomized) will be tabulated by reason for failure.

The number of randomized patients and the number of patients in the ITT Population will be presented by treatment group for each study center within each geographic region.

The number and percentage of randomized patients who are in the ITT Population will be presented by treatment group. The number and percentage of randomized patients who complete the Treatment Period and those who prematurely discontinue treatment will also be presented by treatment group. Furthermore, the number and percentage of randomized patients who prematurely discontinue from the Treatment Period will be presented for each treatment group by reason for premature discontinuation as recorded on the study completion form of the eCRFs.

5.7.4 Demographics and Other Baseline Characteristics

Demographic parameters (age; age group; race; ethnicity; sex) and baseline characterisitics (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, stool consistency, straining,

abdominal discomfort, abdominal pain, and abdominal bloating) will be summarized descriptively by treatment group for the ITT population.
Protocol deviations and important protocol deviations will be identified through blinded data review.

5.7.5 Prior and Concomitant Medicines

Prior medicines are defined as any medicines taken prior to the date of first dose of study drug. Concomitant medicines are defined as any medicines taken on or after the date of first dose of study drug during the Treatment Period. Any medicines taken after the date of last dose of study drug will be excluded from the summaries related to concomitant medicines.

Both prior and concomitant medicine use will be summarized by the number and percentage of patients in each treatment group receiving each medicine within each therapeutic class for the ITT Population. Multiple medicines used by a patient in the same category (based on Anatomical-Therapeutic-Chemical classification) will be counted only once.

5.7.6 Extent of Exposure and Treatment Compliance

5.7.6.1 Exposure to Study Drug

Exposure to study drug, calculated as the number of days from the date of first dose taken to the date of last dose taken, inclusive, will be summarized by treatment group for the Safety Population.

5.7.6.2 Measurement of Treatment Compliance

Dosing compliance for the Treatment Period is defined as the total number of tablets/capsules actually taken by a patient during the Treatment Period divided by the number of tablets/capsules that were expected to be taken during the Treatment Period multiplied by 100. The total number of tablets/capsules actually taken will be calculated by subtracting the total number of tablets/capsules returned from the total number of tablets/capsules dispensed. The total number of tablets/capsules 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.

Descriptive statistics for study drug compliance on the Safety Population will be calculated by treatment group for the Treatment Period as a whole and for each of the three consecutive 4-week periods comprising the Treatment Period (consistent with study drug dispensing).

5.7.6.3 eDiary Compliance

eDiary compliance will be based on the percentage of complete eDiary entries made by a patient. A complete eDiary entry is defined as one in which the patient responds to every eDiary question asked in the evening report on that day. The questions that are asked weekly will not be included in the determination of a complete entry.

Descriptive statistics (number of patients, mean, standard deviation [SD], median, minimum, and maximum) for eDiary compliance will be presented for the ITT population by treatment group. The number and percentage of patients with complete entries ≥ 80% / < 80% of the time during the Pretreatment and Treatment Period, as well as the number and percentage of patients with > 4 / < 4 complete calls each week will be presented by treatment group for the ITT Population.

5.7.7 Efficacy Analyses

Baseline values for efficacy parameters are derived from the eDiary and eCRF data collected in the Pretreatment Period, specifically, the period of time from 14 days prior to 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 associated with the SBMs reported by the patient during this period. Baseline values for patient symptom severity parameters (e.g., abdominal pain, constipation severity) will be the average of the non-missing severity scores reported during this period.

Study centers will be pooled together by geographic region (details to be provided in the Statistical Analysis Plan [SAP]). In lieu of study center, geographic region will be used in analyses adjusting for center-to-center variability.

An observed-case approach to missing data will be applied. Sensitivity analyses of the key endpoints will include, but are not limited to, a multiple imputation approach and a last observation carried forward (LOCF) approach. If the normality assumption of the errors is violated for the key mixed model with repeated measures (MMRM) or analysis of covariance (ANCOVA) analyses, ranked or other appropriate analyses will be applied.

Further sensitivity analyses will be performed employing a modified responder definition that emphasizes the end of treatment (namely, 12-week CSBM Sustained Responder, defined as a patient who is a CSBM Weekly Responder for at least 9 of the 12 weeks and at least 3 of the last 4 weeks of the Treatment Period). Details for these analyses will be provided in the SAP.

