# Clinical Study Protocol: MCP-103-205

## Amendment 1, 29 January 2019

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|---|---|
| **Study Title:** | A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-range-finding Study of MD-7246 Administered Orally for 12 Weeks to Treat Abdominal Pain in Patients with Diarrhea-predominant Irritable Bowel Syndrome |
| **Study Number:** | MCP-103-205 |
| **Study Phase:** | 2 |
| **Product Name:** | MD-7246 |
| **Indication:** | Abdominal Pain in Diarrhea-predominant Irritable Bowel Syndrome |
| **Investigators:** | Multicenter |
| **Sponsor:** | Ironwood Pharmaceuticals, Inc.<br>301 Binney Street<br>Cambridge, MA 02142 |
| **Medical Monitor:** | [redacted] |

| | **Date** |
|---|---|
| **Original Protocol:** | 11 October 2018 |
| **Amendment #1:** | 29 January 2019 |

**SAE Reporting Fax Number/Email:**

| Organization | Email | Safety Hotline Fax | Safety Hotline Phone |
|---|---|---|---|
| PPD | [redacted] | [redacted] | [redacted] |

Note: The preferred method of SAE reporting is via the electronic data capture (EDC) system; reporting should be done via fax/email if the EDC system is not available.

**Sponsor Signatory:**

[redacted]

Refer to the final page of this protocol for electronic signature and date of approval.

# SYNOPSIS

**Study Number:**

MCP-103-205

**Study Title:**

A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-range-finding Study of MD-7246 Administered Orally for 12 Weeks to Treat Abdominal Pain in Patients with Diarrhea-predominant Irritable Bowel Syndrome

**Study Centers:**

Approximately 80 in the United States

**Development Phase:** 2

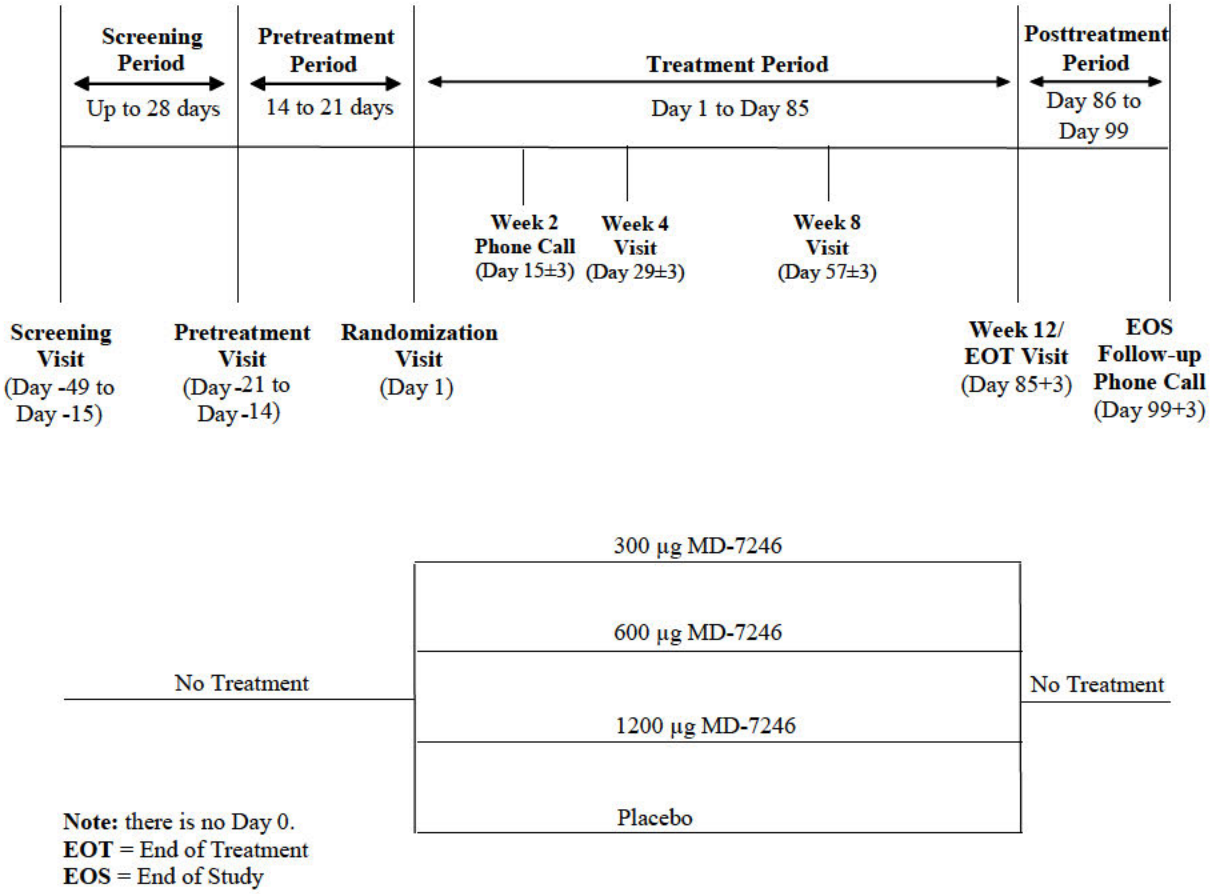
**Objective(s):**

The objectives of this study are to evaluate the safety and tolerability, treatment effect on abdominal pain, and dose response of MD-7246 administered orally to patients with diarrhea-predominant irritable bowel syndrome (IBS-D). An exploratory objective of the study is to assess bowel function changes with MD-7246 in patients with IBS-D.

**Methodology:**

This study is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-range-finding, 12-week study, consisting of 4 distinct periods, as illustrated in the figure below. The study will enroll patients who have IBS-D diagnosed using Rome IV criteria. Eligible patients will be randomized in equal proportions to 1 of 4 treatments: 300, 600, or 1200 µg of MD-7246, or matching placebo, administered once daily. MD-7246 is a delayed release (DR) tablet formulation of linaclotide designed to release linaclotide in the distal ileum near the ileocecal junction, to target guanylate cyclase C (GC-C) receptors in the colon and minimize secretory effects in the gastrointestinal (GI) tract.

***Overview of Study Design***




Study Periods

1. *Screening Period:* The Screening Period starts with the signing of the informed consent form (ICF; Appendix 1) and may last for up to 28 days. During this period, patient eligibility for entry into the Pretreatment Period will be determined. Loperamide, a protocol-permitted over-the-counter (OTC) medication for diarrhea, will be distributed to eligible patients beginning at the Screening Visit. The end of the Screening Period coincides with the start of the Pretreatment Period. If the patient meets the entry criteria assessed at the Screening Visit and does not require a washout of prohibited medicines (see Appendix 2), the Screening Visit and Pretreatment Visit may be combined into one visit.
2. *Pretreatment Period:* The Pretreatment Period is defined as the 14 to 21 days immediately before the Randomization Visit. During this period, patients will provide the following information in a handheld electronic diary (eDiary):

- Daily Assessments:
  - Daily Abdominal Symptom Assessments in a daily evening report
  - Bowel Movement (BM)-related Assessments on an event-driven basis (meaning these are assessments made for each event at the time the event occurs [or during the daily evening report for any events not previously entered for that day])
- Weekly Assessments
  - Weekly Patient Assessment of Degree of Relief of IBS Symptoms
  - Weekly Patient Assessment of Adequate Relief of IBS Pain
  - Weekly Patient Assessment of BM-related Symptom Severity (patient global impression of severity [PGI-S])
  - Weekly Patient Assessment of BM-related Symptom Change (patient global impression of change [PGI-C])
- Use of Loperamide for Diarrhea on an event-driven basis

Patients who satisfy all 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 randomized in equal proportions to 1 of 4 treatments: 300, 600, or 1200 µg of MD-7246, or matching placebo. Patients will take their initial dose of study drug at the study center during the Randomization Visit. On all other days, study drug will be taken once daily at approximately the same time of day without regard to food (patients will be instructed to choose a time that is convenient for them and continue daily dosing at that time throughout the Treatment Period). Patients will continue to use the handheld eDiary to provide their:
   - Daily Assessments:
     - Daily Abdominal Symptom Assessments in a daily evening report
     - BM-related Assessments on an event-driven basis (meaning these are assessments made for each event at the time the event occurs [or during the daily evening report for any events not previously entered for that day])
   - Weekly Assessments
     - Weekly Patient Assessment of Degree of Relief of IBS Symptoms
     - Weekly Patient Assessment of Adequate Relief of IBS Pain
     - Weekly Patient Assessment of Treatment Satisfaction
     - Weekly Patient Assessment of BM-related Symptom Severity (PGI-S)
     - Weekly Patient Assessment of BM-related Symptom Change (PGI-C)
   - Use of Loperamide for Diarrhea on an event-driven basis

- Health-related quality-of-life and patient-outcome assessments will be performed at the Randomization Visit and at study visits throughout the Treatment Period. A list of these assessments and the visits when they will be performed is provided under Study Visit Assessments in the Study Procedures section below

Patients will complete a Week 2 Phone Call, and Week 4, Week 8, and Week 12/End of Treatment (EOT) Visits during the Treatment Period (see Schedule of Evaluations).

4. *Posttreatment Period:* The Posttreatment Period starts on the day following the last day of dosing (Week 12/EOT Visit) and finishes 2 weeks later at the End of Study (EOS) Follow-up Phone Call. During the call, patients will be asked to report any AEs and medicines taken since the Week 12/EOT Visit and detail any other symptoms or comments they may have (at the discretion of the investigator, patients may be requested to return to the study center for their EOS Follow-up).

Overall Study Stopping Criteria and Data Monitoring Committee (DMC)

The Sponsor may stop enrollment prematurely because of low recruitment rates. The Sponsor may suspend or terminate the study prematurely because of a change in opinion of the Institutional Review Board, DMC, or a regulatory authority decision.

An independent DMC will regularly review safety data during the conduct of the study. Periodic safety review meetings will be scheduled when approximately 1/3 and 2/3 of patients have been randomized. The committee will review accumulated safety data, and may request unblinding of the treatment groups, in order to make any recommendations regarding the acceptability of continuing the study based on AEs reported.

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 by the patient into the eDiary each day:

- Diary of IBS Symptoms - Diarrhea (DIBSS-D; Appendix 4)
  - Daily Abdominal Symptom Assessments (entered by the patient in a daily evening report):
    - Rating of abdominal bloating at its worst during the previous 24 hours on an 11-point numerical rating scale (NRS)
    - Rating of abdominal discomfort at its worst during the previous 24 hours on an 11-point NRS
    - Rating of abdominal pain at its worst during the previous 24 hours on an 11-point NRS

- Rating of abdominal cramping at its worst during the previous 24 hours on an 11-point NRS

- Daily BM-related Assessments (entered by the patient for each BM on an event-driven basis):
  - BM date and time
  - Stool consistency on a 5-point ordinal scale
  - Stool consistency on the 7-point Bristol Stool Form Scale (BSFS)
  - BM urgency on a binary (Yes/No) scale

- Use of Loperamide for Diarrhea on an event-driven basis

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

- Patient Assessment of Degree of Relief of IBS Symptoms on a 7-point balanced scale
- Patient Assessment of Adequate Relief of IBS Pain on a binary scale (Yes/No)
- Patient Assessment of Treatment Satisfaction on a 5-point ordinal scale (assessed at each week of the Treatment Period after the Randomization Visit)
- Patient Assessment of BM-related Symptom Severity on a 5-point ordinal scale
- Patient Assessment of BM-related Symptom Change on a 7-point ordinal scale

*Study Visit Assessments:*

- The following information will be captured in the eDiary at the Pretreatment Visit:
  - Pain Catastrophizing Scale
- The following information will be captured in the eDiary at the Randomization Visit before the first dose of study drug and at all subsequent study visits:
  - Short Form-12 Health Survey version 2 (SF-12v2)
  - EuroQol-5 Dimension (EQ-5D-3L)
  - Irritable Bowel Syndrome-Symptom Severity Scale (IBS-SSS)

Protocol-permitted OTC Medication for Diarrhea

- Throughout the study (Screening Period through Posttreatment Period), patients will be allowed to use loperamide (Imodium®) to assist in the management of their diarrhea. Loperamide will be provided to the patient at study visits to use as needed (at the patient's discretion) to stabilize their diarrhea throughout the study. Beginning at the Pretreatment Visit (when the patients receive the eDiary) through the Week 12/EOT Visit, the day (yesterday/today) and dose will be entered by the patient for each use of loperamide for diarrhea on an event-driven basis.
- Prescription medications for the treatment of diarrhea or IBS are not permitted during the study, from 4 weeks (28 days) before the Pretreatment Visit (or 3 months before the Pretreatment Visit for rifaximin) through the EOS Follow-up Phone Call (see Appendix 2).

**Number of Patients:**

Approximately 368 IBS-D patients (approximately 92 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 all of the following criteria:

1. Patient has given consent by signing an ICF.
2. Patient is an ambulatory male or female aged 18 years or older at the Screening Visit.
3. Female patients are not pregnant and lactating females must agree not to breastfeed.
4. Female patients of childbearing potential (ie, women who are not postmenopausal or who have not had a bilateral oophorectomy, hysterectomy, or tubal ligation) who are sexually active with a male partner must agree to use one of the following methods of birth control from the date they sign the ICF until the End of Study Visit:
   a. Hormonal contraception (ie, oral contraceptive, contraceptive implant, or injectable hormonal contraceptive)
   b. Double-barrier birth control (eg, condom plus intrauterine device, diaphragm plus spermicide)
   c. Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy
5. 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.

6. Patient meets the colonoscopy requirements as defined by the American Gastroenterological Association guidelines and described in Appendix 3. (Note: Patients who receive narcotic anesthesia for a colonoscopy are eligible to enter the Pretreatment Period only on the fifth day or later after the colonoscopy.)
7. Patient meets Rome IV criteria for IBS (1): reports recurrent abdominal pain, on average at least 1 day/week during the 3 months before the diagnosis, with the onset at least 6 months before the diagnosis, associated with 2 or more of the following features:
   a. Related to defecation
   b. Associated with a change in frequency of stool
   c. Associated with a change in form (appearance) of stool

   Note: the diagnosis can be made at the Screening Visit or can be based on patient recall of symptoms that the patient had before starting chronic treatment with FDA-approved medications to treat IBS-D (eg, alosetron, rifaximin, or eluxadoline).
8. Patient meets the Rome IV criteria for IBS-D (1), based on stool form on days with at least 1 abnormal BM: >25% of BMs with BSFS score of 6 or 7 and <25% of BMs with BSFS score of 1 or 2.

   Note: IBS-D diagnosis should be based on the patient's BM abnormalities when the patient is not taking medications to treat his/her BM abnormalities.
9. Patient has an average score for abdominal pain at its worst of ≥4.0 and ≤9.0, as reported in the eDiary using an 11-point NRS during the 14 days before the Randomization Visit and including the eDiary entry made in clinic at the Randomization Visit prior to randomization.
10. Patient is compliant (as defined in the study procedures section below) with eDiary completion by adequately responding to eDiary questions (ie, completing the daily evening report) on 10 or more of the 14 days before the Randomization Visit.
11. Patient is able to swallow solid, oral dosage forms whole with the aid of liquid (patient may not chew, divide, crush, or dissolve the study drug).
12. Patient is fluent in English or Spanish.
13. Patient agrees to refrain from making any new, major lifestyle changes that may affect IBS symptoms (eg, 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 has a known or suspected structural abnormality of the gastrointestinal (GI) tract (eg, mechanical gastrointestinal obstruction) or a disease or condition that can affect GI motility.
2. Patient has clinically significant concurrent illness or findings on a physical examination or clinical laboratory tests (clinical chemistry panel, complete blood count [CBC]) after signing the ICF but before receiving the first dose of study drug. (Note: The investigator will determine if a finding is clinically significant. In making this determination, the investigator will consider whether the finding could prevent the patient from performing any of the protocol-specified assessments, represent a condition that would exclude the patient from the study, represent a safety concern if the patient participates in the study, or confound the study-specified assessments of safety or efficacy.)
3. Patient has a positive drug or alcohol screen, including testing positive for marijuana or other drugs that target the endocannabinoid system, such as dronabinol.
4. Patient has been diagnosed with or has a family history of familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, or any other form of familial colorectal cancer.
5. Patient has a history of inflammatory or immune-mediated GI disorders, including inflammatory bowel disease (IBD) and symptomatic biopsy- or serology-positive celiac disease.
6. Patient has symptomatic lactose intolerance, symptomatic non-celiac gluten sensitivity, or other malabsorption syndrome.
7. Patient currently has clinically significant symptoms such as lower GI bleeding (rectal bleeding or heme-positive stool), iron-deficiency anemia, weight loss, or systemic signs of infection or colitis.
8. Patient has any chronic condition with ongoing symptoms that can be associated with abdominal pain or discomfort and could confound the assessments in this study (eg, diverticulitis, ileus, active peptic ulcer disease, uncontrolled gastroesophageal reflux disease, gastroparesis, chronic pancreatitis, polycystic kidney disease, ovarian cysts, endometriosis, urological pain).
9. Patient has a history of intestinal obstruction, toxic megacolon, megarectum, descending perineum syndrome, solitary rectal ulcer syndrome, systemic sclerosis, multiple sclerosis, Parkinson’s disease, spinal cord injury.
10. Patient has ever had a fecal impaction that required hospitalization or emergency room treatment, or has a history of cathartic colon, ischemic colitis, or pelvic floor dysfunction (unless successful treatment has been documented by a normal balloon expulsion test).

11. Patient has currently documented positive stool tests for enteric pathogens, ova or parasites.
12. Patient has a history of a microbiologically documented lower GI infection (eg, Clostridium difficile colitis) or received treatment for a microbiologically documented lower GI infection during the 3 months before the Screening Visit.
13. Patient has a history of hypersensitivity to linaclotide, any of the excipients contained in the study drug (MD-7246 or placebo) as described in Section 7.1, or loperamide.
14. 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 (including cholecystectomy), pelvis, or retroperitoneal structures during the 6 months before the Screening Visit, or during the 3 months before the Screening Visit for laparoscopic surgery
    c. Other major surgery, including appendectomy, during the 3 months before the Screening Visit
15. 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 if the malignancy has been in a complete remission for at least 3 years before the Randomization Visit. A complete remission is defined as the disappearance of all signs of cancer in response to treatment.)
16. Patient has a history of diabetic neuropathy.
17. Patient has a history of human immunodeficiency virus infection.
18. 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.
19. 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 if they have exhibited no actual abuse during the 12 months before the Randomization Visit.)
20. Patient has a history or current evidence of laxative or opioid abuse.
21. Patient has been hospitalized for a major psychiatric condition or has made a suicide attempt during the 2 years before the Randomization Visit.
22. Patient has received an investigational drug during the 30 days before the Screening Visit.
23. Patient reported using a Prohibited Medicine during the Screening or Pretreatment Period, does not meet all the Prohibited Medicine criteria, or is not willing or able to abide by the restrictions regarding use of Prohibited Medicines, as detailed in Appendix 2.

24. 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.
25. Patient has previously entered the Pretreatment Period of this study.
26. Patient is directly or indirectly involved in the conduct and administration of this study as an investigator, sub-investigator, study coordinator, other study staff member, or employee of Ironwood Pharmaceuticals or Allergan; 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 Product, Dosage, and Mode of Administration:**

MD-7246 (formerly known as linaclotide DR2) at 3 dose levels (300, 600, or 1200 μg) administered as oral tablets in a double-blind manner once daily at approximately the same time of day without regard to food.

