**Appendix A**

**Inclusion Criteria**

Patients will be entered into the study only if they meet all of the following criteria:

1. Patient is willing and able to participate in the study for the required duration, can understand and is willing to sign the ICF, and agrees to undergo all protocol-related tests and procedures.
2. Patient is able to complete all required electronic Daily BM Diary and Daily Symptom Diary entries during the 2-week Pre-Treatment assessment period and for the duration of the study (i.e., the 12-week Treatment Period and the 2-week Post-Treatment Period).
3. Males or females between 18 and 80 years of age (inclusive), with a BMI between 18 and 40 kg/m2 (inclusive). Females must not be pregnant or lactating.
4. Female patients of non-childbearing potential who are surgically sterile or postmenopausal.
5. Females who are still menstruating must be able to differentiate the abdominal symptoms associated with CIC from those associated with their menses (otherwise protocol assessments of these symptoms may be confounded).
6. Male and female patients of childbearing potential must agree to use adequate contraception from the time of informed consent to 2 weeks after receiving the last dose of study drug.
7. Patient meets the Rome III functional constipation criteria as modified for this study for ≥ 3 months prior to the Screening visit with symptom onset for ≥ 6 months prior to the diagnosis. The Rome III criteria as modified for this study require the following:
   1. Patient reports that loose stool is rarely present without the use of laxatives.
   2. Patient does not meet the Rome III criteria for IBS-C.
   3. Patient does not use manual maneuvers (e.g., digital evacuation, support of the pelvic floor) to facilitate defecations.
   4. Patient reports a history of < 3 defecations per week.
   5. Patient reports ≥ 2 of the following:
      1. Straining during ≥ 25% of defecations
      2. Lumpy or hard stool in ≥ 25% of defecations
      3. Sensation of incomplete evacuation for ≥ 25% of defecations
      4. Sensation of anorectal obstruction/blockage for ≥ 25% of defecations
8. Patients who meet the modified Rome III criteria based on history must also demonstrate the following during the 2-week Pre-Treatment diary assessment period:
   1. < 3 CSBMs each week
   2. BSFS of 6 or 7 in < 25% of SBMs
   3. One out of the following three:
      1. BSFS of 1 or 2 in ≥ 25% of defecations
      2. A straining value recorded on ≥ 25% of days when a BM was reported
      3. ≥ 25% of BMs result in a sense of incomplete evacuation

**Exclusion Criteria**

Patients will be entered into this study only if they meet none of the following criteria:

1. Patient has not maintained a stable diet for ≥ 30 days prior to the Screening visit or is unwilling to maintain a stable diet during the study. (Note that a patient on a previously established high fiber diet stable for 30 days before screening may be entered as long as they plan to maintain that diet for the duration of participation in the study.)
2. Patient has had major surgery (e.g., requiring general anesthesia) < 60 days of the Screening visit.
3. Patient has a history of cancer (other than basal cell or squamous cell carcinoma of the skin) unless the malignancy has been in a complete remission without maintenance chemotherapy for ≥ 5 years prior to the Screening visit.
4. Patient has any acute or chronic concomitant illness that could confound outcome assessments for this study, including, but not limited to:
   1. Known history of acute or chronic HBV, HCV, or HIV infection
   2. Known or suspected alcoholism, drug addiction, or significant drug abuse within 1 year of the Screening visit
5. Patient has abnormal laboratory results deemed clinically significant by the Investigator at the Screening visit.
6. Patient has any known medical condition, clinical signs and symptoms, vital signs, abnormal laboratory, or ECG considered clinically significant by the Investigator, that could interfere with the patient’s participation in and completion of the study including, but not limited to:
   1. Undiagnosed (i.e., previously untreated), uncontrolled hypertension
   2. Uncontrolled diabetes (defined as hemoglobin A1C > 10% at screening)
   3. Previous anaphylactic reaction to any medication
   4. Clinically significant abnormal ECG
   5. History of adrenal disease, diabetic nephropathy, or gastroparesis
   6. Uncontrolled hypothyroidism
7. Patient has had a cerebrovascular event (stroke) or myocardial infarction (MI) in the last 6 months
8. Patient has plans to travel to a region considered as high risk for developing traveler’s diarrhea while participating in the study.
9. Patient will be ineligible for randomization if, during the 2-week Pre-Treatment assessment, he or she has failed to complete 6 of the 7 required daily diary entries in each of the 2 weeks. The patient will be considered compliant for the day if they complete the Daily BM Diary portion of the call using their diary.
10. Patient has a disease or condition that has been associated with or can cause constipation.
11. Patient has a structural abnormality of the GI tract or disease or condition that can affect GI motility or defecation as noted in medical history or upon PE and testing.
12. History or presence of pseudo-obstruction, colon cancer, malignant polyps, colitis, ischemic colitis, abdominal adhesions, intestinal ischemia, esophageal atresia, laxative or enema abuse, or pelvic floor dysfunction.
13. Patient has active peptic ulcer disease not adequately treated or not stable with therapy.
14. Patient is taking a pharmacologic treatment for GERD / reflux that has not been stable for 15 days before the Screening visit.
15. Patient has a history of substantiated (documented by CT scan or hospitalization) diverticulitis, or any ongoing chronic condition (e.g., chronic pancreatitis, polycystic kidney disease, endometriosis, ovarian cysts, or other) that may be associated with chronic abdominal pain or discomfort and might confound the assessments in this study during the 2 years prior to the Screening visit.
16. Patient has had a fecal impaction that required hospitalization or emergency room treatment < 3 months of the Screening visit.
17. Patient has a history of an eating disorder in the last 5 years.
18. Patient has had surgery that meets any of the following criteria:
    1. Gastric bypass surgery or invasive procedure for the treatment of obesity or surgery to remove a segment of the GI tract at any time prior to screening
    2. Patients who have had a gastric band unless the band has been completely removed > 60 days before the Screening visit.
    3. Open surgery of the abdomen, pelvis, or retroperitoneal structures within 6 months prior to the Screening visit
    4. Laparoscopic appendectomy or cholecystectomy or other instrumentation of the bowel < 60 days before the Screening visit
19. Patient has a clinically significant finding on colonoscopy performed as required in accordance with the AGA guidelines (within AGA time frames). If polyps were found and biopsied, pathology must be reviewed and must be negative for cancer before the patient may be enrolled in the study. This also applies to colonoscopies conducted as part of screening.
20. Patient meets the Rome III criteria for IBS-C. This includes patients who report abdominal pain or discomfort for ≥ 3 days per month in the last 6 months, with symptom onset ≥ 6 months prior to diagnosis, and whose abdominal pain or discomfort is associated with ≥ 2 of the following symptoms:
    1. Improvement of abdominal pain or discomfort with defecation
    2. Onset of pain or discomfort associated with a change in frequency of evacuation
    3. Onset of pain or discomfort associated with a change in form (appearance) of stool
21. Patient uses bisacodyl within 72 hours before the first dose of study drug (Day 1, Week 1), to avoid confounding the data collected in the first week of study drug administration, particularly the time to first BM.
22. Patient reports the use of rescue medication bisacodyl for > 2 days in either of the 2 weeks in the Pre-Treatment Assessment period.
23. Patient has had a barium enema within 7 days of the Screening visit.
24. Patient has taken a protocol-prohibited drug within 15 days of the Screening visit (except for episodic use of antibiotics or opiates) or is not willing to abide by the protocol restrictions regarding use of prohibited drugs.