All hypothesis testing will be performed at a two-sided 0.05 significance level. No adjustment for multiplicity will be applied.

5.7.7.1 Key Efficacy Parameters

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:

1. **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.
2. **Weekly Change from Baseline in CSBM Frequency**

   A patient's weekly CSBM frequency rate is the CSBM rate (CSBMs/week) calculated over that week.
3. **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. The Weekly APC +1 Responder criteria are defined in Section 5.7.7.3.

5.7.7.2 Key Efficacy Analysis

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, and week-by-treatment fixed effects, patient as the random effect, and baseline value as a covariate. The initial covariance structure will be compound symmetry but exploratory analyses with unstructured and autoregressive (1) structures will also be considered, primarily for planning purposes.

Corresponding with the primary efficacy objective of the study, which is to study the dose response of a range of oral doses within the linaclotide DR1 and DR2 formulations, the efficacy analysis of weekly change from baseline will be conducted by employing an overall trend test (i.e., linear contrast) for each formulation to test for a monotonically increasing dose response. Within a formulation, if the overall trend test reaches statistical significance ($\alpha = 0.05$), then that linaclotide DR 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 treatment-by-week interaction will be assessed and, if significant, appropriate trend analyses will be performed at each week.

The efficacy analysis of 6/12 Week APC+1 Responder rate will be confirmatory of the above and conducted by employing an overall trend test (i.e., Cochran-Mantel-Haenszel [CMH] correlation statistic) for each formulation (excluding the Active Control [linaclotide IR]) to test for a monotonically increasing dose response within the formulation. If the overall CMH statistic reaches statistical significance ($\alpha = 0.05$), 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]

5.7.7.3 Other Efficacy Parameters

The other efficacy parameters are as follows:

- **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. The Weekly CSBM +1 Responder criteria are defined below.

- **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. The Weekly CSBM +1 Responder criteria are defined below.

- **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. The Weekly Abdominal Pain Responder criteria are defined below.

- **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. The Weekly Abdominal Pain Responder criteria are defined below.

- **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.

- **Weekly Abdominal Pain Responder**

  For each week in the Treatment Period, a Weekly Abdominal Pain Responder is a patient who has a decrease from baseline of at least 30% in the mean abdominal pain score 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 Abdominal Pain Responder for that week.

- **Weekly APC +1 Responder**

  For each week in 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.

- **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.

- **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.

- **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.

- **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 Per-Protocol 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 the 100 * 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.

- **Assessment of 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.

5.7.7.4 Other Efficacy Analyses

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.

All continuous change-from-baseline in 12-week efficacy parameters will be evaluated by comparing each DR1 and DR2 dose with the placebo group using an ANCOVA model with treatment group and geographic region as fixed-effect terms and baseline value as a covariate.

Least-squares means for each treatment group, least-squares mean differences between each DR1 and DR2 dose and the placebo group 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.

5.7.8 Health Outcomes Analyses

Health outcomes analysis will be based on the ITT Population.

5.7.8.1 SF-12v2

Descriptive statistics (n, mean, SD, median, minimum, and maximum) will be presented for the absolute and change-from-baseline Physical Component Summary and Mental Component Summary scores at Randomization, Week 4, Week 8, and EOT. 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.

5.7.8.2 EQ-5D

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 index score by treatment group. The same statistics will be calculated for the visual analog scale of patient's health rating. Results will be presented for the following study visits: Randomization, Week 4, Week 8, and EOT.

5.7.8.3 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.

5.7.8.4 Irritable Bowel Syndrome-Symptom Severity Scale

At each assessment of the IBS-SSS, the severity scores will be calculated. Descriptive statistics will be presented for the severity score and the other IBS items related to bowel habit (4 items) and site of pain (2 items).

5.7.9 Safety Analyses

All safety parameters will be analyzed descriptively in accordance with the general methods described in Section 5.7.2.