**Reference Therapy, Dosage, and Mode of Administration:**

Placebo oral tablets matching the test product in size and appearance administered in a double-blind manner once daily at approximately the same time of day without regard to food.

**Duration of Treatment:**

The test product and reference therapy will be administered for 12 weeks. Total patient participation will be up to 151 days, including the Screening, Pretreatment, Treatment, and Posttreatment Periods.

**Criteria for Evaluation:**

Key Efficacy Assessment

The following efficacy assessment based on the eDiary question is used to determine the key efficacy endpoints:

- Daily patient assessment of abdominal pain at its worst over the last 24 hours on an 11-point NRS

Additional Efficacy Assessments

Additional efficacy assessments are based on the following eDiary questions:

- Daily patient assessments of abdominal bloating, abdominal discomfort, and abdominal cramping at their worst over the last 24 hours, each on an 11-point NRS
- Weekly patient assessment of degree of relief of IBS symptoms on a 7-point balanced scale
- Weekly patient assessment of adequate relief of IBS pain on a binary scale
- Weekly patient assessment of treatment satisfaction on a 5-point ordinal scale

Exploratory Assessments

Exploratory assessments are based on the following eDiary BM-related questions; these non-efficacy assessments will inform evaluation of whether MD-7246 affects bowel function:

- BM frequency (date and time)
- Stool consistency on a 5-point ordinal scale
- Stool consistency on the 7-point BSFS
- BM urgency on a binary scale
- Use of loperamide for diarrhea
- Weekly patient assessment of BM-related symptom severity on a 5-point ordinal scale
- Weekly patient assessment of BM-related symptom change on a 7-point ordinal scale

**Safety Measures:**

Adverse event (AE) recording (each visit), clinical laboratory measures (chemistry and hematology: Screening, Randomization, Week 4, Week 8, and Week 12/EOT Visits), body weight (each visit), vital sign parameters (each visit).

**Statistical Methods:**

Analysis Populations

The Screened Population consists of all patients who had a Screening Visit (Visit 1) and were assigned a patient identification (PID) number.

The Intent-to-Treat (ITT) Population consists of all randomized patients.

The Safety Population consists of all patients who received at least 1 dose of study drug.

General Methods

Efficacy analyses will be performed on the ITT Population for all outcomes reported during the Treatment Period using treatment group assigned at the Randomization Visit. Unless otherwise specified, all confidence intervals (CIs) will be 2-sided and with a confidence level of 95%. No adjustments will be made for multiplicity in the conduct of comparisons among the MD-7246 doses relative to placebo for the key efficacy endpoints, or in the analysis of the additional efficacy endpoints or exploratory endpoints. Safety analyses will be performed using descriptive summaries based on the Safety Population and on actual treatment received.

For analysis of continuous parameters (eg, change from baseline), descriptive statistics (n, mean, standard deviation, median, and range) will be calculated and presented for each treatment group. For categorical parameters (eg, responder vs. non-responder), the number and percentage of each category will be calculated and presented for each treatment group. Percentages will be based on the total number of non-missing values; the number missing will be presented, but without a percentage.

Key Efficacy Endpoints

- Change from Baseline in Abdominal Pain at its Worst at Each Week

  The weekly abdominal pain at its worst score is the average of the non-missing abdominal pain scores during each week (Weeks 1-12) in the study. The baseline abdominal pain score is the average of the non-missing abdominal pain scores during the last 14 days of the Pretreatment Period and the day of the Randomization Visit reported prior to randomization. Change from baseline will be calculated for each week as the weekly score minus the baseline score.

- 6/12 Week Abdominal Pain 30% Responder

  A 6/12 Week Abdominal Pain 30% Responder is a patient who meets the Weekly Abdominal Pain 30% Responder criteria for at least 6 out of the 12 weeks of the Treatment Period. A Weekly Abdominal Pain 30% Responder is a patient who has a decrease from baseline of at least 30% in the mean abdominal pain at its worst 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 30% Responder for that week.

Key Efficacy Analysis

Comparisons between the MD-7246 dose groups and placebo with regard to the change from baseline in abdominal pain over the Treatment Period will be evaluated employing a mixed model with repeated measures (MMRM) framework with week (categorical), treatment, geographic region, and week-by-treatment fixed effects, patient as the random effect, and baseline value as a covariate. An unstructured covariance structure will be utilized. Descriptive statistics, for the overall Treatment Period effect, based on the MMRM model will include least-squares (LS) mean change from baseline for each treatment, the LS mean difference between each MD-7246 dose and placebo, corresponding 95% CIs, and the p-value associated with the comparison. In addition, weekly treatment differences between each MD-7246 dose group and placebo will be provided using the same MMRM model defined above.

For the 6/12 Week Abdominal Pain 30% Responder endpoint, the proportion of responders in each MD-7246 group will be compared to the proportion of responders in the placebo group using a Cochran-Mantel-Haenszel (CMH) test controlling for geographic region. The number and percent of responders, the difference in responder rates between each MD-7246 group and the placebo group, the odds ratio relative to placebo, all corresponding 95% CIs, and the p-value associated with the CMH test will be presented.

Additional Efficacy Endpoints

- 6/12 Week Abdominal Pain 50% Responder

  ≥50% decrease from baseline in abdominal pain for ≥6 of 12 weeks
- 6/12 Week Abdominal Discomfort 30% Responder

  ≥30% decrease from baseline in abdominal discomfort for ≥6 of 12 weeks
- 6/12 Week Abdominal Bloating 30% Responder

  ≥30% decrease from baseline in abdominal bloating for ≥6 of 12 weeks
- 6/12 Week Abdominal Cramping 30% Responder

  ≥30% decrease from baseline in abdominal cramping for ≥6 of 12 weeks
- 6/12 Week Degree of Relief Responder

  Score of ≤2 ("completely" or "considerably" relieved) for ≥6 of 12 weeks
- 6/12 Week Adequate Relief of IBS Pain Responder

  Patient reports adequate relief of IBS pain ("yes") for ≥6 of 12 weeks
- Treatment Satisfaction
- Change from Baseline in Percent of Abdominal Pain-free Days at Each Week
- Change from Baseline in Abdominal Discomfort at its Worst at Each Week
- Change from Baseline in Abdominal Bloating at its Worst at Each Week
- Change from Baseline in Abdominal Cramping at its Worst at Each Week

Additional Efficacy Analysis

The additional categorical responder (eg, 6/12 Week Abdominal Bloating 30% Responder) and continuous change-from-baseline endpoints will be analyzed utilizing the same methods defined above for the key efficacy endpoints.

Treatment Satisfaction will be analyzed utilizing an MMRM framework with week (categorical), treatment, geographic region, and week-by-treatment fixed effects, and patient as the random effect. An unstructured covariance structure will be utilized. Pairwise comparisons between each treatment group and placebo will be performed for the overall Treatment Period effect. MMRM-associated statistics, as defined above for the key efficacy change-from-baseline endpoint, will be presented.

Exploratory Endpoints

Exploratory endpoints related to bowel function will be studied to address the exploratory objective of the study. These non-efficacy endpoints will include:

- Change from Baseline in BM Frequency Rate at Each Week
- Change from Baseline in BSFS (Stool Consistency) at Each Week
- Change from Baseline in Urgent BM Frequency Rate at Each Week
- Change from Baseline in the Percent of Days Experiencing an Episode of Diarrhea per Week

  An episode of diarrhea is defined as a sequence of ≥2 loose/watery BMs (BSFS 6 or 7) that are never separated by >1 non-loose/watery stool or by a day without a BM.
- Change from Baseline in the Percent of Days Experiencing No Episodes of Diarrhea per Week
- Change from Baseline in BM-related Symptom Severity at Each Week
- BM-related Symptom Change
- Change from Baseline in Percent of Days with Use of Loperamide for Diarrhea at Each Week

Exploratory Analysis

Exploratory change-from-baseline endpoints will be analyzed utilizing the same methods as described above for the key efficacy analysis. BM-related Symptom Change will be analyzed for the Treatment Period overall utilizing the same methods as described above for the additional efficacy analysis of Treatment Satisfaction.

Safety Analysis

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

Sample Size

In a previously conducted Phase 2b trial utilizing MD-7246 (formerly known as linaclotide DR2), MCP-103-204, the standard deviation for the change from baseline to Week 12 in abdominal pain at its worst ranged from 2.32 to 2.88. Assuming a clinically meaningful treatment difference between MD-7246 and placebo of 1.0 for the mean change from baseline to Week 12 in abdominal pain, a standard deviation of 2.4, and 92 patients per treatment group (368 total), the estimated power is approximately 80% to detect a difference between each MD-7246 dose and placebo at a 2-sided significance level of 0.05 using a 2-sample t-test.

**Final Date:** 29 January 2019

# SCHEDULE OF EVALUATIONS

| Schedule of Evaluations MCP-103-205 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Study Period →** | **Screening Period (Up to 28 days)** | **Pretreatment Period (14 to 21 days)** | **Treatment Period (12 weeks)** | | | | | **Posttreatment Period (2 weeks)** |
| **Visit Days →** | **Screening Visit (Day -49 to Day -15)** | **Pretreatment Visit (Day -21 to Day -14)** | **Random-ization Visit (Day 1)** | **Week 2 Phone Call (Day 15±3)** | **Week 4 Visit (Day 29±3)** | **Week 8 Visit (Day 57±3)** | **Week 12/ End-of-Treatment Visit [p] (Day 85+3)** | **End-of-Study Follow-up Phone Call (Day 99+3)** |
| **Visit Numbers →** | **Visit 1** | **Visit 2** | **Visit 3** | **Telephone Call** | **Visit 4** | **Visit 5** | **Visit 6** | **Telephone Call** |
| **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 | X | X |
| Clinical Laboratory Tests [f] | X | | X* | | X | X | X | |
| Pregnancy Test [g] | X | | X* | | | | X | |
| Prohibited Medications Washout Instructions | X | | | | | | | |
| Loperamide for Diarrhea Dispensed [h] | X | X | X | | X | X | X | |
| AE Evaluations [i] | | X | X* | X | X | X | X | X |
| eDiary Registration and Training [j] | | X | X* | | X | X | X | |
| Pain Catastrophizing Scale | | X | | | | | | |
| Daily and Weekly Assessments [k] | | X | | | | | | |
| Patient eDiary Entry, in Clinic | | X | X* | | X | X | X | |

| Schedule of Evaluations MCP-103-205 | | | | | | | | |
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| **Visit Numbers →** | **Visit 1** | **Visit 2** | **Visit 3** | **Telephone Call** | **Visit 4** | **Visit 5** | **Visit 6** | **Telephone Call** |
| **Study Procedure ↓** | | | | | | | | |
| eDiary Compliance Verification and Reminder [l] | | | X* | X | X | X | X | |
| Randomization | | | X† | | | | | |
| SF-12v2 | | | X† | | X | X | X | |
| EQ-5D-3L | | | X† | | X | X | X | |
| IBS-SSS | | | X† | | X | X | X | |
| Study Drug Dispensed | | | X | | X | X | | |
| Study Drug Administration [m] | | | X | | | | | |
| Safety Phone Call [n] | | | | X | | | | X |
| Study Drug Accountability | | | | | X | X | X | |
| Investigator Consultation with Patient [o] | | X (Activity Triggered by eDiary Alert) | | | | | | |

AE=adverse event; BM=bowel movement; CBC=complete blood count; eDiary=electronic diary; EOS=End-of-Study; EOT=End-of-Treatment; EQ-5D-3L=EuroQol-5 Dimension 3-level; IBS=irritable bowel syndrome; IBS-SSS= Irritable Bowel Syndrome-Symptom Severity Scale; ICF=informed consent form; IWRS=interactive web response system; SF-12v2=Short Form-12 Health Survey version 2.

* Assessment done prior to randomization; † Assessment done predose

a. Site personnel will interact with IWRS to register the patient visit. Refer to the IWRS User Manual.
b. A physical examination includes, at minimum, the following: general appearance, HEENT (head, ears, eyes, nose, and throat), cardiac, respiratory, gastrointestinal, musculoskeletal, neurological, and dermatological systems. Rectal examinations should be performed at the discretion of the investigator; the purpose of the rectal examination is to rule out pathologies that might be caused by obstruction. Breast and genitourinary examinations are not required.
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. Pulse and blood pressure readings will be taken after the patient has been sitting for 5 minutes.
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 (approved or unapproved).

f. Chemistry and CBC. Urine drug screen will be performed at the Screening Visit only.
g. Required for females of childbearing potential only. 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 serum pregnancy test results must be documented at the Week 12/EOT Visit.
h. Protocol-permitted loperamide for diarrhea will be supplied to patients at the Screening Visit and, if needed, at the Pretreatment Visit, subsequent study drug dispensing visits, and the Week 12/EOT Visit.
i. All AEs occurring after the patient signs the ICF will be captured.
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 Abdominal Symptom Assessments, BM-related Assessments, Weekly Assessments, Pain Catastrophizing Scale (Pretreatment Visit only), SF-12v2, EQ-5D, IBS-SSS, and any use of loperamide for diarrhea. Patients will enter BMs and loperamide use in the eDiary on an event-driven basis, and will complete an evening entry each day to record daily assessments, including any BMs and/or loperamide use not previously recorded for that day, and weekly assessments. At the Randomization Visit, eDiary assessments will be completed in clinic prior to randomization.
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 compliance reminder will also occur during the Week 2 Phone Call.
m. Study drug will be administered in the clinic at the Randomization Visit. On all other days, study drug will be taken once daily at approximately the same time of day without regard to food.
n. Appropriate site personnel will contact patients by phone to assess for AEs, record concomitant medicines, and (at Week 2 only) remind patients to comply with study drug and eDiary completion. Any AE or concomitant medicine reported during the phone call will be captured on the eCRF. Patients who report AEs during the call will be provided with instructions on the appropriate follow-up care. At the discretion of the investigator, patients may be requested to return to the clinic for this contact or an unscheduled visit may be conducted following the phone call.
o. Throughout the Pretreatment and Treatment Periods, the eDiary will send automated alerts to the investigator if patients experience episodes of constipation with excessive use of loperamide or diarrhea that is not well managed with the use of loperamide (as defined in Section 8.2.6). In the event of an alert, the investigator must review with the patient their use of loperamide and their pattern of constipation or diarrhea.
p. 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).

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| ANCOVA | analysis of covariance |
| BM | bowel movement |
| BP | blood pressure |
| BSFS | Bristol Stool Form Scale |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| 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 |
| DIBSS-M | Diary of IBS Symptoms – Mixed |
| DMC | data monitoring committee |
| DR | delayed release |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| $EC_{50}$ | half maximal effective concentration |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| eDiary | electronic diary |
| EOS | End of Study |
| EOT | End of Treatment |

| | |
|---|---|
| EQ-5D-3L | EuroQol-5 Dimension 3-level |
| FDA | Food and Drug Administration |
| GC-C | guanylate cyclase-C |
| GCP | good clinical practice |
| GI | gastrointestinal |
| GPS | Global Patient Safety |
| HEENT | head, ears, eyes, nose, and throat |
| HEOR | health economics and outcomes research |
| 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-SSS | Irritable Bowel Syndrome – Symptom Severity Scale |
| IBS-U | unclassified irritable bowel syndrome |
| ICF | informed consent form |
| ICH | International Council on Harmonisation |
| IPD | important protocol deviation |
| IR | immediate release |
| IRB | Institutional Review Board |
| ITT | intent-to-treat |
| IWRS | interactive web response system |
| $K_i$ | inhibitory constant |
| LLOQ | lower limit of quantitation |
| LS | least squares |
| MAOI | monoamine oxidase inhibitor |

| | |
|---|---|
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | mixed model with repeated measures |
| NDA | New Drug Application |
| NRS | numerical rating scale |
| NSAID | nonsteroidal anti-inflammatory drug |
| OTC | over-the-counter |
| PCS | potentially clinically significant |
| PD | pharmacodynamic(s) |
| PEG | polyethylene glycol |
| PGI-C | patient global impression of change |
| PGI-S | patient global impression of severity |
| PID | patient identification |
| PK | pharmacokinetic(s) |
| QOL | quality of life |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SF-12v2 | Short Form-12 Health Survey version 2 |
| SNRI | serotonin-norepinephrine reuptake inhibitor |
| SOC | system organ class |
| SSRI | selective serotonin reuptake inhibitor |
| TCA | tricyclic antidepressant |
| TEAE | treatment-emergent adverse event |
| US | United States |

# 1. ETHICAL CONSIDERATIONS

This clinical study is designed to comply with the International Council on Harmonisation (ICH) Guidance on General Considerations for Clinical Trials, ICH E8 (published in the US Federal Register Volume 62, page 66113, December 17, 1997) and Good Clinical Practice (GCP): Consolidated Guidance, ICH E6 (published in the US Federal Register, Volume 62, page 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.

## 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 1), and associated documentation will be approved by the IRB prior to study initiation, in compliance with 21 CFR 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 per 21 CFR Part 50. 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 and any currently enrolled patient will be made aware of the new information and asked if he/she wishes to continue in the study. 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).

Ironwood Pharmaceuticals, Inc. and Allergan Sales, LLC are development partners for this study.

# 3. INTRODUCTION

## 3.1 IRRITABLE BOWEL SYNDROME (IBS)

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal (GI) disorder characterized by recurrent abdominal pain associated with defecation and/or a change in stool frequency or form. In addition to the characteristic abdominal pain, IBS is often associated with abdominal distension and bloating.(1-6) 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 based on predominant stool form as IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), or IBS mixed (IBS-M; mixed constipation and diarrhea), according to the Rome diagnostic criteria. IBS patients who rarely or never have abnormal stools or do not fit into 1 of the 3 main IBS subtypes are subtyped as unclassified IBS (IBS-U).(8)

## 3.2 MD-7246

MD-7246 is currently being developed for the treatment of abdominal pain associated with IBS-D. MD-7246 is an orally administered, delayed release (DR) tablet formulation of linaclotide designed to target guanylate cyclase C (GC-C) receptors in the colon and minimize secretory effects.

Linaclotide is a minimally absorbed 14-amino acid synthetic peptide agonist of GC-C. Linaclotide and its active metabolite bind to and activate GC-C on the luminal surface of the intestinal epithelial cells. As a GC-C agonist, linaclotide (and its active metabolite) improves bowel symptoms and abdominal pain via agonism of cyclic guanosine monophosphate (cGMP) on the intestinal mucosa. Activation of GC-C results in an increase in concentrations of cGMP, both extracellularly and intracellularly. Orally administered linaclotide has also been shown to reduce visceral hypersensitivity in animal models and abdominal pain in patients with IBS-C.(9) Extracellular cGMP in the serosal space is believed to modulate the activity of local afferent (sensory) nerve fibers. Increases in cGMP within the intestinal epithelial cells triggers a signal transduction cascade, leading to activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channels. This activation causes secretion of chloride and bicarbonate into the intestinal lumen, resulting in increased luminal fluid secretion and acceleration of intestinal transit.(10) 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.

LINZESS® is an orally administered, immediate release (IR) capsule formulation of linaclotide approved by the US FDA in 2012 at two dosage strengths: 290 µg for the treatment of IBS-C in adults, and 145 µg for the treatment of chronic idiopathic constipation (CIC) in adults. In 2017, US FDA also approved linaclotide (LINZESS®) 72 µg IR capsules for the treatment of CIC. The FDA-approved linaclotide IR formulation is a rapidly dissolving capsule, and dissolution tests suggest that it is released primarily in the stomach.

DR tablet formulations of linaclotide were developed with the hypothesis that delayed delivery of linaclotide will limit fluid secretion in the small intestine and maintain the nociceptive effects of the drug by enabling higher concentrations of linaclotide to interact with GC-C in the colon.

[redacted]

- [redacted]
- DR formulation 2 (DR2), also referred to as MD-7246, was designed to target the distal ileum near the ileocecal junction to relieve pain and minimize secretory effects in the GI tract.

Although GC-C is found throughout the GI tract, when administered as LINZESS®, linaclotide and its active metabolite are likely to have the greatest activity in the proximal region of the small intestine, due to metabolism within the GI tract. Preclinical experiments 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.(11) This degradation may reduce the amount of linaclotide available to engage GC-C receptors in the distal ileum and colon when administered as LINZESS®. Some linaclotide or its active metabolite can traverse the entire GI tract; in a Phase 1 clinical study with LINZESS®, approximately 5% of the oral dose was recovered in the feces of healthy volunteers, primarily in the form of the active metabolite. However, linaclotide is not expected to reliably reach the colon at high concentrations following oral administration of LINZESS®. MD-7246 (the DR2 formulation) may allow higher concentrations of linaclotide to be delivered to the colon, bypassing the GC-C receptors in the duodenum, jejunum, and proximal ileum (where the effects of increased luminal fluid secretion are more pronounced than in the colon, which has a higher re-absorptive capability), and avoiding degradation in the proximal small intestine.

The MD-7246 tablets consist of linaclotide tablet cores coated with pH-dependent enteric polymers that dissolve at the pH levels encountered in the distal small intestine. Once the functional delayed-release coat dissolves, the linaclotide tablet core dissolves [redacted] It is anticipated that delivery of linaclotide to the lower intestine will limit CFTR-mediated fluid secretion, thus having little impact on bowel function and stool form, and will enable the delivery of higher concentrations of linaclotide directly to interact with GC-C in the large intestine, the hypothesized source of pain for patients with IBS.

## 3.3 MD-7246 CLINICAL DEVELOPMENT

In previous clinical studies, MD-7246 was referred to as linaclotide DR2. A Phase 1 food-effect study in healthy volunteers and a Phase 2b dose-range-finding study in IBS-C patients have been performed to evaluate the 2 different DR tablet formulations ([redacted] and DR2) of linaclotide. An additional Phase 1 study was recently performed in healthy volunteers to evaluate multiple doses of the linaclotide DR2 formulation.

In the Phase 1 food-effect study (MCP-103-104) of the 2 DR tablet formulations, 16 subjects (8 Fed/Fasted; 8 Fasted/Fed) were randomized to the DR1 formulation (300 µg) and 16 subjects (8 Fed/Fasted; 8 Fasted/Fed) were randomized to the DR2 formulation (300 µg). Linaclotide and its metabolite were not quantifiable in any plasma samples from this study (lower limit of quantitation [LLOQ] of 0.100 ng/mL for both analytes) and pharmacokinetic (PK) parameters could not be calculated, confirming that systemic exposure is negligible following single, oral administration of linaclotide DR2 300 µg in healthy subjects under both fed and fasted conditions.

There were no serious adverse events (SAEs) or deaths in this Phase 1 study. All adverse events (AEs) were mild in severity. No subject discontinued due to an AE. Treatment-emergent AEs (TEAEs) were reported by 25.0% and 18.8% of linaclotide DR2 fasted and fed subjects, respectively. The most commonly reported AE in the linaclotide DR2 group was dizziness (25.0% and 0.0% of fasted and fed subjects, respectively); no other AE was reported by >1 linaclotide DR2 subject in the fed or fasted state. There were no AEs of diarrhea reported in the DR2 group, under either fed or fasted conditions. There were no clinically significant abnormal clinical laboratory, vital sign, physical examination, or electrocardiogram (ECG) results that were considered indicative of a safety concern.

The Phase 2b study (MCP-103-204) was a multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, dose-range-finding study evaluating the two DR tablet formulations of linaclotide administered once daily for 12 weeks. A total of 532 patients with IBS-C (Rome III criteria) were randomized in equal proportions to 1 of 8 treatment groups:

- Linaclotide DR1 (30 µg, 100 µg, or 300 µg)
- Linaclotide DR2 (30 µg, 100 µg, or 300 µg)
- LINZESS® (Linaclotide IR) 290 µg
- Placebo

All patients randomized to treatment (Intent-to-treat [ITT] Population) took at least 1 dose of study drug (Safety Population). Patients were instructed to take the study drug in the morning, under fasted conditions. Demographics and baseline clinical characteristics were generally similar across the treatment groups, which each included 66-67 patients. Efficacy results for the linaclotide DR2 and placebo groups and safety results for the linaclotide DR2, linaclotide IR, and placebo groups are summarized below.

As hypothesized, the linaclotide DR2 formulation had minimal effects on bowel function (frequency and stool form) but showed a signal of benefit on abdominal pain relief. Mean reductions and percent reductions from baseline in abdominal pain for all linaclotide DR2 groups were numerically greater than for the placebo group over the entire Treatment Period and at each week. All linaclotide DR2 groups showed numerically higher responder rates than the placebo group for the following abdominal pain responder endpoints: 6/12 Week Abdominal Pain Sustained Responder and 9/12 Week Abdominal Pain Responder and Sustained Responder. For change in complete spontaneous bowel movement (CSBM) frequency over the entire Treatment Period, the linaclotide DR2 groups showed no dose response, with only the lowest dose group having a numerically higher CSBM frequency compared with the placebo group. There was no dose response for any CSBM +1 responder rate for linaclotide DR2. Overall, the linaclotide DR2 formulation showed an abdominal pain relief signal with minimal to no secretory effects.

The linaclotide DR2 formulation was well tolerated and did not identify any new safety signals relative to the linaclotide IR formulation. There were no deaths reported in the study. Two patients (1 each in the placebo and linaclotide IR groups) reported a total of 3 on-therapy SAEs, (pneumonia, sepsis, and gastroenteritis) that were considered by the investigator to be unrelated to study drug. TEAEs occurred in 30.3% of placebo-treated patients, 40.9% of linaclotide IR-treated patients, and 22.4-30.3% of linaclotide DR2 patients. No TEAE was reported by ≥5% of patients in any of the linaclotide DR2 groups. Diarrhea was the most common TEAE in the study, but was reported infrequently in the placebo (1.5%) and linaclotide DR2 groups (0.0-3.0%) compared with the linaclotide IR group (13.6%). All diarrhea TEAEs were mild to moderate in severity. Diarrhea resulted in the discontinuation of 4 patients in the linaclotide IR group; no patient in the placebo or linaclotide DR2 groups discontinued due to diarrhea.

In the Phase 1 multiple-dose study (MCP-103-105) of the linaclotide DR2 formulation, 3 cohorts of 8 subjects each were randomized to receive linaclotide DR2 (6 subjects) or placebo (2 subjects) for 7 days. In total, 6 subjects each were randomized to linaclotide DR2 300, 1200, or 3000 µg or placebo. Linaclotide and its metabolite were not quantifiable in any plasma samples from this study (LLOQ of 0.100 ng/mL for both analytes) and PK parameters could not be calculated, indicating negligible systemic exposure following 7 days of oral administration of the linaclotide DR2 formulation at doses up to 3000 µg/day under fed conditions.

There were no SAEs, deaths, or AEs leading to discontinuation in this Phase 1 multiple-dose study. All AEs were mild in severity. TEAEs were reported by 16.7%, 16.7%, and 33.3% of subjects in the linaclotide DR2 300, 1200, and 3000 µg groups, respectively, and 50.0% of subjects in the placebo group. No TEAE was reported by >1 subject. TEAEs were most frequently reported in the GI disorders system organ class (SOC); 16.7% of linaclotide DR2 3000 µg subjects and 50.0% of placebo subjects reported TEAEs in the GI disorders SOC. No diarrhea TEAEs were reported.

The linaclotide DR2 formulation (hereafter referred to as MD-7246) will be evaluated in this study for the treatment of abdominal pain associated with IBS-D. This is the first study of linaclotide in IBS-D patients.

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

# 4. STUDY OBJECTIVES

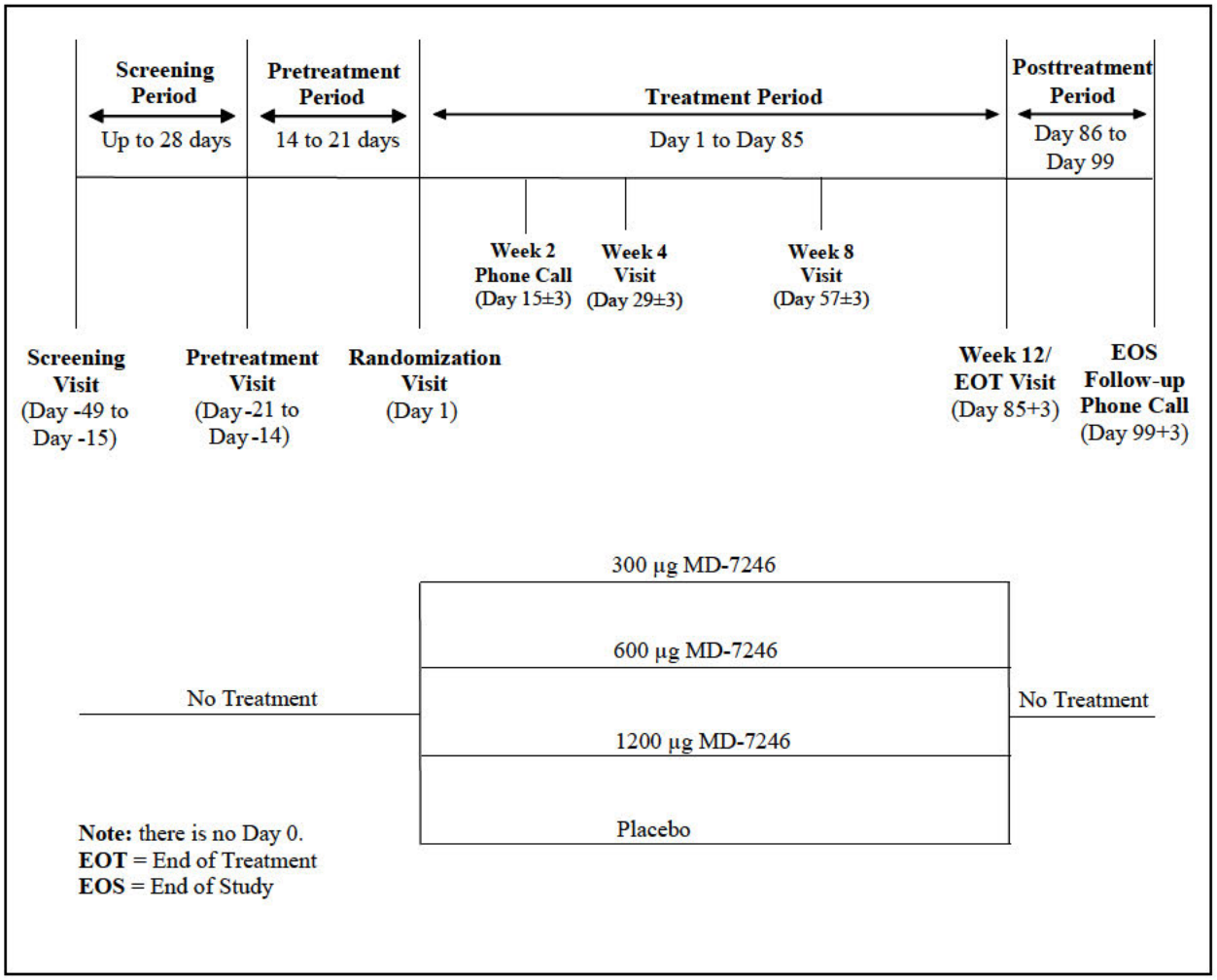
The objectives of this study are to evaluate the safety and tolerability, treatment effect on abdominal pain, and dose response of MD-7246 administered orally to patients with diarrhea-predominant irritable bowel syndrome (IBS-D). An exploratory objective of the study is to assess bowel function changes with MD-7246 in patients with IBS-D.

# 5. INVESTIGATIONAL PLAN

## 5.1 OVERALL STUDY DESIGN AND PLAN

This study is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-range-finding, 12-week study, consisting of 4 distinct periods, as illustrated in Figure 1 below. The study will enroll patients who have IBS-D diagnosed using Rome IV criteria. Eligible patients will be randomized in equal proportions to 1 of 4 treatments: 300, 600, or 1200 µg of MD-7246, or matching placebo.

**Figure 1. Overview of Study Design**



### 5.1.1 Study Periods

#### 5.1.1.1 Screening Period

The Screening Period starts with the signing of the ICF (Appendix 1) and may last for up to 28 days. During this period, patient eligibility for entry into the Pretreatment Period will be determined. Loperamide, a protocol-permitted OTC medication for diarrhea, will be distributed to eligible patients beginning at the Screening Visit. The end of the Screening Period coincides with the start of the Pretreatment Period. If the patient meets the entry criteria assessed at the Screening Visit and does not require a washout of prohibited medicines (see Appendix 2), the Screening Visit and Pretreatment Visit may be combined into one visit.

#### 5.1.1.2 Pretreatment Period

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

- Daily Assessments
  - Daily Abdominal Symptom Assessments in a daily evening report
  - Bowel Movement (BM)-related Assessments on an event-driven basis (meaning these are assessments made for each event at the time the event occurs [or during the daily evening report for any events not previously entered for that day])
- Weekly Assessments
  - Weekly Patient Assessment of Degree of Relief of IBS Symptoms
  - Weekly Patient Assessment of Adequate Relief of IBS Pain
  - Weekly Patient Assessment of BM-related Symptom Severity (patient global impression of severity [PGI-S])
  - Weekly Patient Assessment of BM-related Symptom Change (patient global impression of change [PGI-C])
- Use of Loperamide for Diarrhea on an event-driven basis

Patients who satisfy all 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 randomized in equal proportions to 1 of 4 treatments: 300, 600, or 1200 µg of MD-7246 or matching placebo. Patients will take their initial dose of study drug at the study center during the Randomization Visit. On all other days, study drug will be taken once daily at approximately the same time of day without regard to food (patients will be instructed to choose a time that is convenient for them and continue daily dosing at that time throughout the Treatment Period). Patients will continue to use the handheld eDiary to provide their:

- Daily Assessments
  - Daily Abdominal Symptom Assessments in a daily evening report
  - BM-related Assessments on an event-driven basis (meaning these are assessments made for each event at the time the event occurs [or during the daily evening report for any events not previously entered for that day])
- Weekly Assessments
  - Weekly Patient Assessment of Degree of Relief of IBS Symptoms
  - Weekly Patient Assessment of Adequate Relief of IBS Pain
  - Weekly Patient Assessment of Treatment Satisfaction
  - Weekly Patient Assessment of BM-related Symptom Severity (PGI-S)
  - Weekly Patient Assessment of BM-related Symptom Change (PGI-C)
- Use of Loperamide for Diarrhea on an event-driven basis
- Health-related quality-of-life and patient-outcome assessments (ie, Short Form-12 Health Survey version 2 [SF-12v2], EuroQol-5 Dimension [EQ-5D-3L], and Irritable Bowel Syndrome-Symptom Severity Scale [IBS-SSS]) will be performed at the Randomization Visit and at study visits throughout the Treatment Period. A list of these assessments and the visits when they will be performed is provided in the Schedule of Evaluations.

Patients will complete a Week 2 Phone Call, and Week 4, Week 8, and Week 12/End of Treatment (EOT) Visits during the Treatment Period (see Schedule of Evaluations).

#### 5.1.1.4 Posttreatment Period

The Posttreatment Period starts on the day following the last day of dosing (Week 12/EOT Visit) and finishes 2 weeks later at the End of Study (EOS) Follow-up Phone Call. During the call, patients will be asked to report any AEs and medicines taken since the Week 12/EOT Visit and detail any other symptoms or comments they may have (at the discretion of the investigator, patients may be requested to return to the study center for their EOS Follow-up).

### 5.1.2 Stopping Criteria and Data Monitoring Committee (DMC)

#### 5.1.2.1 Study Drug Discontinuation Criteria for Individual Patients

A patient will be discontinued from study drug dosing in the event of a confirmed pregnancy (see Section 8.2.1.4.2).

Dosing of study drug for an individual patient will be suspended for up to 5 days and a patient may be discontinued from study drug dosing for the following reasons:

- An SAE considered by the investigator or Sponsor to be related to study drug (per causality definitions in Section 8.2.1.2.2 and SAE definition in Section 8.2.1.1)
- Evidence of significant volume depletion and/or significant electrolyte abnormalities that are considered by the investigator or Sponsor to be associated with diarrhea related to study drug
- A vital sign and/or laboratory abnormality judged to be clinically significant by the investigator and that, in the opinion of the investigator or Sponsor, is related to study drug
- The occurrence of any other AE that, in the opinion of the investigator or Sponsor, is related to study drug and represents a clinically significant safety risk to the patient

The investigator will determine if the patient can continue in the study based on seriousness and severity of the AE and the patient's history. Procedures required for discontinued patients are detailed in Section 6.3.

#### 5.1.2.2 Overall Study Stopping Criteria

The Sponsor may stop enrollment prematurely because of low recruitment rates.

The Sponsor may suspend or terminate the study prematurely because of a change in opinion of the IRB, DMC (as detailed in Section 5.1.2.3), or a regulatory authority decision.

#### 5.1.2.3 Data Monitoring Committee

An independent DMC will regularly review safety data during the conduct of the study. Periodic safety review meetings will be scheduled when approximately 1/3 and 2/3 of patients have been randomized. The committee will review accumulated safety data, and may request unblinding of the treatment groups, in order to make any recommendations regarding the acceptability of continuing the study based on AEs reported. Details of the DMC membership, standard operational procedures for data monitoring/review, frequency of review, and other pertinent details will be provided in a separate DMC Charter.

## 5.2 RATIONALE FOR STUDY DESIGN AND CONTROL GROUP

A double-blind, placebo-controlled, parallel-group study design was chosen in accordance with the concepts in ICH E10, Choice of Control Groups and Related Issues in Clinical Trials, in order to provide comparable treatment groups and minimal chance of selection or investigator bias. The study has a 14-21 day Pretreatment Period to establish a baseline without study drug and to familiarize patients with data collection methodology (ie, eDiary), a 12-week Treatment Period to compare the test treatment to a placebo control, and a 2-week Posttreatment Period to assess safety after MD-7246 treatment has been withdrawn.

The study will evaluate the effect of the test treatment on abdominal pain in IBS-D patients. Because the test treatment is not expected to significantly affect bowel function, loperamide will be provided beginning at the Screening Visit for patients to use as needed, at the patients' discretion, to stabilize their diarrhea throughout the study; utilization of loperamide for diarrhea will be recorded on an event-driven basis.

## 5.3 STUDY DURATION

The test product and reference therapy will be administered for 12 weeks. Total patient participation will be up to 151 days, including the Screening, Pretreatment, Treatment, and Posttreatment Periods.