5.7.9.1 Adverse Events

Adverse Event Verbatim Terms will be coded in the EDC system against the most current version of MedDRA available at the start of the study. A treatment-emergent AE (TEAE) is an AE that occurs during the Treatment Period (up to one day after the last dose of double-blind study drug) and was not present prior to the date of the first dose, or was present prior to the date of the first dose but increased in severity during the Treatment Period.

If more than one AE is reported prior to the first dose of double-blind study drug and coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs occurring during the Treatment Period that were also coded to that preferred term. An AE that occurs more than one day after the last dose of double-blind study drug will not be counted as a TEAE.

For the Treatment Period, the number and percentage of patients reporting TEAEs in each treatment group will be tabulated by system organ class (SOC) and preferred term; by SOC, preferred term, and severity; and by SOC, preferred term, and relationship to study drug. If a patient has more than one TEAE coded to the same preferred term, the patient will be counted only once for that preferred term by identifying those TEAEs with the highest severity and the closest relationship to study drug.

The distribution of TEAEs by severity and relationship to study drug will be summarized by treatment group for the Treatment Period.

The incidence of common TEAEs, on-therapy SAEs, and AEs leading to premature discontinuation of study drug will be summarized by preferred term and treatment group for the Treatment Period. In addition, the incidence of fatal SAEs (i.e., events that caused death), if any, will be summarized separately by treatment group and preferred term for the Treatment Period.

Listings will be presented for patients with SAEs, patients with AEs leading to discontinuation, and patients who die (if any).

5.7.9.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in standard units) and changes from the baseline values at each assessment time point will be presented by treatment group for the Treatment Period for each clinical laboratory parameter.

The number and percentage of patients with potentially clinically significant (PCS) post-baseline clinical laboratory values will be tabulated by treatment group for the Treatment Period. The criteria for PCS laboratory values will be detailed in the SAP. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least one 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 one 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, study center, and baseline and post-baseline values. A listing of all AEs for patients with PCS laboratory values will also be provided.

5.7.9.3 Vital Signs

Descriptive statistics for vital signs (i.e., pulse rate, systolic and diastolic BP, respiratory rate, temperature, and body weight) and changes from baseline at each visit and at the end of the study will be presented by treatment group for the Treatment Period.

The number and percentage of patients with PCS post-baseline vital signs will be tabulated by treatment group for the Treatment Period. A vital sign value will be considered PCS if it meets

both the observed value criterion and the change from baseline value criterion. The criteria for PCS vital sign values will be detailed in the SAP. The percentages will be calculated relative to the number of patients with baseline values and at least one 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 one 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, study center, and baseline and post-baseline values. A listing of all AEs for patients with PCS vital sign values will also be provided.

5.7.10 Interim Analysis

No interim analysis is planned for this study.

5.7.11 Development of Scoring and Psychometric Analysis

The daily completed IBS-C bowel functioning and abdominal symptoms items will be examined for the purpose of determining their measurement property and performance as outcomes in this sample. If deemed appropriate based on item level performance, scoring algorithms will be developed and tested. These analyses will utilize blinded data pooled across treatment and dosing groups. If appropriate, factor analysis and/or item response theory (IRT) or Rasch analysis will also be performed (to be determined during the development of the SAP). A stand alone psychometric statistical analysis plan (SAP) will be developed pror to database lock. The psychometric SAP will detail assessments of reliability (test-retest reliability and, where appropriate, internal consistency), construct validity (including possible factor analysis, possible IRT/Rasch analysis, concurrent/convergent validity and known groups validity), and ability to detect change over time. In addition, analyses will be performed to provide guidance for interpretation of changes in scores.

5.7.12 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 deviations 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 treatment difference (-1.975), the lowest active treatment arms with each formulation (DR1 30 µg; DR2 30 µg) would reflect 50% of the observed treatment difference (-1.586), and placebo would reflect the previously observed difference (-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, $\alpha = 0.05$).

5.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Any amendment to this protocol will be provided to the investigator in writing by Ironwood or designee. No protocol amendment regarding reportable deviations as defined by the IRB may be implemented (with the exceptions noted below) before it has been approved by the IRB and the signature page, signed by the investigator, has been received by Ironwood or designee. If the protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IRB review and approval. However, the IRB must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits. Deviating from the protocol is permitted only if absolutely necessary for the safety of the patients and must immediately be reported to Ironwood or designee.