# 6. SELECTION OF STUDY POPULATION

## 6.1 INCLUSION CRITERIA

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

1. Patient has given consent by signing an ICF.
2. Patient is an ambulatory male or female aged 18 years or older at the Screening Visit.
3. Female patients are not pregnant and lactating females must agree not to breastfeed.
4. Female patients of childbearing potential (ie, women who are not postmenopausal or who have not had a bilateral oophorectomy, hysterectomy, or tubal ligation) who are sexually active with a male partner must agree to use one of the following methods of birth control from the date they sign the ICF until the End of Study Visit:
   a. Hormonal contraception (ie, oral contraceptive, contraceptive implant, or injectable hormonal contraceptive)
   b. Double-barrier birth control (eg, condom plus intrauterine device, diaphragm plus spermicide)
   c. Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy
5. 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.
6. Patient meets the colonoscopy requirements as defined by the American Gastroenterological Association guidelines and described in Appendix 3. (Note: Patients who receive narcotic anesthesia for a colonoscopy are eligible to enter the Pretreatment Period only on the fifth day or later after the colonoscopy.)
7. Patient meets Rome IV criteria for IBS (1): reports recurrent abdominal pain, on average at least 1 day/week during the 3 months before the diagnosis, with the onset at least 6 months before the diagnosis, associated with 2 or more of the following features:
   a. Related to defecation
   b. Associated with a change in frequency of stool
   c. Associated with a change in form (appearance) of stool

   Note: the diagnosis can be made at the Screening Visit or can be based on patient recall of symptoms that the patient had before starting chronic treatment with FDA-approved medications to treat IBS (eg, alosetron, rifaximin, or eluxadoline).

8. Patient meets the Rome IV criteria for IBS-D (1), based on stool form on days with at least 1 abnormal BM: >25% of BMs with BSFS score of 6 or 7 and <25% of BMs with BSFS score of 1 or 2.

   Note: IBS-D diagnosis should be based on the patient's BM abnormalities when the patient is not taking medications to treat his/her BM abnormalities.
9. Patient has an average score for abdominal pain at its worst of ≥4.0 and ≤9.0, as reported in the eDiary using an 11-point numerical rating scale (NRS) during the 14 days before the Randomization Visit and including the eDiary entry made in clinic at the Randomization Visit prior to randomization.
10. Patient is compliant (as defined in the study procedures section below) with eDiary completion by adequately responding to eDiary questions (ie, completing the daily evening report) on 10 or more of the 14 days before the Randomization Visit.
11. Patient is able to swallow solid, oral dosage forms whole with the aid of liquid (patient may not chew, divide, crush, or dissolve the study drug).
12. Patient is fluent in English or Spanish.
13. Patient agrees to refrain from making any new, major lifestyle changes that may affect IBS symptoms (eg, starting a new diet or changing his or her exercise pattern) from the time of signature of the ICF to the last study visit.

## 6.2 EXCLUSION CRITERIA

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

1. Patient has a known or suspected structural abnormality of the gastrointestinal (GI) tract (eg, mechanical gastrointestinal obstruction) or a disease or condition that can affect GI motility.
2. Patient has clinically significant concurrent illness or findings on a physical examination or clinical laboratory tests (clinical chemistry panel, complete blood count [CBC]) after signing the ICF but before receiving the first dose of study drug. (Note: The investigator will determine if a finding is clinically significant. In making this determination, the investigator will consider whether the finding could prevent the patient from performing any of the protocol-specified assessments, represent a condition that would exclude the patient from the study, represent a safety concern if the patient participates in the study, or confound the study-specified assessments of safety or efficacy.)
3. Patient has a positive drug or alcohol screen, including testing positive for marijuana or other drugs that target the endocannabinoid system, such as dronabinol.
4. Patient has been diagnosed with or has a family history of familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, or any other form of familial colorectal cancer.

5. Patient has a history of inflammatory or immune-mediated GI disorders, including inflammatory bowel disease (IBD) and symptomatic biopsy- or serology-positive celiac disease.
6. Patient has symptomatic lactose intolerance, symptomatic non-celiac gluten sensitivity, or other malabsorption syndrome.
7. Patient currently has clinically significant symptoms such as lower GI bleeding (rectal bleeding or heme-positive stool), iron-deficiency anemia, weight loss, or systemic signs of infection or colitis.
8. Patient has any chronic condition with ongoing symptoms that can be associated with abdominal pain or discomfort and could confound the assessments in this study (eg, diverticulitis, ileus, active peptic ulcer disease, uncontrolled gastroesophageal reflux disease, gastroparesis, chronic pancreatitis, polycystic kidney disease, ovarian cysts, endometriosis, urological pain).
9. Patient has a history of intestinal obstruction, toxic megacolon, megarectum, descending perineum syndrome, solitary rectal ulcer syndrome, systemic sclerosis, multiple sclerosis, Parkinson's disease, spinal cord injury.
10. Patient has ever had a fecal impaction that required hospitalization or emergency room treatment, or has a history of cathartic colon, ischemic colitis, or pelvic floor dysfunction (unless successful treatment has been documented by a normal balloon expulsion test).
11. Patient has currently documented positive stool tests for enteric pathogens, ova or parasites.
12. Patient has a history of a microbiologically documented lower GI infection (eg, Clostridium difficile colitis) or received treatment for a microbiologically documented lower GI infection during the 3 months before the Screening Visit.
13. Patient has a history of hypersensitivity to linaclotide, any of the excipients contained in the study drug (MD-7246 or placebo) as described in Section 7.1, or loperamide.
14. 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 (including cholecystectomy), pelvis, or retroperitoneal structures during the 6 months before the Screening Visit, or during the 3 months before the Screening Visit for laparoscopic surgery
    c. Other major surgery, including appendectomy, during the 3 months before the Screening Visit
15. 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 if the malignancy has been in a

complete remission for at least 3 years before the Randomization Visit. A complete remission is defined as the disappearance of all signs of cancer in response to treatment.)

16. Patient has a history of diabetic neuropathy.
17. Patient has a history of human immunodeficiency virus infection.
18. 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.
19. 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 if they have exhibited no actual abuse during the 12 months before the Randomization Visit.)
20. Patient has a history or current evidence of laxative or opioid abuse.
21. Patient has been hospitalized for a major psychiatric condition or has made a suicide attempt during the 2 years before the Randomization Visit.
22. Patient has received an investigational drug during the 30 days before the Screening Visit.
23. Patient reported using a Prohibited Medicine during the Screening or Pretreatment Period, does not meet all the Prohibited Medicine criteria, or is not willing or able to abide by the restrictions regarding use of Prohibited Medicines, as detailed in Appendix 2.
24. 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.
25. Patient has previously entered the Pretreatment Period of this study.
26. Patient is directly or indirectly involved in the conduct and administration of this study as an investigator, sub-investigator, study coordinator, other study staff member, or employee of Ironwood Pharmaceuticals or Allergan; 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.

## 6.3 DISCONTINUATION 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. In addition to the individual discontinuation criteria detailed in Section 5.1.2.1, 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 (Screening or Pretreatment Failure)
- 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
- 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 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) 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 5 days should an intolerable AE occur. If the investigator believes that the patient is unable to resume dosing or requires a temporary suspension of dosing on more than 1 occasion, the investigator should contact the Medical Monitor to discuss the patient's continued participation in the study.

## 6.4 REPLACEMENT PROCEDURES

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

# 7. TREATMENTS

## 7.1 TREATMENTS ADMINISTERED

Study drug in the form of oral tablets will be provided by [redacted] on behalf of Ironwood Pharmaceuticals. For the double-blind Treatment Period, patients will be supplied with identically appearing tablets containing MD-7246 (linaclotide DR2; 300 µg) and/or placebo (packaged as described in Section 7.2), to be administered once daily in a double-blind manner as follows:

- MD-7246 300 µg group: 1 MD-7246 (linaclotide DR2) 300-µg oral tablet and 3 matching placebo oral tablets
- MD-7246 600 µg group: 2 MD-7246 (linaclotide DR2) 300-µg oral tablets and 2 matching placebo oral tablets
- MD-7246 1200 µg group: 4 MD-7246 (linaclotide DR2) 300-µg oral tablets
- Placebo group: 4 matching placebo oral tablets

[redacted]

## 7.2 IDENTITY AND STORAGE OF INVESTIGATIONAL PRODUCT

All study drug will be supplied in blinded cartons containing five 4x7 blister cards, a total of thirty-five (35) days of study drug doses per carton. Each blister card will contain 7 days of study drug doses (a total of 28 tablets of MD-7246 [labeled as linaclotide DR2] 300 µg and/or matching placebo, as described in Section 7.1); patients will take 1 row of tablets (4 tablets) each day, as clearly marked on the blister card. Blister strips will be manufactured using Dessiflex® desiccated film and assembled into cardstock for the blister cards. Blister cards and cartons will be uniquely numbered and labeled in a double-blind fashion that conforms to regulatory requirements.

All study drug will be provided by [redacted] on behalf of Ironwood Pharmaceuticals. MD-7246 (labeled as linaclotide DR2) and matching placebo tablets will be stored at refrigerated conditions at the study center in an appropriate secure, temperature-controlled area at 36-46°F (2-8°C), with excursions permitted up to 77°F (25°C) for up to 24 hours. 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.

Patients will be instructed to store study drug at room temperature (68-77°F [20-25°C]).

## 7.3 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUPS

The patient identification (PID) number will consist of 7 digits; the first 3 digits represent the study center number, followed by a 1-digit study indicator (‘5’) and a 3-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 and Posttreatment Periods.

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 368 patients will be randomized to 1 of 4 treatments: MD-7246 300, 600, or 1200 µg or placebo (1:1:1:1), as described in Section 7.1. Randomization numbers will be assigned by IWRS.

## 7.4 SELECTION OF DOSAGE IN THE STUDY

This protocol is intended to evaluate the safety and tolerability, treatment effect on abdominal pain, and dose response of MD-7246 (previously referred to as linaclotide DR2) in IBS-D patients. The doses of MD-7246 were selected based on safety and tolerability results from prior clinical experience with this DR formulation of linaclotide and nonclinical pharmacology models of visceral pain.

In the Phase 1 PK/pharmacodynamic (PD) study MCP-103-105, linaclotide DR2 was well tolerated by 18 healthy subjects when administered for 7 days at doses of 300, 1200, and 3000 µg per day (6 subjects at each dose); AEs for linaclotide DR2 subjects were similar to placebo and all AEs were mild in severity. The 300-µg dose was also well tolerated in 2 prior clinical studies: as a single dose in 16 healthy subjects in the Phase 1 PK and food effect study MCP-103-104, and as chronic dosing (once daily for 12 weeks) in 66 IBS-C patients in the Phase 2b study MCP-103-204.

Linaclotide binds the GC-C receptor on human intestinal epithelial cell lines (T84 cells) at both high-affinity ($K_{i1}$ of 1.23 nM) and low-affinity ($K_{i2}$ of 156 nM) sites with high specificity. Binding of linaclotide to human intestinal (T84) cells stimulates cGMP production in a concentration-dependent manner, with a half maximal effective concentration ($EC_{50}$) of about 100 nM. A dose of 300 µg of linaclotide administered to the colon in humans will result in localized concentrations 2- to 10-fold the $EC_{50}$ of linaclotide. Efficacy was observed on non-clinical models of visceral hypersensitivity at doses of 2.5 µg/kg, which is a human equivalent of approximately 300 µg.

The 600-µg and 1200-µg doses of MD-7246 were selected as incremental steps from the 300-µg dose to allow for evaluation of dose response in efficacy. Based on the safety and tolerability at doses up to 3000 µg in healthy subjects, the planned MD-7246 doses of 300, 600, and 1200 µg are expected to be safe and well tolerated in IBS-D patients.

## 7.5 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, Pretreatment, and Randomization Visits will be randomized to treatment at the Randomization Visit (as described in Section 7.3; randomization number assigned by IWRS) and dispensed a carton with 5 blister cards, each containing 28 tablets (140 tablets total). Additional blister cards will be dispensed at subsequent visits per the Schedule of Evaluations. Patients will take their initial dose of study drug (1 row of tablets from the blister card; 4 tablets) at the study center during the Randomization Visit. For the remainder of the Treatment Period, patients will be instructed to take 1 row of tablets (4 tablets) from the blister card each day, at approximately the same time of day without regard to food (patients will be instructed to choose a time that is convenient for them and continue once-daily dosing at that time throughout the Treatment Period). Patients will be instructed to return all unused study drug and blister cards to the study center at the visits defined in the Schedule of Evaluations.

The investigator may allow a patient to stop taking study drug for up to 5 days should an intolerable AE occur, as described in Section 6.3.

## 7.6 BLINDING

The Sponsor study personnel, the investigator and all other site study personnel, and the patient will remain blinded to individual patient treatment assignments throughout the study. Specific designated personnel in the Global Patient Safety (GPS) group at Ironwood may be unblinded to the treatment assignment of individual patients for regulatory reporting purposes.

Patient randomization codes for the Treatment Period will be generated by Allergan and implemented by the IWRS vendor (an electronic version will be stored on a secure server). The randomization list will identify each patient by randomization number and include the patient's corresponding treatment assignment. The medication code list will be supplied by [redacted] to the IWRS vendor.

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 Sponsor immediately. An explanation for breaking the blind will be recorded on the relevant eCRF. Breaking the blind at the study center will disqualify the patient from further participation in the study (refer to Section 6.3 for details regarding procedures and follow-up for patients who are discontinued from therapy).

## 7.7 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 is provided in Appendix 2. Throughout the study (Screening Period through Posttreatment Period), patients will be allowed to use loperamide to assist in managing their diarrhea. Loperamide 2-mg caplets will be provided to the patient at study visits to use as needed (at the patient's discretion) to manage their diarrhea throughout the study. Patient dosing of loperamide should not exceed 16 mg/day (8 unit doses), consistent with the product label. Beginning at the Pretreatment Visit (when the patients receive the eDiary) through the Week 12/EOT Visit, the day and dose will be entered by the patient for each use of loperamide on an event-driven basis.

At the Screening Visit, all ongoing medicines or investigational products taken by the patient will be recorded. Past use of certain prescription medications (approved or unapproved) to manage IBS symptoms (including alosetron [Lotronex®], rifaximin [Xifaxan®], and eluxadoline [Viberzi®]), even if not ongoing at the time of the Screening Visit, will be recorded at the Screening Visit.

Prescription medications used to treat IBS-D may not be used during the 4 weeks (28 days) before the Pretreatment Visit (or during the 3 months before the Pretreatment Visit for rifaximin). OTC medications used to treat IBS-D, other than loperamide, may not be used during the study (from the time of the Screening Visit through the EOS Follow-up Phone Call). Other prohibited medicines may not be used during the Pretreatment, Treatment, and Posttreatment Periods, and may not be used during some or all of the Screening Period (refer to Appendix 2). Any changes in concomitant medicines or new medicines added after the Screening Visit will be recorded on the eCRF. Concomitant medicines will be recorded at study visits throughout the entire study. Use of loperamide for diarrhea will be documented by the patient via eDiary.

## 7.8 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 at approximately the same time of day without regard to food.

Study drug accountability will be closely monitored during the Treatment Period by counting the number of tablets returned and recording that information on the eCRF. Every effort will be made to collect all unused study drug. Additionally, patients will be asked about the number of tablets lost and that information will be recorded on the eCRF.

# 8. STUDY PROCEDURES AND ASSESSMENTS

## 8.1 EFFICACY ASSESSMENTS

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. Event-driven and daily assessments of abdominal and bowel symptoms will be collected using the Diary of IBS Symptoms - Diarrhea (DIBSS-D; Appendix 4).

### 8.1.1 Key Efficacy Assessment

The efficacy assessment that will be used to determine the key efficacy endpoints (Section 10.4.1) is the daily patient assessment of abdominal pain at its worst.

***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">*

### 8.1.2 Additional Efficacy Assessments

The efficacy assessments that will be used to determine the additional efficacy endpoints are the daily patient assessments of abdominal pain at its worst (as described in Section 8.1.1), and abdominal bloating, abdominal discomfort, and abdominal cramping at their worst; and weekly patient assessments of degree of relief of IBS symptoms, adequate relief of IBS pain, and treatment satisfaction.

***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">*

***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 Cramping at its Worst***

Patient assessment of abdominal cramping at its worst will be collected via a daily evening report in the eDiary. The rating of abdominal cramping 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 cramping in the past 24 hours?"

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

***Weekly Patient Assessment of Degree of Relief of IBS Symptoms***

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

"Compared to before you started the study, how would you rate your IBS symptoms during the past 7 days?"

1=Significantly relieved
2=Moderately relieved
3=Somewhat relieved
4=Unchanged
5=Somewhat worse
6=Moderately worse
7=Significantly worse

***Weekly Patient Assessment of Adequate Relief of IBS Pain***

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

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

1=Yes
2=No

***Weekly Patient Assessment of Treatment Satisfaction***

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

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

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

### 8.1.3 Exploratory Assessments

In addition to the key/additional efficacy assessments, the following non-efficacy exploratory assessments are used in determining the exploratory endpoints.

Each day of the Pretreatment and Treatment Periods, the patient will complete eDiary entries on an event-driven basis to report BMs. (The patient is also asked to provide assessments of stool consistency and urgency, which are described below.) The patient will also complete eDiary entries on an event-driven basis to report use of loperamide for diarrhea. Patients will complete a daily evening report to enter any BMs and loperamide usage not previously reported by the patient for that day (recall is limited to 24 hours or to the time of the previous evening's report).

***Bowel Movement Frequency***

The assessment of BM frequency is based on the eDiary questions that record BM date 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.

***Stool Consistency (5-point ordinal scale)***

Patient assessment of stool consistency will be collected using 2 questions by eDiary entry on an event-driven basis (ie, for each BM reported in the eDiary).

For each BM, patients will assess stool consistency by daily eDiary entry on an event-driven basis using a 5-point ordinal scale:

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

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

The patient also assesses his/her stool consistency using the 7-point BSFS described below.

***Stool Consistency (BSFS)***

In addition to the patient assessment of stool consistency using the 5-point ordinal scale (described above), the patient assesses the stool consistency of each BM by daily eDiary entry on an event-driven basis using the BSFS (Appendix 5), 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.(12) The 7-point ordinal BSFS is provided below (see Appendix 5 for full scale including pictures):

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

1=Separate hard lumps like nuts (difficult to pass)

2=Like a sausage but lumpy

3=Like a sausage but with cracks on the surface

4=Like a sausage or snake, smooth and soft

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

6=Fluffy pieces with ragged edges, a mushy stool

7=Watery, no solid pieces (entirely liquid)

***BM Urgency***

Patient assessment of BM urgency will be collected by eDiary entry on an event-driven basis (ie, for each BM reported in the eDiary). For each BM, urgency will be assessed by the patient using a binary scale:

"Did you feel the need to rush to the toilet in order to avoid an accident before your bowel movement?"

1=Yes

2=No

***Use of Loperamide for Diarrhea***

Patients will report use of loperamide (Imodium®) for diarrhea on an event-driven basis (ie, for each use of the medication). An evening report will ask whether the patient entered all loperamide use for that day and collect all loperamide use not previously entered for that day (recall is limited to 24 hours or to the time of the previous evening's report).

"Did you use Imodium® (loperamide) for diarrhea that you have not yet reported in the Diary?"

1=Yes

2=No

"Was the Imodium® (loperamide) taken yesterday or today?"

1=Yesterday
2=Today

"How many Imodium® (loperamide) pills did you take?"

__ pill(s)

***Weekly Patient Assessment of Bowel Movement-related Symptom Severity***

Patient global impression of severity (PGI-S) of BM-related symptoms will be reported weekly by eDiary entry. The rating of BM-related symptom severity during the previous 7 days on a 5-point ordinal scale will be provided by the patient answering the following question:

"How would you rate your bowel movement-related symptoms during the past 7 days?"

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

***Weekly Patient Assessment of Bowel Movement-related Symptom Change***

Patient global impression of change (PGI-C) of BM-related symptoms will be reported weekly by eDiary entry. The rating of BM-related symptom change during the previous 7 days on a 7-point ordinal scale will be provided by the patient answering the following question:

"Compared to before you started the study, please rate the overall change in your bowel movement-related symptoms during the past 7 days."

1=Very much better

2=Moderately better

3=A little better

4=No change

5=A little worse

6=Moderately worse

7=Very much worse

### 8.1.4 Health Economics and Outcomes Research Assessments

***Pain Catastrophizing Scale***

The Pain Catastrophizing Scale is an instrument for assessing catastrophic thinking related to pain and consists of 13 questions assessing the following 3 dimensions: rumination, magnification, and helplessness (Appendix 6).(13) The Pain Catastrophizing Scale will be completed at the Pretreatment Visit as specified in the Schedule of Evaluations; the assessment will be triggered by site personnel on the patient's eDiary for the questionnaire to be self-administered by the patient.

***Short Form-12 Health Survey version 2 (SF-12v2)***

The SF-12v2 is a widely used generic measure of health status (Appendix 7).(14) The SF-12v2 measures 8 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 8 scales are aggregated into 2 summary measures: the Physical and Mental Component Summary Scores. The SF-12v2 will be completed at the Randomization Visit prior to the patient receiving study drug and at subsequent visits as specified in the Schedule of Evaluations. At each of the designated visits, the assessment will be triggered by site personnel on the patient's eDiary for the questionnaire to be self-administered by the patient.

***EuroQol-5 Dimension 3-level (EQ-5D-3L)***

The EQ-5D-3L is a generic measure of health status that is widely used in Europe (Appendix 8).(15) The descriptive system consists of 5 questions assessing the following dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Responses to the 5 questions define a health state for which a utility index can be derived from published algorithms.(16) The second component of the EQ-5D-3L is a visual analogue scale, asking patients to rate their health from 0 to 100 (0 represents worst imaginable health state and 100 represents best imaginable health state). The EQ-5D-3L will be completed at the Randomization Visit prior to the patient receiving study drug and at subsequent visits as specified in the Schedule of Evaluations. At each of the designated visits, the assessment will be triggered by site personnel on the patient's eDiary for the questionnaire to be self-administered by the patient.

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

The IBS-SSS contains 7 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 (Appendix 9).(17) The IBS-SSS will be completed at the Randomization Visit prior to the patient receiving study drug and at subsequent visits as specified in the Schedule of Evaluations. At each of the designated visits, the assessment will be triggered by site personnel on the patient's eDiary for the questionnaire to be self-administered by the patient.

### 8.1.5 Completion of eDiary Assessments

To ensure patient compliance with the completion of the evening eDiary report, alarms occurring at 7, 8, 9, 10, and 11 PM will be programmed to alert the patient that he/she has not completed the evening eDiary report. Upon completion of the evening eDiary report, the alarm will no longer be active for the remainder of that day. If the patient does not complete the evening report prior to midnight, that day's evening report will no longer be available for reporting by the patient and all evening assessments for that day will be considered missing.

Patient compliance with the daily eDiary completion requirement will be verified by site staff as specified in the Schedule of Evaluations.

## 8.2 SAFETY ASSESSMENTS

Safety will be evaluated by AE reports (discussed herein), standard clinical laboratory assessments, vital signs, physical examinations, and medical history. Planned timepoints for all safety assessments are provided in the Schedule of Evaluations.

### 8.2.1 Adverse Events

#### 8.2.1.1 Definitions

Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

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.

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

Serious Adverse Event

An AE is considered “serious” if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Death
- Life-threatening experience: An AE is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of an existing hospitalization: AEs requiring hospital admissions that are less than 24 hours in duration do not meet this criterion. A scheduled hospitalization for a preexisting condition that has not worsened during participation in the study does not meet this criterion. Preplanned hospitalizations for an elective medical/surgical procedure or routine check-ups do not meet this criterion.

- Persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly or birth defect
- Is considered to be an important medical event: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they 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.

Treatment-emergent Adverse Event

A TEAE is an event that emerges, or a preexisting event that worsens, any time after administration of the first dose of study drug (Day 1).

#### 8.2.1.2 Classification of an Adverse Event

8.2.1.2.1 Severity

The investigator or delegated physician will provide an assessment of the severity of each AE by recording a severity rating in the patient's source documentation and on the AE page 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**: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

**Moderate**: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research participant.

**Severe**: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

AEs should be recorded using the maximum intensity of the event (eg, if a patient reported nausea lasting 3 days, 1 start date and 1 stop date should be recorded along with the maximum intensity experienced for that event over that 3-day timeframe).

#### 8.2.1.2.2 Relationship to Study Drug

For all AEs, the investigator must provide an assessment of causal relationship to study drug. The investigator must assess the relationship of each AE (including SAEs) to the use of a study drug using a 2-category scale (not related or related) based on clinical judgment and using all available information, and may include consideration of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, preexisting conditions, concomitant use of other drugs, and presence of environmental or genetic factors
- The temporal association between drug exposure and onset of the AE
- Whether the manifestations of the AE are consistent with known actions or toxicity of the investigational product
- Whether the AE resolved or improved with stopping use of the study drug; judgment should be used if multiple products are discontinued at the same time

The causality assessment must be recorded in the patient's source documentation and on the AE page of the patient's eCRF. The causal relationship between study drug and the AE will be assessed using the categories shown in Table 1.

**Table 1. Adverse Event Causality**

| Category | Definition |
|---|---|
| Not related | An AE is not associated with study medication if:<br>- Lack of a temporal relationship to study drug administration makes a causal relationship improbable (eg, the event did not occur within a reasonable time frame following administration of the study medication); and/or<br>- Other causative factor(s) (eg, a preexisting clinical condition, other concomitant treatments) more likely explain the occurrence of the event, and<br>- The event did not improve with stopping of the investigational product, and/or<br>- The event did not recur upon re-exposure with investigational product |
| Related | An AE is attributed to the study medication if:<br>- A temporal relationship to study drug administration makes a causal relationship plausible (eg, the event occurred within a reasonable time frame following administration of study medication); and/or<br>- Other causative factor(s) (eg, the patient's clinical condition, other concomitant treatments) either do not explain the event or are less equally likely to have led to the occurrence of the event, or<br>- The event improved with stopping of the investigational product, and/or<br>- The event recurred upon re-exposure with investigational product |

8.2.1.2.3 Laboratory and Vital Sign Abnormalities

The investigator will review clinical laboratory and vital sign values for significance and consideration as an AE. An abnormality should be captured as an AE if it meets any of the following criteria:

- Meets criteria for an SAE
- Results in discontinuation or temporary dose suspension
- Requires the patient to receive specific corrective therapy
- Is considered by the investigator to be clinically significant

Ongoing abnormal laboratory/vital sign values or conditions that are being treated at baseline will be captured as an AE if the condition increases in severity and/or frequency during the course of the study or if the condition requires more frequent treatment. If a patient is treated for an abnormal laboratory/vital sign value just before the Screening Visit, then the medical history should reflect the severity of the condition before treatment.

#### 8.2.1.3 Procedures for Recording Adverse Events

The investigator will record all AEs from the time informed consent is obtained until completion of study participation (eg, early termination or EOS Follow-up Phone Call). At each study visit, the investigator will inquire about the occurrence of AEs/SAEs since the last visit.

The occurrence of an AE or SAE may come to the attention of study center personnel during study visits and interviews of a study patient presenting for medical care, or upon review by a site monitor. All AEs including SAEs will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study drug (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All SAEs will be followed to adequate resolution or stabilization for up to a maximum of 30 days after last dose.

Any medical condition that is present at the time that the patient is screened and does not deteriorate (worsen in severity and/or frequency) should be recorded as Medical History and not as an AE. However, if the patient's condition deteriorates at any time during the study, it will be recorded as an AE. AEs characterized as intermittent require documentation of onset and duration of each episode.

Pretreatment AEs will be collected and captured in the patient's source documentation from the time the patient signs the ICF until the patient receives study drug. Pretreatment AEs in randomized patients will additionally be entered on the AE page of the patient's eCRF.

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

#### 8.2.1.4 Procedures for Collecting and Reporting Serious Adverse Events

The investigator or designee is to report any SAE to PPD within 24 hours of becoming aware of the event that occurred during the reporting period.

All SAEs will be submitted within the EDC system. The system will prompt the Investigator or designee to provide as much information as possible, including the following:

- SAE term
- Serious criteria
- Severity
- Causality assessment
- Action taken with study drug
- Narrative explaining the context of the SAE outcome

If all SAE information is not available at the time of the initial report, follow-up SAE reports will be completed and submitted within the same reporting timelines as initial reports using the EDC system. If the EDC system is not available, the investigator or designee will complete the hard-copy SAE form, including all of the required information noted above. The completed form should then be provided to PPD using the contact information below:

[redacted]

The investigator or designee should receive email confirmation from PPD that the SAE information was received within 24 hours after its submission (whether submitted via EDC or hard-copy form). In the event this receipt confirmation is not received, the investigator or designee will alert PPD.

The investigator or designee is required to follow SAEs until resolution or stabilization for up to a maximum of 30 days after last dose. Resolution is defined as:

- Resolved with or without residual effects (sequelae)

- A return to baseline for a preexisting condition
- The investigator does not expect any further improvement or worsening of the event
- Fatal outcome: If an autopsy is performed on a deceased patient, the autopsy report and death certificate must be provided to PPD as soon as it is available.

#### 8.2.1.4.1 Reporting of SAEs to the IRB

The investigator will receive prompt notification of SAEs, with the use of the study product, that are both unexpected and related, or any finding that suggests a significant risk for patients. The investigator will promptly inform the IRB of the notification and insert the notification in the Investigator's Regulatory Binder in accordance with local regulations.

All applicable expedited safety reports will be forwarded, by Ironwood, to the investigator.

The investigator will inform Ironwood of any local regulatory or IRB requirements not covered by the procedures in this or the prior section.

#### 8.2.1.4.2 Reporting of Pregnancy

Any female patient who becomes pregnant while participating in the study will be withdrawn from the study.

Information on any pregnancies in female patients, or the female partner of a male patient, will be collected from the Screening Visit until the completion of the EOS Follow-up Phone Call.

If the patient or the female partner of a male patient becomes pregnant after receiving study drug during the course of study, the investigator will collect and record the pregnancy information on the Pregnancy Reporting Form and submit it to PPD within 24 hours of learning of the pregnancy. (Note: If the female partner of a male patient becomes pregnant, the investigator must attempt to obtain consent to collect pregnancy information [including status of the newborn, if applicable] before reporting information to Ironwood). If not all information on the Pregnancy Reporting Form is available at the time of the initial report, follow-up Pregnancy Reporting Forms will be completed and submitted within 24 hours of becoming aware of new information.

The investigator is required to attempt follow-up on the pregnancy until the completion of the pregnancy. Information on the status of the mother and newborn will be forwarded to PPD within 24 hours of the investigator becoming aware. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.

While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be an SAE and reported as such. A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as a result of a post-study pregnancy and considered reasonably related to the investigational product by the investigator, will be reported to PPD using the hard-copy SAE form as described in Section 8.2.1.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

### 8.2.2 Clinical Laboratory Determinations

See below for the list of clinical laboratory tests to be performed and refer to the Schedule of Evaluations for the timing and frequency. All protocol-required laboratory assessments, as defined below, must be conducted in accordance with the laboratory manual and the Schedule of Evaluations.

The tests detailed below will be performed (additional tests may be performed at any time during the study as determined necessary by the investigator or as required by local regulations):

- **Hematology**: Absolute and differential white blood cell count, erythrocyte count, hemoglobin, hematocrit, platelet count, and red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration)
- **Chemistry**: Sodium, magnesium, potassium, calcium, chloride, glucose, blood urea nitrogen, creatinine, total protein, alkaline phosphatase, albumin, total bilirubin, aspartate aminotransferase, alanine aminotransferase, bicarbonate, phosphate, cholesterol, and uric acid

- **Other**: Urine drug screening (cocaine, barbiturates, amphetamines, opiates, benzodiazepine, alcohol, and cannabinoids) (Screening Visit only). By definition, a positive drug screen (including testing positive for marijuana in states where marijuana is legalized) is clinically significant and, therefore, exclusionary.
- **Pregnancy test**: Serum human chorionic gonadotropin pregnancy test (for women of childbearing potential only) should be conducted at the Screening Visit and Week 12/EOT Visit. A negative urine pregnancy test must be documented at the Randomization Visit for women of childbearing potential 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.

The investigator must review each laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. All laboratory tests with abnormal values considered clinically significant during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or Medical Monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified. If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the investigator (eg, SAE or AE or study drug discontinuation), the results must be recorded in the eCRF.

### 8.2.3 Vital Signs

Vital sign measurements will be performed as outlined in the Schedule of Evaluations. Oral temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure (BP) will be assessed with the patient in a seated position. BP and pulse measurements will be assessed with a completely automated device; manual techniques will be used only if an automated device is not available.

BP and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones).

### 8.2.4 Physical Examination

A complete physical examination will be performed as outlined in the Schedule of Evaluations, 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 complete physical examination will include, at a minimum, assessment of the general appearance of the patient and the HEENT (head, eyes, ears, nose, and throat), cardiac, respiratory, gastrointestinal, musculoskeletal, neurological, and dermatological systems. Height (only at screening) and weight will also be measured and recorded.

Rectal examinations should be performed at the discretion of the investigator; the purpose of the rectal examination is to rule out pathologies that might be caused by obstruction. For all physical examinations, the breast and genitourinary examinations are not required.

### 8.2.5 Medical History

A complete medical history, including disease-specific history, will be provided by the patient at the Screening Visit.

As part of their disease-specific history, patients will be asked about any prior IBS diagnosis.

Patients will be enrolled based on the Rome IV criteria for IBS-D, as detailed in Section 6.1 and described below.

Patient reports recurrent abdominal pain, on average at least 1 day/week during the 3 months before the diagnosis, with the onset at least 6 months before the diagnosis, associated with 2 or more of the following features:

a. Related to defecation
b. Associated with a change in frequency of stool
c. Associated with a change in form (appearance) of stool

According to the Rome IV criteria, patients are subtyped as IBS-D if they have >25% of BMs with BSFS score of 6 or 7 and <25% of BMs with BSFS score of 1 or 2, based on stool form on days with at least 1 abnormal BM.

### 8.2.6 Required Investigator Consultation with the Patient

Patients will be allowed use of loperamide on an as-needed basis to control their diarrhea. Throughout the Pretreatment and Treatment Periods, the eDiary will send automated alerts to the investigator if patients experience constipation with excessive use of loperamide or diarrhea that is not well managed with the use of loperamide, as described below.

If a patient reports no BMs for ≥3 consecutive days with daily use of loperamide, the investigator must review the use of loperamide and pattern of constipation with the patient. An unscheduled visit to further evaluate the patient should be arranged if deemed necessary by the investigator. The decision to continue, interrupt, or permanently discontinue study drug will be left to the discretion of the investigator on a patient-by-patient basis.

If the eDiary alert indicates that a patient took ≥8 unit doses (≥16 mg) of loperamide in a 24-hour period for ≥5 consecutive days, the investigator must review the use of loperamide and pattern of diarrhea with the patient. An unscheduled visit to further evaluate the patient should be arranged if deemed necessary by the investigator. The decision to continue, interrupt, or permanently discontinue study drug due to excessive use of loperamide will be left to the discretion of the investigator on a patient-by-patient basis.

# 9. DATA QUALITY ASSURANCE

## 9.1 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 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.

## 9.2 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 (eg, 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 [redacted], 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.

# 10. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

## 10.1 ANALYSIS POPULATIONS

### 10.1.1 Screened Population

The Screened Population consists of all patients who had a Screening Visit (Visit 1) and were assigned a PID number.

### 10.1.2 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population consists of all randomized patients.

### 10.1.3 Safety Population

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

## 10.2 GENERAL METHODS

Efficacy analyses will be performed on the ITT Population for all outcomes reported during the Treatment Period using treatment group assigned at the Randomization Visit. Unless otherwise specified, all confidence intervals (CIs) will be 2-sided and with a confidence level of 95%. No adjustments will be made for multiplicity in the conduct of comparisons among the MD-7246 doses relative to placebo for the key efficacy endpoints, or in the analysis of the additional efficacy endpoints or exploratory endpoints. Safety analyses will be performed using descriptive summaries based on the Safety Population and on actual treatment received.

For analysis of continuous parameters (eg, change from baseline), descriptive statistics (n, mean, standard deviation [SD], median, and range) will be calculated and presented for each treatment group. For categorical parameters (eg, responder vs. non-responder), the number and percentage of each category will be calculated and presented for each treatment group. Percentages will be based on the total number of non-missing values; the number missing will be presented, but without a percentage.

### 10.2.1 Patient Disposition

Screen failures (ie, patients who entered the Screening Period but not the Pretreatment Period) and pretreatment failures (ie, patients who entered the Pretreatment Period but were not randomized) and reason for failure will be tabulated.

Patient counts for the ITT Population will be provided by study center and geographic region.

Descriptive summaries will be presented for the ITT Population, the Safety Population, for those who completed the Treatment Period and for those who prematurely discontinued during the Treatment Period, along with the reason for premature discontinuation as recorded on the study completion form. Additionally, similar summaries will be provided for those who completed the study (ie, completed the Treatment Period and 2-week Posttreatment Period) and for those who discontinued prior to completing the study.

### 10.2.2 Demographics and Baseline Characteristics

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

### 10.2.3 Protocol Deviations

Protocol deviations and Important Protocol Deviations (IPD) will be identified and documented for all ITT patients prior to unblinding. IPDs will be determined based on blinded review of all protocol deviations and protocol deviation categories. IPD categories include, but are not limited to:

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

### 10.2.4 Prior and Concomitant Medicines

Prior and concomitant medicines will be classified using the most current version of the WHO Drug Dictionary available at the start of the study (or newer).

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. Posttreatment medicines are defined as any medicines started after the date of last dose of study drug for the Treatment Period.

Both prior and concomitant medicine use, classified by therapeutic class, will be summarized by treatment group 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.

Posttreatment medicines will be presented in data listings.

## 10.3 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

### 10.3.1 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, will be summarized by treatment group for the Safety Population.

### 10.3.2 Measurement of Treatment Compliance

Dosing compliance for a specified period is defined as the total number of tablets actually taken by a patient during that period divided by the number of tablets that were expected to be taken during the same period, multiplied by 100. The total number of tablets actually taken will be calculated based on the following equation: total number of tablets dispensed – (number of tablets returned + number of tablets lost). The total number of tablets expected to be taken during a specified period equals the number of days in the period, multiplied by 4.

Descriptive statistics for study drug compliance for the Treatment Period overall, and for each of the 3 consecutive 4-week periods in the Treatment Period (consistent with study drug dispensing) will be presented for the Safety Population.

### 10.3.3 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. The percentage of complete eDiary entries will be calculated as 100 times the number of completed evening reports divided by the total number of days in the study period (Pretreatment and Treatment).

Descriptive statistics for eDiary compliance (%) and the patients with ≥80%/<80% complete eDiary entries during the Pretreatment and Treatment Periods will be presented.

## 10.4 EFFICACY ANALYSES

All efficacy analyses to address the objectives of the study will be based on the ITT Population. Exploratory analyses to address the exploratory objective of the study also will be based on the ITT Population.