6. STUDY SPONSORSHIP

6.1 STUDY TERMINATION

Ironwood reserves the right to terminate the study in its entirety or at a specific center at any time.

6.2 REPORTING AND PUBLICATION

All data generated in this study will be the property of Ironwood and Forest Laboratories, LLC (an affiliate of Actavis, Inc.). An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the investigator will be subject to mutual agreement between the investigator and Ironwood.

7. INVESTIGATOR OBLIGATIONS

7.1 DOCUMENTATION

The investigator must provide the following to Ironwood or designee prior to the start of the study in accordance with ICH E6:

- A completed and signed Form FDA 1572. If, during the course of the study, any changes are made that are not reflected on Form FDA 1572, a new Form FDA 1572 must be completed and returned to Ironwood or designee for submission to the FDA
- A fully executed Clinical Trial Agreement
- The curricula vitae for the investigator and all sub-investigators listed on Form FDA 1572, including a copy of each physician's license
- A copy of the original IRB approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals. All subsequent amendments to the protocol must be submitted and approved by the IRB, as stated in Section 1.1
- A copy of the IRB-approved ICF
- A copy of the IRB-approved HIPAA authorization form
- A list of the IRB members or the DHHS general assurance number
- A copy of the laboratory reference ranges
- The Investigator's Statement page in this protocol signed and dated by the investigator
- A financial disclosure agreement completed and signed by the investigator and all subinvestigators listed on Form FDA 1572. If applicable, the investigator will provide an updated financial disclosure agreement to the Sponsor one year after the completion of the study

7.2 PERFORMANCE

The investigator must demonstrate reasonable efforts to obtain qualified patients for the study.

7.3 USE OF INVESTIGATIONAL MATERIALS

The investigator will acknowledge that the drug supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the investigator or subinvestigators listed on Form FDA 1572. Study drug must be stored in a safe and secure place. The investigator must maintain adequate records documenting the receipt, registration within IWRS, and disposition of all study supplies. Ironwood or designee will supply forms on which to record the date the study drug was received, the lot number and expiration date of the study drug, and a dispensing record in which to record each patient's use. All unused study drug must be returned to Ironwood's designee. It is the investigator's responsibility to ensure that patients return their study drug.

7.4 CASE REPORT FORMS

All data relating to the study will be recorded on eCRFs to be provided by Ironwood or designee via the EDC system, or if applicable, paper CRFs. The eCRFs and paper CRFs are to be completed at the time of the patient's visit, except for results of tests performed outside the investigator's office. The investigator is responsible for verifying that all data entries on the eCRFs and paper CRFs are accurate and correct. The investigator must sign the completed eCRF before its submission to Ironwood or designee.

7.5 RETENTION AND REVIEW OF RECORDS

The investigator must maintain the documentation relating to this study. If Ironwood or the FDA wishes to review any documentation relating to the study, the investigator must permit access to such records.

Federal regulations require that the investigator retain a copy of all records that support eCRFs and paper CRFs for this study (e.g., ICFs, clinical laboratory reports, source documents, study drug dispensing records) for whichever of the following is the shortest:

- Two years following the date of approval by the FDA of the study drug for the purposes that were the subject of the investigation; or
- Five years following the date on which the results of the investigation were submitted to the FDA in support of, or as part of, a New Drug Application (NDA) for the study drug for the purposes that were the subject of the investigation

If the investigation does not result in the submission of the data in support of, or as part of, an NDA, records must be retained for two years following notification by Ironwood that the entire clinical investigation (not merely the investigator's portion) is completed, terminated, or discontinued or for two years following withdrawal of the Investigational New Drug Application or NDA.

If the investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Ironwood must be notified in writing of the name and address of the new custodian.

7.6 PATIENT CONFIDENTIALITY

All patient records will only be identified by initials and PID number. Patients' names are not to be transmitted to Ironwood or its authorized designee. The investigator will keep a Master Patient List on which the PID number and the full name, address, and telephone number of each patient is listed.

8. SPONSOR SIGNATURES

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
Final Date:	09 October 2015

This clinical study protocol was subject to critical review and has been approved by the sponsor.