Baseline values for efficacy and exploratory 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. Baseline values for patient symptom severity parameters (eg, abdominal symptoms [pain, bloating, discomfort, cramping]) will be the average of the non-missing severity scores reported during this period. The baseline BM and urgent BM weekly rates will be derived based on the number of BMs and urgent BMs a patient had during this period. Baseline BSFS score and stool consistency will be calculated as the average of the non-missing values reported by the patient 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.

Sensitivity analyses of the key endpoints will include, but are not limited to, a multiple imputation 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.

All hypothesis testing will be performed at a 2-sided 0.05 significance level. No adjustment for multiplicity will be applied.

### 10.4.1 Key Efficacy Endpoints

The 2 key efficacy endpoints are:

- **Change from Baseline in Abdominal Pain at its Worst at Each Week**
  The weekly abdominal pain at its worst score is the average of the non-missing abdominal pain scores during each week (Weeks 1-12) in the study. The baseline abdominal pain score is the average of the non-missing abdominal pain scores during the last 14 days of the Pretreatment Period and the day of the Randomization Visit reported prior to randomization. Change from baseline will be calculated for each week as the weekly score minus the baseline score.
- **6/12 Week Abdominal Pain 30% Responder**
  A 6/12 Week Abdominal Pain 30% Responder is a patient who meets the Weekly Abdominal Pain 30% Responder criteria for at least 6 out of the 12 weeks of the Treatment Period. A Weekly Abdominal Pain 30% Responder is a patient who has a decrease from baseline of at least 30% in the mean abdominal pain at its worst 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 30% Responder for that week.

### 10.4.2 Key Efficacy Analysis

Comparisons between the MD-7246 dose groups and placebo with regard to the change from baseline in abdominal pain over the Treatment Period will be evaluated employing a MMRM framework with week (categorical), treatment, geographic region, and week-by-treatment fixed effects, patient as the random effect, and baseline value as a covariate. An unstructured covariance structure will be utilized. Descriptive statistics, for the overall Treatment Period effect, based on the MMRM model will include least-squares (LS) mean change from baseline for each treatment, the LS mean difference between each MD-7246 dose and placebo, corresponding 95% CIs, and the p-value associated with the comparison. In addition, weekly treatment differences between each MD-7246 group and placebo will be provided using the same MMRM model defined above.

For the 6/12 Week Abdominal Pain 30% Responder endpoint, the proportion of responders in each MD-7246 group will be compared to the proportion of responders in the placebo group using a Cochran-Mantel-Haenszel (CMH) test controlling for geographic region. The number and percent of responders, the difference in responder rates between each MD-7246 group and the placebo group, the odds ratio relative to placebo, all corresponding 95% CIs, and the p-value associated with the CMH test will be presented.

### 10.4.3 Additional Efficacy Endpoints

The additional efficacy endpoints are:

- 6/12 Week Abdominal Pain 50% Responder

  A 6/12 Week Abdominal Pain 50% Responder is a patient who meets the Weekly Abdominal Pain 50% Responder criteria for at least 6 out of the 12 weeks of the Treatment Period. For each week in the Treatment Period, a Weekly Abdominal Pain 50% Responder is a patient who has a decrease from baseline of at least 50% in the mean abdominal pain at its worst 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 50% Responder for that week.

- 6/12 Week Abdominal Discomfort 30% Responder

  A 6/12 Week Abdominal Discomfort 30% Responder is a patient who meets the Weekly Abdominal Discomfort 30% Responder criteria for at least 6 out of the 12 weeks of the Treatment Period. The Weekly Abdominal Discomfort 30% Responder criteria are defined the same as the Weekly Abdominal Pain 30% Responder criteria above.

- 6/12 Week Abdominal Bloating 30% Responder

  A 6/12 Week Abdominal Bloating 30% Responder is a patient who meets the Weekly Abdominal Bloating 30% Responder criteria for at least 6 out of the 12 weeks of the Treatment Period. The Weekly Abdominal Bloating 30% Responder criteria are defined the same as the Weekly Abdominal Pain 30% Responder criteria above.

- 6/12 Week Abdominal Cramping 30% Responder

  A 6/12 Week Abdominal Cramping 30% Responder is a patient who meets the Weekly Abdominal Cramping 30% Responder criteria for at least 6 out of the 12 weeks of the Treatment Period. The Weekly Abdominal Cramping 30% Responder criteria are defined the same as the Weekly Abdominal Pain 30% Responder criteria above.

- 6/12 Week Degree of Relief Responder

  A 6/12 Week Degree of Relief Responder is a patient who scores ≤2 ("completely" or "considerably" relieved) for at least 6 out of the 12 weeks of the Treatment Period.

- 6/12 Week Adequate Relief of IBS Pain Responder

  A 6/12 Week Adequate Relief of IBS Pain Responder is a patient who reports adequate relief of IBS pain ("yes") for at least 6 out of the 12 weeks of the Treatment Period.

- Treatment Satisfaction

  For each week of the Treatment Period, patients will rate their satisfaction with the study medication's ability to relieve their IBS symptoms on a 5-point ordinal scale.

- Change from Baseline in Percent of Abdominal Pain-free Days at Each Week

  Abdominal pain is measured daily using an 11-point NRS. Abdominal pain-free days will be those days where the patient reports a score of 0 for abdominal pain at its worst. The percent of abdominal pain-free days will be calculated as the number of Abdominal Pain-free Days during a particular week, divided by the total number of days with non-missing daily abdominal pain at its worst assessments for that week, multiplied by 100. Due to the potential of this data to not meet parametric normality assumptions, the baseline percent abdominal pain-free days and change from baseline in percent abdominal pain-free days will be ranked first, respectively, and then transformed to the expected values of the order statistics of the standard normal distribution (ie, normal scores).

- Change from Baseline in Abdominal Discomfort at its Worst at Each Week

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

- Change from Baseline in Abdominal Bloating at its Worst at Each Week

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

- Change from Baseline in Abdominal Cramping at its Worst at Each Week

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

### 10.4.4 Additional Efficacy Analysis

The additional categorical responder (eg, 6/12 Week Abdominal Bloating 30% Responder) and continuous change-from-baseline endpoints will be analyzed utilizing the same methods defined for the key efficacy endpoints in Section 10.4.2. Treatment Satisfaction will be analyzed utilizing an MMRM framework with week (categorical), treatment, geographic region, and week-by-treatment fixed effects, and patient as the random effect. An unstructured covariance structure will be utilized. Pairwise comparisons between each treatment group and placebo will be performed for the overall Treatment Period effect. MMRM-associated statistics, as defined in Section 10.4.2 for the key efficacy change-from-baseline endpoint, will be presented.

### 10.4.5 Exploratory Endpoints

Exploratory endpoints related to bowel function will be studied to address the exploratory objective of the study. These non-efficacy endpoints will include:

- Change from Baseline in BM Frequency Rate at Each Week
  A patient's weekly BM frequency rate is the BM rate (BMs/week) calculated for that week.
- Change from Baseline in BSFS (Stool Consistency) at Each Week
  Stool consistency is measured using the 7-point BSFS. The patient's BSFS score for each week on treatment is the mean of the non-missing BSFS scores from the BMs reported by the patient during the week.
- Change from Baseline in Urgent BM Frequency Rate at Each Week
  An urgent BM is a BM that is associated with urgency (ie, the need to rush to the toilet to avoid an accident). A patient's weekly urgent BM frequency rate is the urgent BM rate (urgent BMs/week) calculated for that week.

- Change from Baseline in the Percent of Days Experiencing an Episode of Diarrhea per Week

  An episode of diarrhea is defined as a sequence of 2 or more loose/watery BMs (BSFS 6 or 7) that are never separated by >1 non-loose/watery stool or by a day without a BM. The Treatment Period percent of days experiencing an episode of diarrhea will be calculated as 100 times the number of days with a diarrhea episode at each week divided by 7. For baseline, the number of days with a diarrhea episode will be determined for the last 14 days of the Pretreatment Period. The baseline percent of days experiencing an episode of diarrhea will be calculated as 100 times the number of days experiencing an episode during the baseline period divided by the length in days of the baseline period (typically 14 days). The change from baseline will be calculated for each week as the weekly percent minus the baseline percent.

- Change from Baseline in the Percent of Days Experiencing No Episodes of Diarrhea per Week

  Episodes of diarrhea are described above. The percent of days experiencing no episodes of diarrhea per week will be calculated using the same method as described above for episodes of diarrhea.

- Change from Baseline in BM-related Symptom Severity at Each Week

  BM-related Symptom severity is measured weekly using a 5-point ordinal scale comparing the severity for the past 7 days.

- BM-related Symptom Change

  BM-related symptom change is measured weekly using a 7-point ordinal scale comparing the severity for the past 7 days to the severity before starting the study.

- Change from Baseline in Percent of Days with Use of Loperamide for Diarrhea at Each Week

  The percent of days using loperamide for diarrhea at each week will be calculated as 100 times the number of days loperamide was used during the week divided by 7.

### 10.4.6 Exploratory Analysis

Exploratory change-from-baseline endpoints will be analyzed utilizing the same methods as described in Section 10.4.2 for the key efficacy analysis. BM-related Symptom Change will be analyzed utilizing an MMRM framework with week (categorical), treatment, geographic region, and week-by-treatment fixed effects, and patient as the random effect. An unstructured covariance structure will be utilized. Pairwise comparisons between each treatment group and placebo will be performed for the overall Treatment Period effect. MMRM-associated statistics, as defined in Section 10.4.2 for the key efficacy change-from-baseline endpoint, will be presented.

## 10.5 HEALTH ECONOMICS AND OUTCOMES RESEARCH ANALYSES

Health economics and outcomes research (HEOR) analyses will be based on the ITT Population.

### 10.5.1 Pain Catastrophizing Scale

The Pain Catastrophizing Scale is a 13-item instrument that asks patients to reflect on their thoughts and feelings of past painful experiences. The patient responds to each statement using a 5-point scale (0=None at all to 4=All the time). The total Pain Catastrophizing Scale score plus the 3 subscale scores (Rumination, Magnification, and Helplessness) will be derived and summarized by treatment for the Pretreatment Visit.

### 10.5.2 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 for all visits at which the SF-12v2 is completed. Treatment differences for the change from baseline at each post-dose visit will be analyzed using MMRM as described in Section 10.4.2 for the key efficacy change-from-baseline endpoint.

### 10.5.3 EQ-5D-3L

Patient responses to the descriptive system (i.e., health state) will be converted to the corresponding utility score and the descriptive statistics (n, mean, SD, median, minimum and maximum) will be presented for utility 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 each visit.

### 10.5.4 IBS-SSS

The IBS-SSS parameters consist of 5 individual items and the IBS-SSS total score. The 5 individual items (severity of abdominal pain, frequency of abdominal pain, severity of abdominal distension, dissatisfaction with bowel habits, and interference of IBS with life in general) are based on a 0-100 scale (10 times the original scale) and the IBS-SSS total score parameter is the sum of the 5 IBS-SSS individual item scores (0-500 scale).

For each post-baseline visit, change from baseline in the IBS-SSS total score and individual items will be analyzed using an ANCOVA model with fixed effect terms for treatment group and geographic region and the corresponding baseline IBS-SSS score as a covariate.

## 10.6 SAFETY ANALYSES

All safety parameters will be analyzed descriptively in accordance with the general methods described in Section 10.2.

### 10.6.1 Adverse Events

Adverse Event Verbatim Terms will be coded in the EDC system against the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) available at the start of the study (or newer).

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

If more than 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 1 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 (ie, events with an outcome of 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 died (if any).

### 10.6.2 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 1 assessment in the corresponding post-baseline period. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS value in the corresponding post-baseline period. A supportive listing of patients with PCS post-baseline values will be provided, including the PID number, study center, and baseline and post-baseline values. A listing of all AEs for patients with PCS laboratory values will also be provided.

### 10.6.3 Vital Signs

Descriptive statistics for vital signs (ie, 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 period/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 1 assessment in the corresponding post-baseline period. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS value in the corresponding post-baseline period. A supportive listing of patients with PCS post-baseline values will be provided, including the PID number, study center, and baseline and post-baseline values. A listing of all AEs for patients with PCS vital sign values will also be provided.

## 10.7 INTERIM ANALYSIS

An optional interim analysis of unblinded safety and efficacy data may be performed to assess futility. If it is decided to perform such an interim futility analysis, details regarding the interim futility analysis (eg, alpha spending and statistical boundaries) will be included in the SAP, along with updates to the data management plan as necessary.

## 10.8 DETERMINATION OF SAMPLE SIZE

In a previously conducted Phase 2b trial utilizing MD-7246 (MCP-103-204), the SD for the change from baseline to Week 12 in abdominal pain at its worst ranged from 2.32 to 2.88. Assuming a clinically meaningful treatment difference between MD-7246 and placebo of 1.0 for the mean change from baseline to Week 12 in abdominal pain, an SD of 2.4, and 92 patients per treatment group (368 patients total), the estimated power is approximately 80% to detect a difference between each MD-7246 dose and placebo at a 2-sided significance level of 0.05 using a 2-sample t-test.

# 11. 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, submitted by the Sponsor to the FDA, 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.

# 12. STUDY SPONSORSHIP

## 12.1 STUDY TERMINATION

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

## 12.2 REPORTING AND PUBLICATION

All data generated in this study will be the property of Ironwood and its partner, Allergan Sales, LLC. 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.

# 13. INVESTIGATOR OBLIGATIONS

## 13.1 DOCUMENTATION

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

- 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 initial IRB approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals. All 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 Health Insurance Portability and Accountability Act (HIPAA) authorization form
- A list of the IRB members **or** the Department of Health and Human Services (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
- Financial disclosure agreements completed and signed by the investigator and each sub-investigator listed on Form FDA 1572. If there are any relevant changes, the investigator (and any sub-investigator) will provide an updated financial disclosure agreement to the Sponsor at the time of the change, and up to 1 year after the completion of the study

## 13.2 PERFORMANCE

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

## 13.3 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 sub-investigators 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 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.

## 13.4 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.

## 13.5 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 (eg, 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 2 years following notification by Ironwood that the entire clinical investigation (not merely the investigator's portion) is completed, terminated, or discontinued or for 2 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.

## 13.6 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.

# 14. APPENDICES

# APPENDIX 1 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. 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 contract research organization (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 (eg, "I agree to participate...")
- A place for the patient's signature and date of signing
- A statement that a description of this clinical study will be available on http://www.ClinicalTrials.gov

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

# APPENDIX 2 CONCOMITANT AND PROHIBITED MEDICATIONS

**Protocol-permitted OTC Medication for Diarrhea**

Protocol-permitted over-the-counter (OTC) medication for diarrhea, loperamide (Imodium®), will be dispensed to patients. Throughout the study (Screening Period through Posttreatment Period), patients will be allowed to use loperamide to assist in the management of their diarrhea. Loperamide will be provided to the patient at study visits to use as needed (at the patient's discretion) to manage their diarrhea throughout the study. Patient dosing of loperamide should not exceed 16 mg/day (8 unit doses), consistent with the product label. Beginning at the Pretreatment Visit through the Week 12/EOT Visit, patients will report loperamide use in the eDiary on an event-driven basis. In order to be eligible for the study, patients must discontinue use of other OTC and prescription medications for the treatment of IBS (as detailed below).

**Prohibited Medicine**

All medicines listed in the sections below are excluded during the Pretreatment, Treatment, and Posttreatment Periods. Washout periods in relation to the Screening and/or Pretreatment Visits are detailed below.

**PRESCREEN WASHOUT** ***(medicines must have been stopped prior to the Screening Visit, unless otherwise specified)***

***No medicine during the 3 months before the Screening Visit:***

1. Chronic oral or parenteral glucocorticoids (however, one 10-day course of oral or one injection of parenteral glucocorticoids is permitted during the Pretreatment, Treatment, or Posttreatment Periods)

***No medicine during the 3 months before the Pretreatment Visit:***

1. Rifaximin

***No medicine during the 30 days before the Screening Visit:***

1. Any investigational or imported drugs that have not been approved for human use by the US FDA
2. Cannabinoid drugs (eg, medical marijuana, dronabinol, nabilone)
3. The following antidepressants, if used daily for treatment of IBS symptoms (Note: Other use of these medications will be allowed 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.)
   a. Tricyclic antidepressants (TCAs; eg, amitriptyline, imipramine, nortriptyline)
   b. Selective serotonin reuptake inhibitors (SSRIs; eg, fluoxetine, sertraline, paroxetine, citalopram)
   c. Serotonin-norepinephrine reuptake inhibitors (SNRIs; eg, venlafaxine, desvenlafaxine succinate)
4. Phenergan and ondansetron if used daily for treatment of IBS symptoms (Note: Will be allowed for occasional use as needed for the treatment of nausea/vomiting.)

**SCREENING PERIOD WASHOUT** ***(medicines must be stopped beginning at the Screening Visit, unless otherwise specified, with minimum washouts prior to the Pretreatment Visit as specified below)***

1. Alosetron or eluxadoline (prescription medications for IBS-D) during the 28 days before the Pretreatment Visit
2. Barbiturates (eg, butalbital, phenobarbital, Fioricet®) during the 28 days before the Pretreatment Visit
3. Any medication used to treat abdominal pain/discomfort or diarrhea (eg, antispasmodics, peppermint oil, narcotics, bismuth subsalicylate, kaolin), and any herbal or natural agent that a person might take for abdominal pain/discomfort or diarrhea; all of these medications must be stopped beginning at the Screening Visit, and the following washouts are required prior to the Pretreatment Visit:
   - No washout required for loperamide (protocol-permitted)
   - 14-day washout (ie, no medication during the 14 days before the Pretreatment Visit):
     - Prokinetic agents (eg, metoclopramide, itopride, prucalopride, domperidone)
     - Antispasmodic/anticholinergic agents (eg, dicyclomine, flavoxate, scopolamine, hyoscyamine, propantheline, oxybutynin, tolterodine, solefenacin, darifenacin, trospium). Note: Inhaled ipratropium and tiotropium are permitted.

- All narcotics either alone or in combination (eg, propoxyphene, diphenoxylate, paregoric). Note: narcotics used as anesthesia for a colonoscopy require a 5-day wash-out prior to the Pretreatment Visit.

◦ 3-day washout (ie, no medication during the 3 days before the Pretreatment Visit)

- Peppermint oil, bismuth subsalicylate, kaolin, and herbal or natural agents

(Note: The use of fiber, probiotics, or stool softeners [such as docusate] is acceptable.)

4. Opioid and centrally acting (eg, tramadol, codeine, gabapentin, pregabalin) analgesic medications beginning at the Screening Visit, with a required 14-day washout (ie, no medication during the 14 days before the Pretreatment Visit) (Note: Acetaminophen will be allowed for occasional use as needed for the treatment of mild non-IBS pain. Gabapentin and pregabalin are acceptable if not prescribed for IBS symptoms, and 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.)
5. Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin or aspirin-containing medications, if used daily for treatment of IBS symptoms, beginning at the Screening Visit, with a required 14-day washout (ie, no medication during the 14 days before the Pretreatment Visit) (Note: NSAIDs will be allowed for occasional use as needed for the treatment of mild non-IBS pain; low-dose aspirin (81 mg) is acceptable for daily use.)
6. Any other drugs affecting GI motility (known to cause constipation or diarrhea) during the 14 days before the Pretreatment Visit.