Signed: [redacted]

Date: [redacted]

9. INVESTIGATOR'S STATEMENT

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
Final Date:	09 October 2015

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____
<Investigator Name>

10. APPENDICES

APPENDIX I ELEMENTS OF INFORMED CONSENT

Procedures will comply with 21 CFR, Parts 50 and 312. Signed informed consent will be obtained from each patient participating in a clinical research study or from the patient's LAR. This consent must include the following items:

- A statement that the study involves research and an explanation of the purposes of the research; a description of the procedures to be followed and the identification of any procedures that are experimental; and the expected duration of the patient's participation
- A description of any reasonably foreseeable risks or discomforts to the patient
- A description of any benefits to the patient or to others that may reasonably be expected from the research. If the patient is to be paid for participating in the study, the consent form must state the amount that he/she will receive and the schedule of payment (to ensure neither coercion nor undue influence)
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient
- A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and noting the possibility that the FDA, Ironwood, the IRB, or an authorized CRO may inspect the records
- For research involving more than minimal risk, an explanation of whether any medical treatment is available if injury occurs and, if so, what it consists of or where further information may be obtained
- An explanation of whom to contact, including the relevant telephone number, for answers to pertinent questions about the research and the research patient's rights and whom to contact in the event of a research-related injury to the patient. (Note: in some cases, it may be necessary to identify a person other than the investigator as the contact. The guidance of the IRB may be required.)
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled
- A statement that the particular treatment or procedures may involve risks to the patient (or to the embryo or fetus if the patient is, or may become, pregnant) that are at present unforeseeable

- The expected circumstances for which the patient's participation may be terminated by the investigator without regard to the patient's consent
- Any additional costs to the patient that may result from participation in the research
- The consequences of a patient's decision to withdraw from the research and procedures for an orderly termination of the patient's participation
- A statement that significant new findings developed during the course of the research that may relate to the patient's willingness to continue participation will be provided to the patient
- The approximate number of patients involved in the study
- A statement of consent (e.g., "I agree to participate . . .")
- A place for the patient's signature and date of signing

A copy of the signed consent form should be given to the patient.

APPENDIX II CONCOMITANT AND PROHIBITED MEDICINES

Rescue Medicine

Rescue Medicine, which will be selected by and dispensed to patients, will be a choice of 5-mg bisacodyl tablets or 10-mg bisacodyl suppositories. During the Pretreatment and Treatment Periods, patients may use dispensed, protocol-permitted laxatives (bisacodyl tablets or suppositories) as Rescue Medicine when at least 72 hours have passed since their previous BM or when their symptoms become intolerable. In order to qualify for randomization into the Treatment Period, patients must have refrained from using Rescue Medicine on the calendar day before the Randomization Visit and on the day of the Randomization Visit up until the time of the clinic visit. Patients must agree to refrain from using Rescue Medicine from the time they arrive at the clinic for the Randomization Visit through the calendar day after the Randomization Visit.

Prohibited Medicine

All medicine listed in the sections below ("1-day Washout" and "14-day Washout") are excluded during the Pretreatment and Treatment Periods. A 1-day washout means that the particular medicine is not allowed during the calendar day before the Pretreatment Visit; a 14-day washout means that the particular medicine is not allowed during the 14 calendar days before the Pretreatment Visit.

1-DAY WASHOUT ***(no medicine during the calendar day before the Pretreatment Visit)***

1. Any over-the-counter or prescription laxative, suppository, or enema (e.g., polyethylene glycol, lactulose, Fleet's) and any herbal or natural agent that a person might take for constipation. Note: The use of fiber, bulk laxatives, stool softeners (surfactants such as docusate), and probiotics is acceptable, provided the patient has been on a stable dose during the 30 days before the Screening Visit and plans to continue stable dosing throughout the study.
2. Any medicine used to treat diarrhea (e.g., bismuth subsalicylate, kaolin).
3. NSAIDs if taken for abdominal pain or discomfort.

14-DAY WASHOUT ***(no medicine during the 14 calendar days before the Pretreatment Visit)***

1. Drugs with known pharmacological activity at 5-hydroxytryptophan (HT)4, 5-HT2b or 5-HT3 receptors (e.g., cisapride, tegaserod, ondansetron, tropisetron, granisetron, dolasetron, and mirtazapine).
2. Any treatment specifically taken for IBS-C or CIC alone or in combination, including lubiprostone, an approved chloride channel activator that enhances intestinal fluid secretion, linaclotide, plecanatide, colchicine, and misoprostol. Note: Patients may not have taken commercially available linaclotide or participated in a linaclotide or plecanatide clinical study during the 30 days before the Screening Visit.
3. Prokinetic agents (e.g., metoclopramide, itopride, prucalopride, and domperidone).
4. Anti-cholinergic agents (e.g., dicyclomine, flavoxate, scopolamine, hyoscyamine, propantheline, oxybutynin, tolterodine, solefenacin, darifenacin, and trospium). Note: inhaled ipratropium and tiotropium are permitted.
5. Bile acid sequestrants (e.g., cholestyramine and colestipol).
6. Cholinomimetic agents (e.g., bethanechol, pyridostigmine, tacrine, and physostigmine). Note: intraocular cholinomimetic agents (e.g., pilocarpine) are permitted.
7. Antipsychotic agents (e.g., risperidone, haloperidol, droperidol, chlorpromazine, perphenazine, all phenothiazines, quetiapine, olanzapine, and clozapine) unless the patient has been on a stable dose for 30 days before the Screening Visit and there is no plan to change the dose after the Screening Visit. Note: paliperidone is permitted without restriction.
8. Antidepressants unless the patient has been on a stable dose for 30 days before the Screening Visit and there is no plan to change the dose after the Screening Visit. Specifically included are the following:
   - Tricyclic antidepressants (e.g., amitriptyline, imipramine, and nortriptyline);
   - Monoamine oxidase inhibitors (e.g., furazolidone, isocarboxazid, pargyline, phenelzine, and selegiline tranylcypromine);
   - Selective serotonin reuptake inhibitors (e.g., fluoxetine, sertraline, paroxetine, and citalopram);
   - Serotonin and norepinephrine reuptake inhibitors (e.g., venlafaxine and desvenlafaxine succinate)
   - Others (e.g., trazodone, and bupropion).

9. Calcium channel blocker verapamil unless the patient has been on a stable dose for 30 days before the Screening Visit and there is no plan to change the dose after the Screening Visit. Note: all other calcium channel blockers (e.g., nifedipine, diltiazem, amlodipine, felodipine, nicardipine, nimodipine, nisoldipine, etc.) are permitted and may be used without restriction.
10. Oral and parenteral antibiotics (However, a standard regimen [up to 10 days] of oral antibiotics is permitted.)
11. Any investigational or imported drugs that have not been approved for human use by the US FDA.
12. All narcotics either alone or in combination (e.g., tramadol, codeine, morphine, propoxyphene, loperamide, diphenoxylate, and paregoric). Note: narcotics used as anesthesia for a colonoscopy require a 5 calendar day wash-out prior to the patient entering into the Pretreatment Period.
13. Any medicine taken for the purpose of losing weight (e.g., orlistat, phentermine, phendimetrazine, diethylpropion, benzphetamine, and sibutramine).
14. Any medicine that is known to cause diarrhea (e.g., acarbose).
15. Proton pump inhibitors (e.g., omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole) unless the patient has been on a stable dose for 30 days before the Screening Visit and there is no plan to change the dose after the Screening Visit.
16. Iron (as either a supplement or to treat iron-deficiency anemia) is acceptable, provided the patient has been on a stable dose for 30 days before the Screening Visit and plans to continue stable dosing throughout the trial.
17. Others: barbiturates (e.g., butalbital and phenobarbital) and chronic oral or parenteral glucocorticoids (which must be discontinued at least three months before the Screening Visit; however, one 10-day course of oral or one injection of parenteral glucocorticoids is permitted during the Pretreatment or Treatment Periods). Pregabalin is acceptable, provided the patient has been on a stable dose during the 30 days before the Screening Visit and plans to continue stable dosing throughout the study.