**14-DAY WASHOUT** (***no medicine during the 14 days before the Pretreatment Visit, unless otherwise specified, but allowed earlier in the Screening Period if applicable)***

1. Drugs with known pharmacological activity at 5-hydroxytryptophan (HT)4, 5-HT2b or 5-HT3 receptors (eg, cisapride, tropisetron, granisetron, dolasetron, mirtazapine)
2. Bile acid sequestrants (eg, cholestyramine and colestipol)
3. Cholinomimetic agents (eg, bethanechol, pyridostigmine, tacrine, and physostigmine). Note: intraocular cholinomimetic agents (eg, pilocarpine) are permitted.
4. Antipsychotic agents (eg, 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 plans to continue on a stable dose throughout the study. Note: paliperidone is permitted without restriction.

5. Monoamine oxidase inhibitors (MAOIs; eg, furazolidone, isocarboxazid, pargyline, phenelzine, selegiline tranylcypromine) or other antidepressants (eg, trazodone, bupropion), unless the patient has been on a stable dose for 30 days before the Screening Visit and plans to continue on a stable dose throughout the study. Note: TCAs, SSRIs, and SNRIs require a longer (prescreen) washout as discussed above.
6. Calcium channel blocker verapamil unless the patient has been on a stable dose for 30 days before the Screening Visit and plans to continue on a stable dose throughout the study. Note: all other calcium channel blockers (eg, nifedipine, diltiazem, amlodipine, felodipine, nicardipine, nimodipine, nisoldipine) are permitted and may be used without restriction.
7. Oral and parenteral antibiotics (however, 1 standard regimen [up to 10 days] of oral antibiotics is permitted during the Treatment or Posttreatment Periods, with the exception of erythromycin).
8. Any medicine taken for the purpose of losing weight (eg, orlistat, phentermine, phendimetrazine, diethylpropion, benzphetamine, and sibutramine).
9. Proton pump inhibitors (eg, omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole) unless the patient has been on a stable dose for 30 days before the Screening Visit and plans to continue on a stable dose throughout the study.
10. 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 on a stable dose throughout the study.

# APPENDIX 3 SUMMARY OF AMERICAN GASTROENTEROLOGICAL ASSOCIATION GUIDELINES

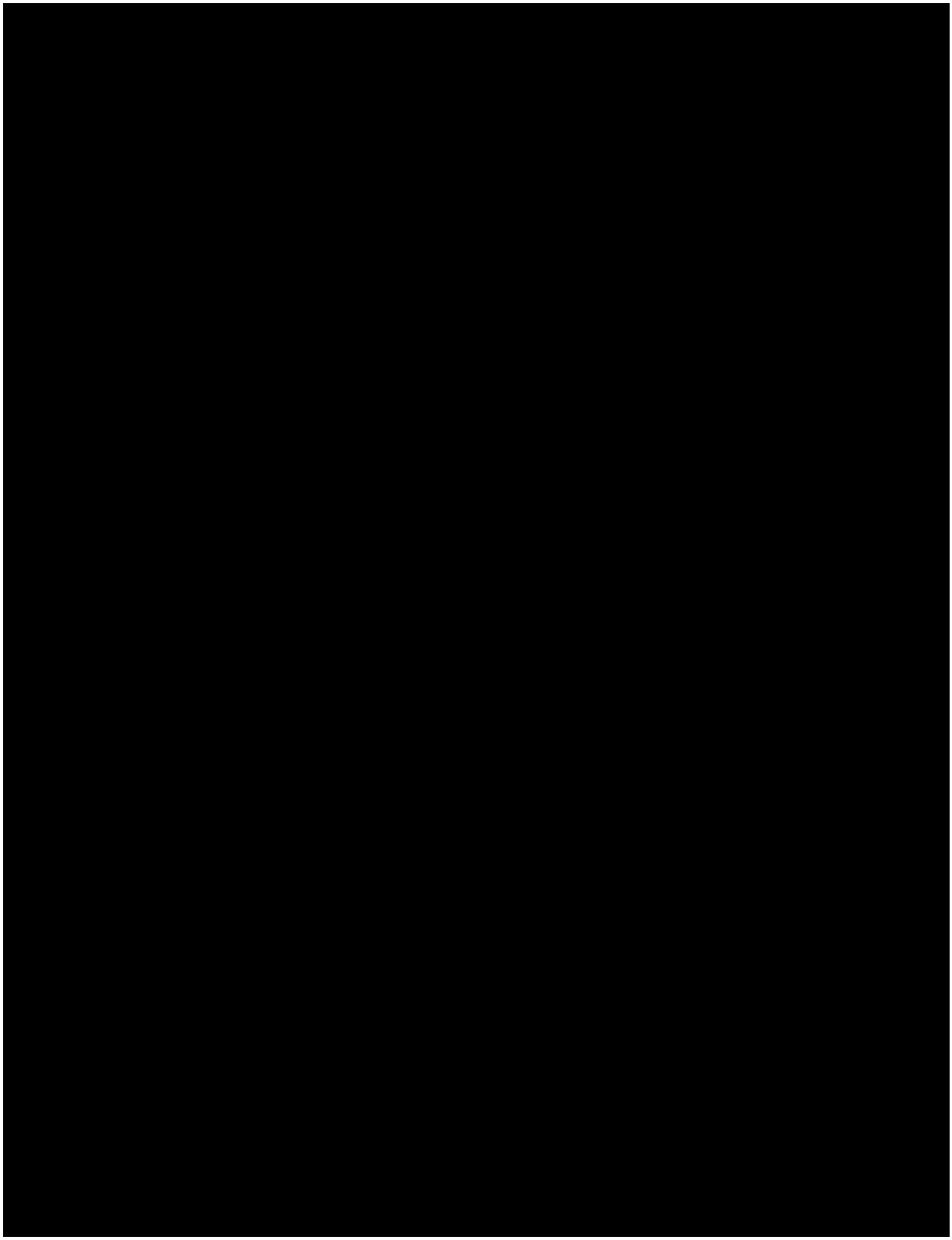
1. Patients aged 50 years and older must have had a colonoscopy with negative findings during the 10 years before the Screening Visit. If there were polyps on the most recent colonoscopy, the patient may be enrolled, provided there were 2 or fewer small (<1 cm) tubular adenomas without appreciable villous tissue or high-grade dysplasia and provided the colonoscopy was performed during the 5 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 2 first-degree relatives with colorectal cancer diagnosed at any age must have had a colonoscopy with negative findings during the 5 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 2 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 5 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. Patients who receive narcotic anesthesia for a colonoscopy are eligible to enter the Pretreatment Period only on the fifth day or later after the colonoscopy.

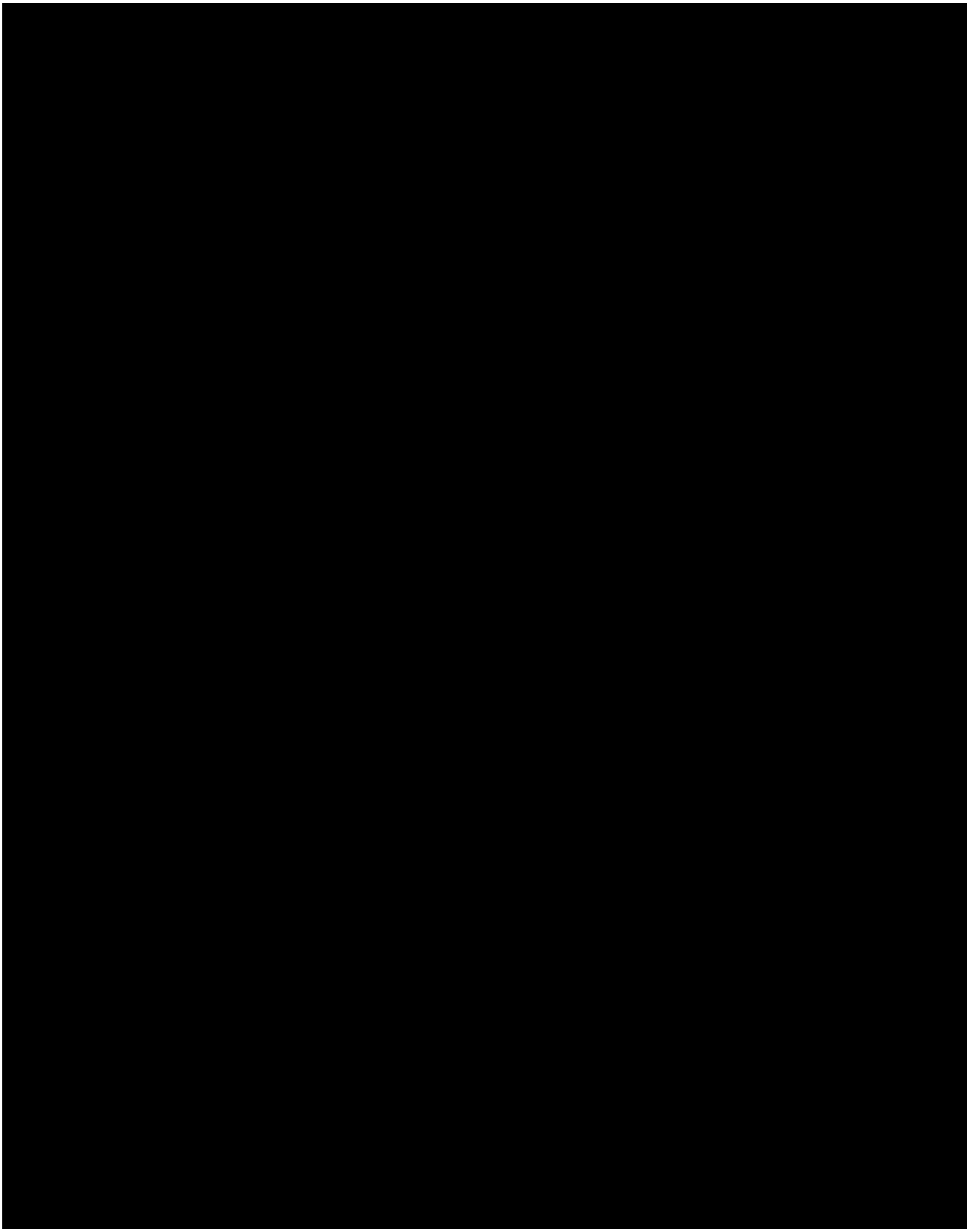
Source: Winawer, et al (2003)

# APPENDIX 4 DIBSS-D

***Diary of Irritable Bowel Syndrome Symptoms – D* (*DIBSS-D*) v0.1**



***Diary of Irritable Bowel Syndrome Symptoms – D* (*DIBSS-D*) v0.1**



# APPENDIX 5 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)

Source: Lewis SJ, Heaton KW. Scand J Gastroenterol (1997)

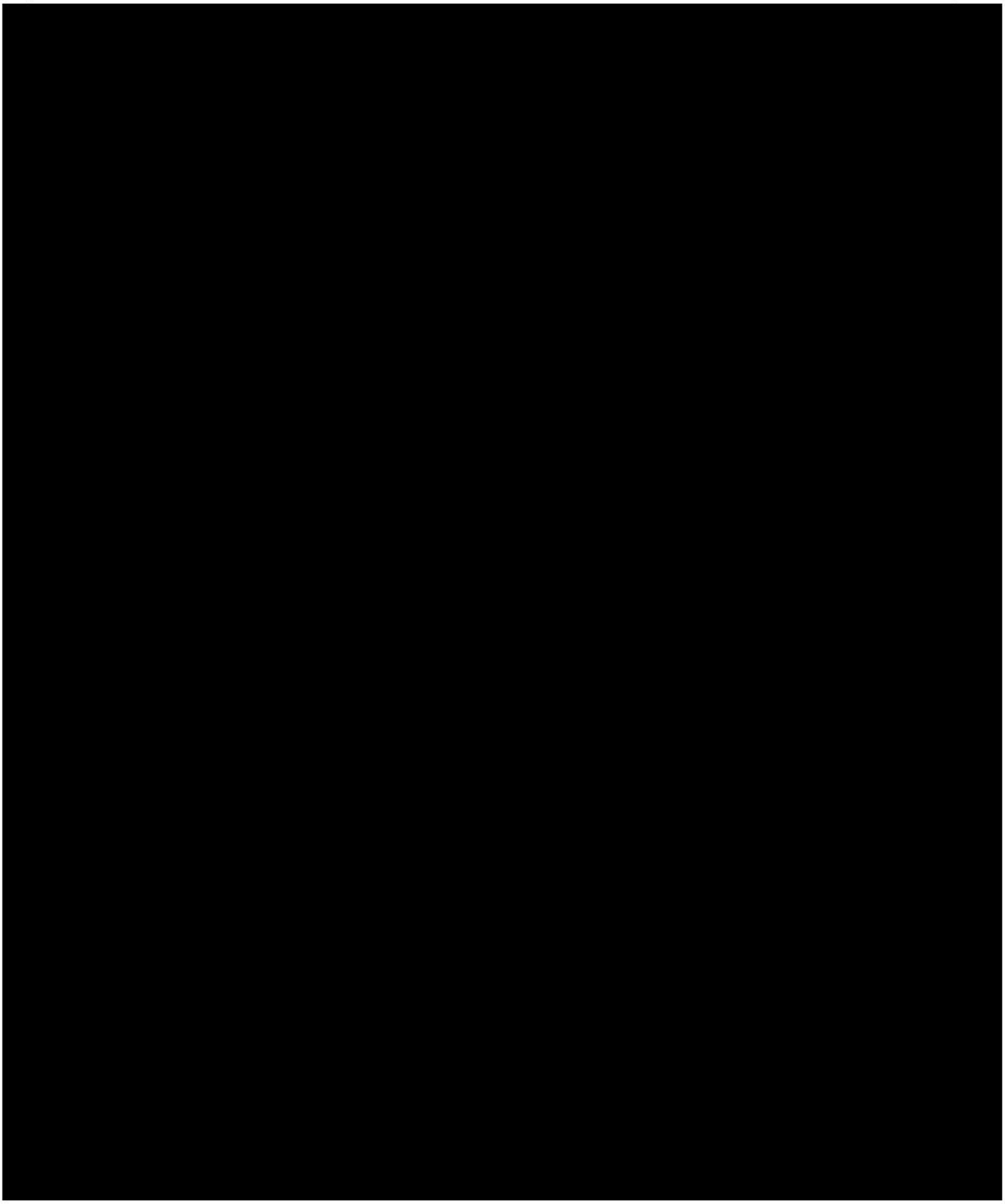
# APPENDIX 6 PAIN CATASTROPHIZING SCALE

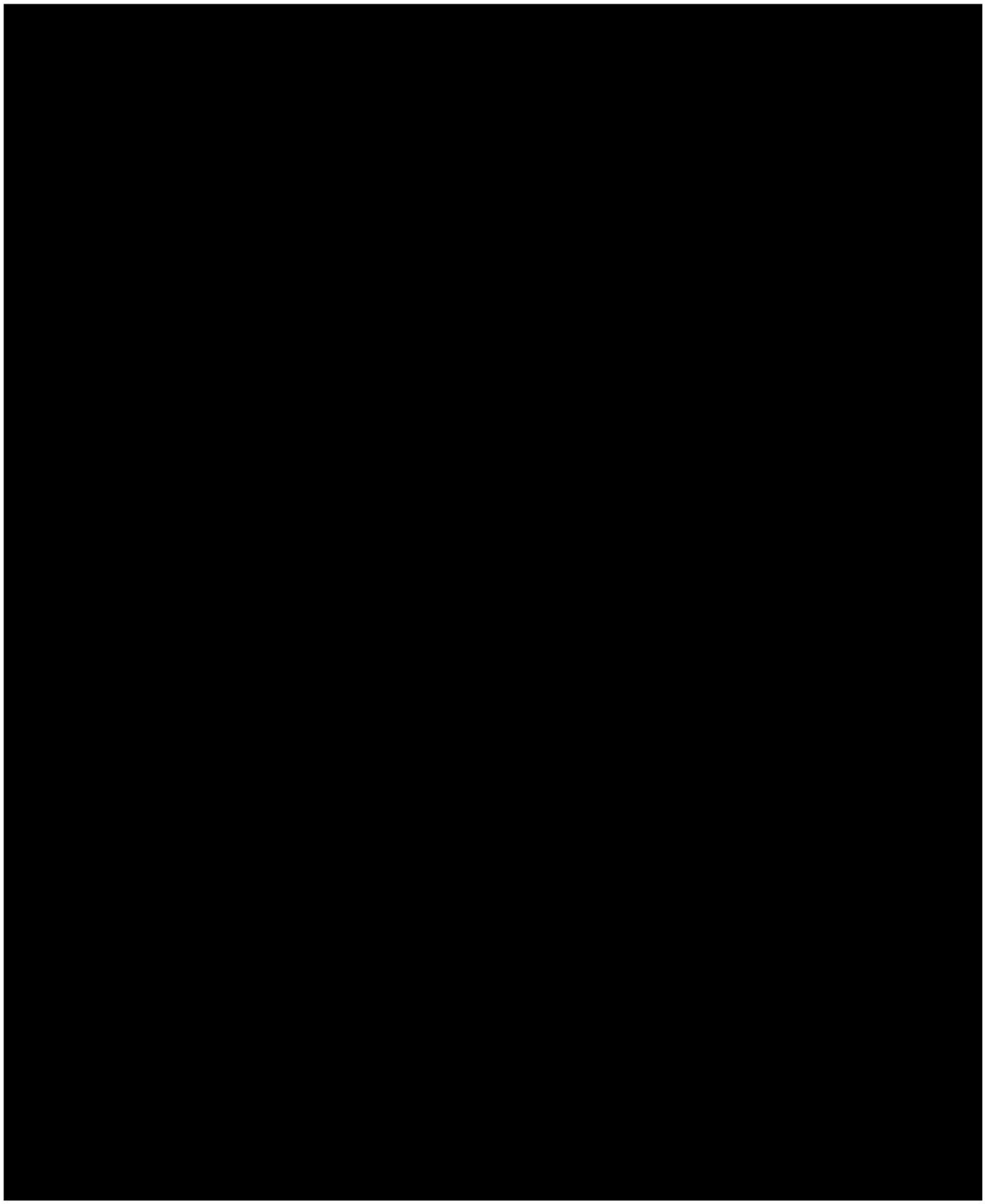
**Pain Catastrophizing Scale**

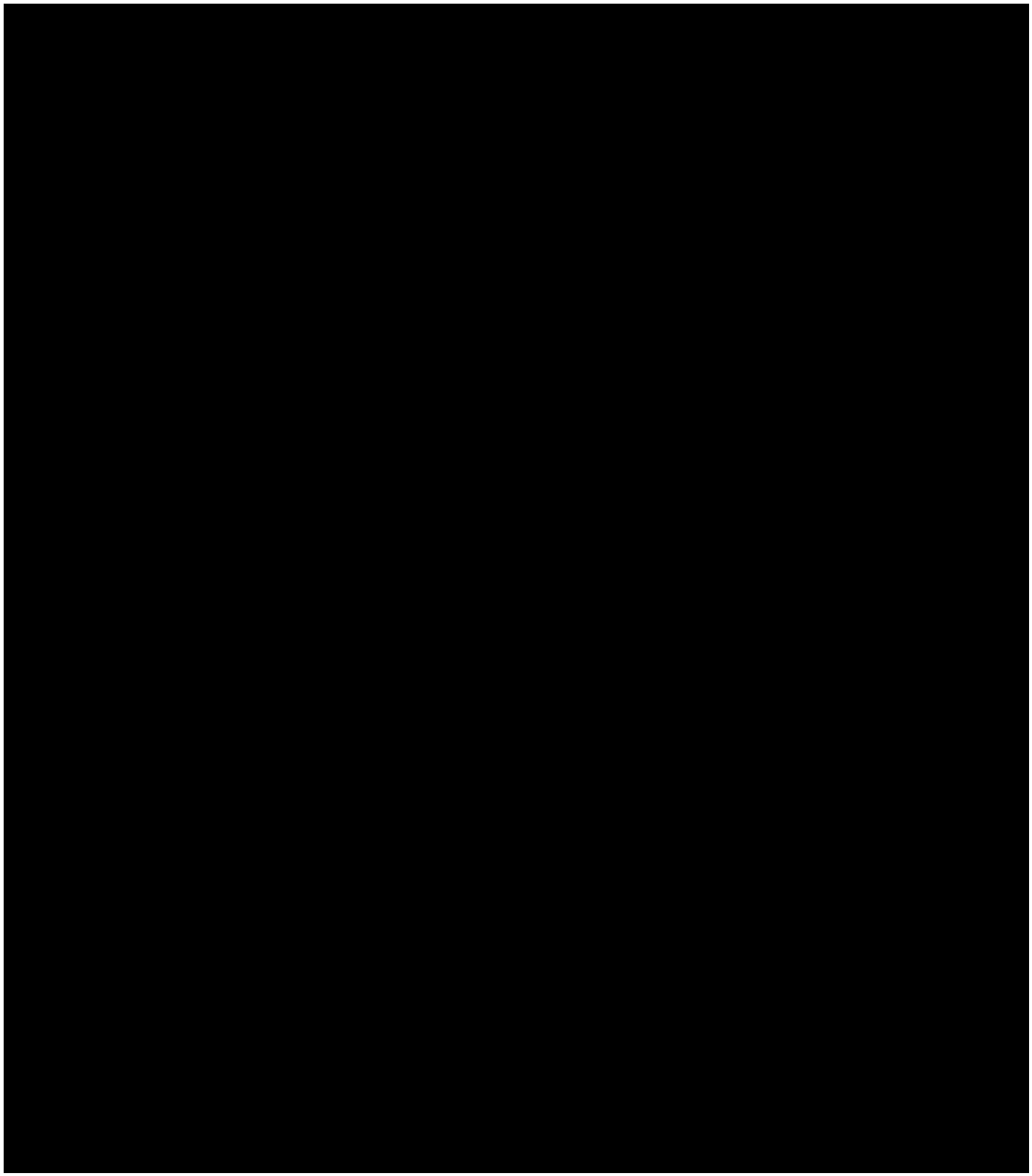
**Sullivan** MJL, **Bishop** S, **Pivik** J. (1995)