APPENDIX III SUMMARY OF AMERICAN GASTROENTEROLOGICAL ASSOCIATION GUIDELINES

1. Patients aged 50 years and older must have had a colonoscopy with negative findings during the 10 years before the Screening Visit. If there were polyps on the most recent colonoscopy, the patient may be enrolled, provided there were two or fewer small (< 1 cm) tubular adenomas without appreciable villous tissue or high-grade dysplasia and provided the colonoscopy was performed during the five years before the Screening Visit. (Note: Patients who have only hyperplastic polyps are eligible.)
2. Patients who have a first-degree relative with colorectal cancer or adenomatous polyps diagnosed before age 60 or two first-degree relatives with colorectal cancer diagnosed at any age must have had a colonoscopy with negative findings during the five years before the Screening Visit. This applies to patients who are ≥ 40 years old and to patients < 40 years old who are ≤ 10 years from the age when their youngest relative was found to have one of the conditions described above.
3. Patients who have a first-degree relative with colorectal cancer or adenomatous polyps diagnosed at age 60 or older or two second-degree relatives with colorectal cancer diagnosed at any age must have had a colonoscopy with negative findings during the 10 years before the Screening Visit. This applies to patients who are ≥ 40 years old and to patients < 40 years old who are ≤ 10 years from the age when their youngest relative was found to have one of the conditions described above.
4. Patients of any age who have alarm symptoms must have had a colonoscopy with negative findings after the onset of the alarm symptoms and during the five years before the Screening Visit. Alarm symptoms include lower GI bleeding (rectal bleeding or heme-positive stool), iron-deficiency anemia, unexplained clinically-significant weight loss, and systemic signs of infection or colitis. In addition, patients with a family history of celiac disease or inflammatory bowel disease must have had a colonoscopy with negative findings during the five years before the Screening Visit.

Note: All information required by the Inclusion Criterion will be captured on the eCRFs. Because narcotics are used as anesthesia for a colonoscopy, patients are eligible to enter the Pretreatment Period on the fifth calendar day after a colonoscopy.

Source: Winawer, et al, (2003)

APPENDIX IV 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 V KEY EFFICACY ASSESSMENTS

Complete Spontaneous Bowel Movement

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

1 = Yes

2 = No

Daily Patient Assessment of Abdominal Pain at its Worst

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

0	1	2	3	4	5	6	7	8	9	10
No abdominal pain										**Worst possible abdominal pain**

APPENDIX VI OTHER EFFICACY ASSESSMENTS

Stool Consistency

[BSFS]

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)

[Note: This item (BSFS) will be administered with pictures.]

[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

How much did you strain during your bowel movement?

- ☐ Not at all
- ☐ A little (mild straining)
- ☐ A fair amount (moderate straining)
- ☐ A large amount (severe straining)
- ☐ An extreme amount (extremely severe straining)

Daily Patient Assessment of Abdominal Discomfort at its Worst

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

0	1	2	3	4	5	6	7	8	9	10
No abdominal discomfort										**Worst possible abdominal discomfort**

Daily Patient Assessment of Abdominal Bloating at its Worst

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

0	1	2	3	4	5	6	7	8	9	10
No abdominal bloating										**Worst possible abdominal bloating**

Weekly Patient Assessment of Constipation Severity

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

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

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

1 = Yes

2 = No

Treatment Satisfaction Assessment

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

APPENDIX VII 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 VIII EQ-5D 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 ☐

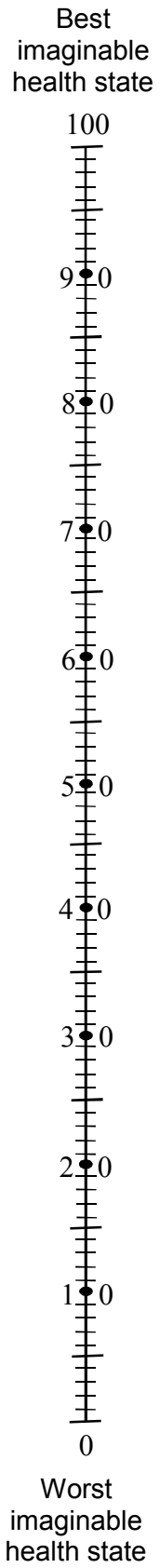
Anxiety/Depression

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 IX 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 X 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

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