[redacted]

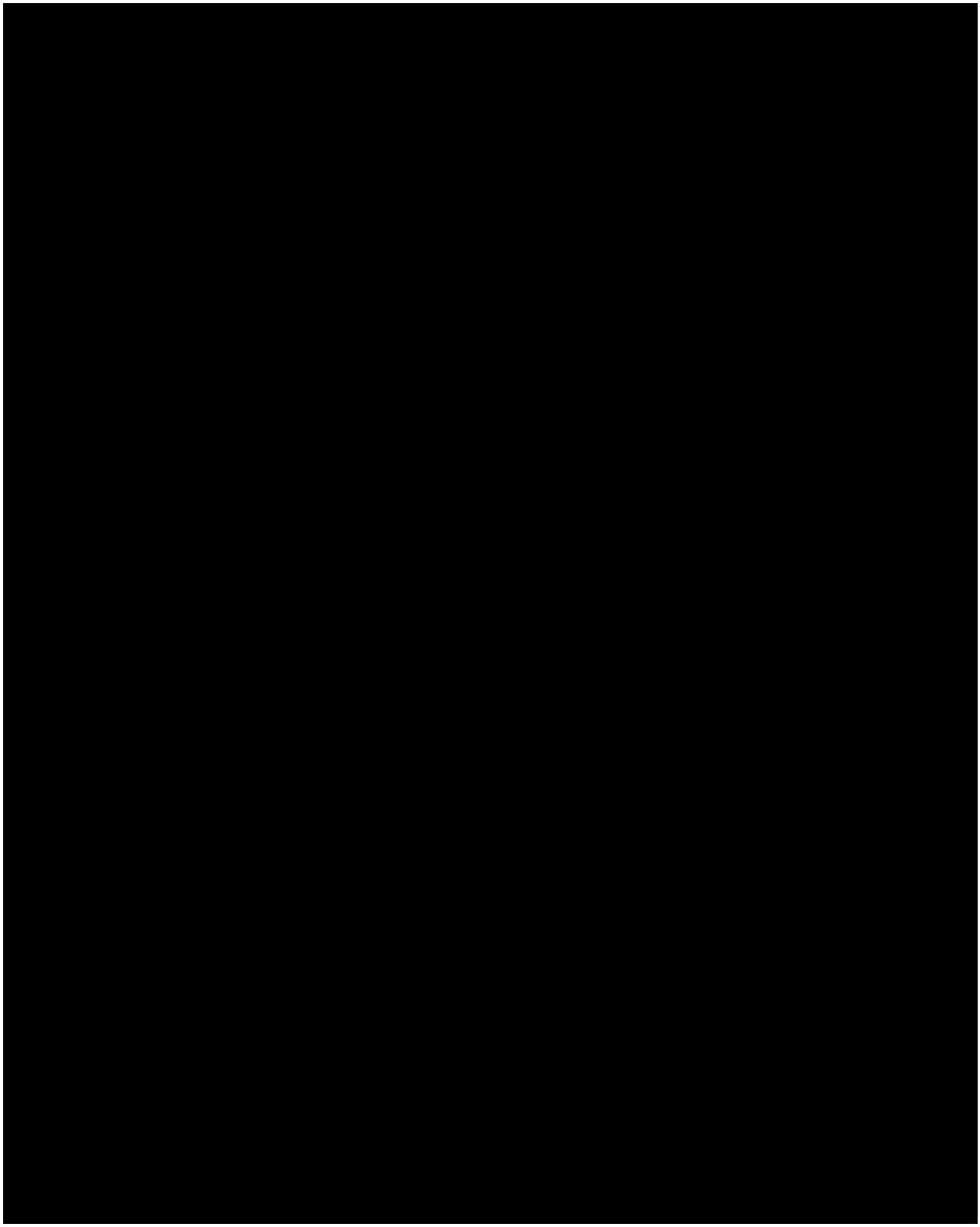
# APPENDIX 7 SF-12V2

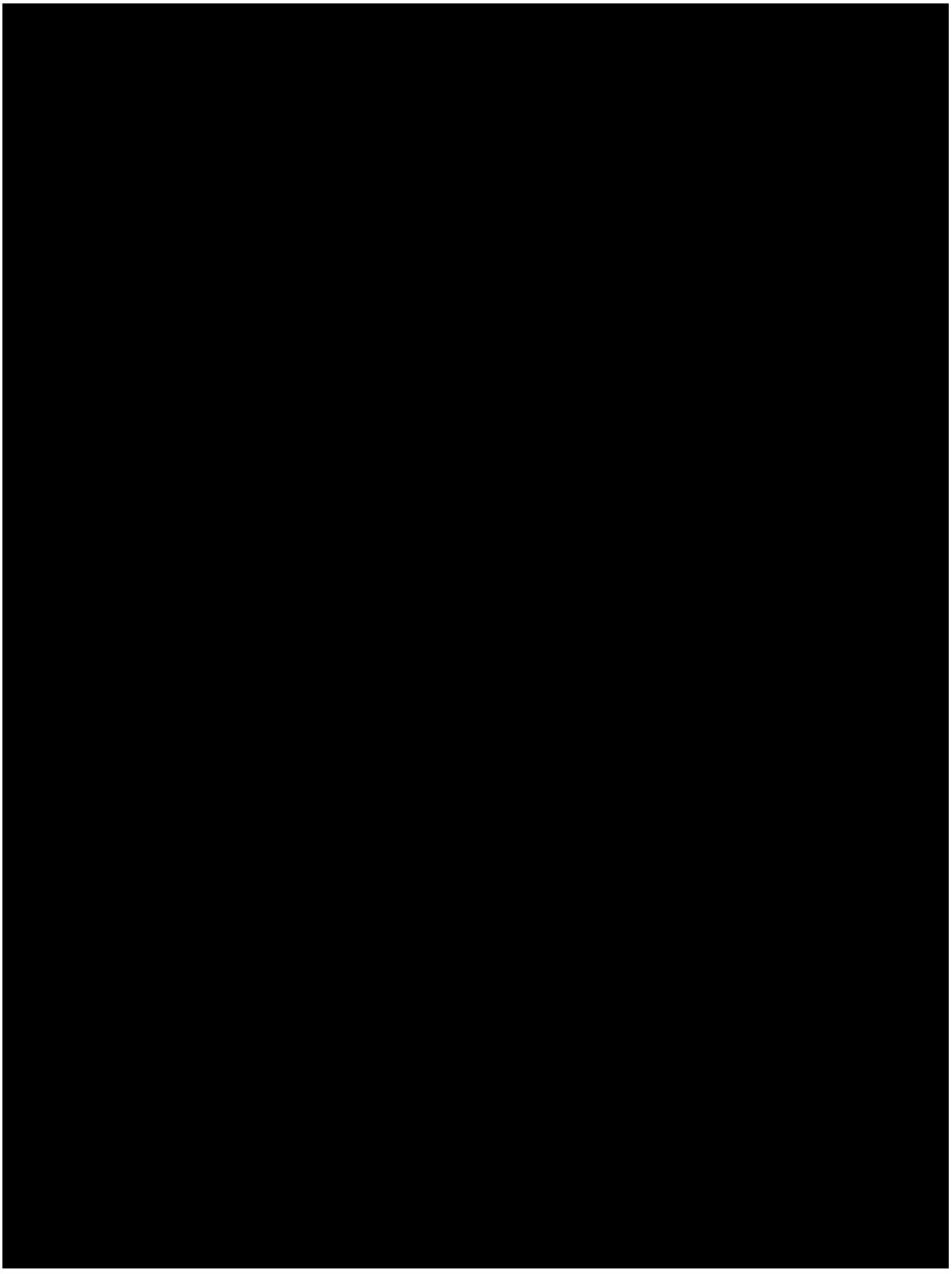






# APPENDIX 8 EQ-5D-3L





# APPENDIX 9 IBS-SSS

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

# APPENDIX 10 INVESTIGATOR'S SIGNATURE

| | |
|---|---|
| **Study Title:** | A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-range-finding Study of MD-7246 Administered Orally for 12 Weeks to Treat Abdominal Pain in Patients with Diarrhea-predominant Irritable Bowel Syndrome |
| **Study Number:** | MCP-103-205 |
| **Final Date:** | 29 January 2019 |

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:_____

Print Name:_____

# 15. REFERENCE LIST

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The data and information related to my line function, which has been included with this file, are truthful and accurate.

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| Approval | [redacted] |
| Approval | [redacted] |
| Approval | [redacted] |

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v2.0

# Summary of Changes for Protocol Amendment 1: MCP-103-205

## Final Version, 29 January 2019

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|---|---|---|---|
| Product Name: | | MD-7246 | |
| Protocol Number: | | MCP-103-205 | |
| Original Protocol Date: | | 11 October 2018 | |
| Protocol Amendment 1: | Date<br>29 January 2019 | Countries<br>United States | Sites<br>All Sites |

## SPONSOR SIGNATURE

[redacted]

[redacted]

Ironwood Pharmaceuticals, Inc.

Refer to the final page of this document for electronic signature and date of approval.

# TABLE OF CONTENTS

# 1. SUMMARY OF THE PROTOCOL AMENDMENT

The major changes from clinical protocol MCP-103-205 Original Protocol to MCP-103-205 Protocol Amendment 1 are summarized below.

The following changes were made to the protocol:

- The indication was changed from irritable bowel syndrome (IBS) to abdominal pain in diarrhea-predominant IBS (IBS-D); constipation and mixed subtypes were removed from the study.
  - The study title, objectives, introduction, and other sections as described below, were updated to reflect this change.
- The contact information for SAE reporting was changed from Ironwood to PPD ([redacted]).
- The Rome IV questionnaire was removed for diagnosis and subtyping (Rome IV criteria are still used, as detailed in the inclusion criteria).
  - Rome IV diagnostic questionnaire IBS Module was removed from the appendices.
- Stratification by IBS subtype and minimum enrollment for each subtype were removed from descriptions of randomization and enrollment.
- The Pretreatment Period was shortened from 21-28 days to 14-21 days.
  - Timing of the Screening and Pretreatment Visits, and total duration of patient participation in the study, were adjusted accordingly: Screening Visit (Day -49 to Day -15), Pretreatment Visit (Day -21 to Day -14), and duration (up to 151 days).
- The Week 2 and Week 14/EOS Visits were changed to phone calls collecting only adverse events (AEs) and concomitant medicines, and an eDiary compliance reminder was added at Week 2.
  - Other assessments at these timepoints were removed: IWRS registration, body weight and height, vital signs, eDiary registration, patient eDiary entry in clinic, eDiary compliance verification and reminder (removed at EOS only), EQ-5D-3L, and IBS-SSS
  - Because the last visit to the clinic will now be the Week 12/End-of-Treatment (EOT) Visit, eDiary entry (including daily, weekly, and study visit assessments) was removed during the Posttreatment Period; statistical analyses related to the Posttreatment Period were updated accordingly.
  - Details regarding the Week 2 and Week 14/EOS calls were added in the Schedule of Evaluation footnotes and in the descriptions of the study periods.

- Protocol-permitted over-the-counter (OTC) medications for constipation and diarrhea (MiraLAX® [polyethylene glycol 3350], Ex-Lax® [sennosides], and Imodium® [loperamide]) were changed to loperamide for diarrhea to reflect the indication change to IBS-D only.
  - The assessment of use of these medications on an event-driven basis, corresponding eDiary questions and exploratory endpoints, and concomitant and prohibited medicines were updated accordingly.
- The Diary of IBS Symptoms – Mixed (DIBSS-M) was changed to the DIBSS – Diarrhea (DIBSS-D) for daily abdominal symptom and BM-related assessments, to reflect the indication change to IBS-D only.
  - Assessments of straining and completeness of evacuation (and corresponding eDiary questions and exploratory endpoints) were removed to reflect the components of the DIBSS-D.
- The IBS-QOL and HADS were removed from the study visit assessments.
  - Corresponding statistical analyses and appendices were also removed.
- The number of patients was reduced from approximately 400 IBS patients (approximately 100 patients per treatment group) to approximately 368 IBS-D patients (approximately 92 patients per treatment group).
  - Sample size determination was updated to reflect this change.
- Inclusion criteria were updated as follows:
  - #7 and 8 (related to Rome IV diagnosis and subtyping, respectively) were updated to reflect the indication change to IBS-D only, by removing medications and criteria specific to IBS-C and IBS-M.
  - #11 was added to ensure patients are able to swallow the study drug whole, as study drug may not be chewed, divided, crushed, or dissolved.
- Exclusion criteria were updated as follows:
  - #5-7 in the original protocol were consolidated into #5-6 in the amended protocol
  - #12 was broadened to exclude patients with a history of a microbiologically documented lower GI infection, or received treatment for a microbiologically documented lower GI infection during the 3 months before Screening; Clostridium difficile colitis was given as an example of such an infection, rather than the only such infection excluded
  - #13 was updated to exclude patients with a history of hypersensitivity to loperamide, in addition to linaclotide or any of the excipients in the study drug (MD-7246 or placebo)
  - #14b was updated to add details regarding laparoscopic surgery of the abdomen, pelvis, or retroperitoneal structures (excluded during the 3 months before Screening)

  - #15 was updated to allow patients whose cancer had been complete remission for 3 years before Randomization (reduced from 5 years)
  - #17 was added to exclude patients with a history of human immunodeficiency virus infection
  - #20 was added to exclude patients with a history or current evidence of laxative or opiod abuse
  - #23 in the original protocol was removed because it was specific to IBS-C
  - Minor revisions for structure, clarity, and to reduce redundancy were made to #2, 9, and 10

- Efficacy and exploratory statistical analyses were updated to remove IBS subtype and treatment-by-IBS-subtype from fixed effects and to remove by-subtype analyses.
- The exploratory endpoints were updated to reflect the changes in indication and protocol-permitted OTC medications, and the change from DIBSS-M to DIBSS-D:
  - Removed Change from Baseline in Straining at Each Week and Change from Baseline in the Proportion of Days Experiencing an Episode of Constipation per Week
  - Removed constipation from Change from Baseline in the Proportion of Days Experiencing No Episodes or Constipation or Diarrhea per Week
  - Updated Change from Baseline in Percent of Days with Use of Protocol-permitted OTC Medications for Constipation and Diarrhea to reflect the change to Loperamide for Diarrhea
- The rectal examination as part of the physical examination was changed to be at the discretion of the investigator, rather than required at Screening for all patients not requiring colonoscopy and not required at subsequent visits.
- Overall study stopping criteria were updated to remove text related to stopping enrollment after the required number of patients have been enrolled (considered self-evident based on target enrollment) and reference to IBS subtypes.
- The rationale for study design was updated to reflect the study design changes described above, including the shortened Pretreatment Period, removal of Posttreatment Period eDiary assessment, indication change to IBS-D only, removal of stratification by IBS subtype, and changes to protocol-permitted OTC medications.
- Prohibited medicines were refined to be more specific to IBS-D and to clarify washout periods and exceptions.
  - Opioids and centrally acting analgesic medications were moved from Prescreen Washout to Screening Period Washout and clarifications regarding washout exceptions were added
  - Cannabinoid drugs were added to the Prescreen Washout (30 days before Screening)

  - Prescription medications for IBS-C were removed
  - Barbiturates were moved to the Screening Period Washout (28 days before Pretreatment), from 14-day Washout
  - Medications used to treat constipation or diarrhea were updated to remove medications for constipation (eg, osmotic and stimulant laxatives, prokinetics), prohibit medications used to treat abdominal pain/discomfort, and clarify washout periods and exceptions
  - Clarified that erythromycin is not allowed, even as part of a standard regimen of oral antibiotics

- The section describing the criteria for reporting laboratory abnormalities as AEs was expanded to include vital signs.
- The procedures for recording AEs were corrected for consistency with the Safety Management Plan to state that all SAEs will be followed to adequate resolution or stabilization for up to a maximum of 30 days after last dose (changed to SAEs from AEs and specified maximum follow-up).
- The procedures for collecting and reporting SAEs were revised to detail reporting via the electronic data capture (EDC) system, back-up reporting with the hard-copy SAE form, and confirmation of receipt of SAE information; to update contact information from Ironwood to PPD; and to require SAE follow-up until resolution or stabilization for up to a maximum of 30 days after last dose.
- The procedures for reporting pregnancy and pregnancy-related SAEs were revised to update the contact information from [redacted] and specify that SAEs occurring as a result of post-study pregnancy are to be reported using the hard-copy SAE form.
- The required investigator consultation with the patient was updated to reflect the indication and protocol-permitted OTC medications changes, and to refine the thresholds that trigger eDiary alerts (ie, no BMs for ≥3 consecutive days with daily use of loperamide; ≥8 unit doses (≥16 mg) of loperamide in a 24-hour period for ≥5 consecutive days).
- Minor administrative changes and revisions (ie, grammar, formatting, style, and sentence structure) were also made throughout the document to improve clarity, consistency, and succinctness.

The data and information related to my line function, which has been included with this file, are truthful and accurate.

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