NCT02959983

Study ID: CMO-US-GI-0429

Title: A Phase 4 Multicenter, Multinational, Prospective, Randomized, Placebo-Controlled, Double-Blinded Parallel Group Study to Assess Efficacy of Eluxadoline in the Treatment of Irritable Bowel Syndrome with Diarrhea (IBS-D) in Patients Who Report Inadequate Control of IBS-D Symptoms with Prior Loperamide Use (RELIEF)

Protocol Date: 12-Aug-2016

CLINICAL STUDY PROTOCOL
IND Number: 79,214

A Phase 4 Multicenter, Multinational, Prospective, Randomized, Placebo-Controlled, Double-Blinded Parallel Group Study to Assess Efficacy of Eluxadoline in the Treatment of Irritable Bowel Syndrome with Diarrhea (IBS-D) in Patients Who Report Inadequate Control of IBS-D Symptoms with Prior Loperamide Use (RELIEF)

PROTOCOL NUMBER: CMO-US-GI-0429

Sponsor:	Allergan Harborside Financial Center Plaza 5, Suite 1900 Jersey City, NJ 07311, USA
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Project Manager:	[redacted]
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Medical Safety Physician:	[redacted]
Version of Protocol:	1.0 (FINAL)
Date of Protocol:	12 August 2016

CONFIDENTIAL

All financial and nonfinancial support for this study will be provided by Allergan. The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed, written consent of Allergan.

The study will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice.

The following information can be found on US Food and Drug Administration Form 1572 and/or study contacts page: Name and contact information of Allergan study personnel and Emergency Telephone Numbers; name, address, and statement of qualifications of each investigator; name of each subinvestigator working under the supervision of the investigator; name and address of the research facilities to be used; name and address of each reviewing Institutional Review Board; US Title 21 Code of Federal Regulations 312.23 section 6(iii)b.

Protocol Approval – Sponsor Signatory

Study Title	A Phase 4 Multicenter, Multinational, Prospective, Randomized, Placebo-Controlled, Double-Blinded Parallel Group Study to Assess Efficacy of Eluxadoline in the Treatment of Irritable Bowel Syndrome with Diarrhea (IBS-D) in Patients Who Report Inadequate Control of IBS-D Symptoms with Prior Loperamide Use (RELIEF)
Protocol Number	CMO-US-GI-0429
Protocol Date	12 August 2016

Protocol accepted and approved by:

[redacted]

Protocol Approval – Principal/Coordinating Investigator

Study Title A Phase 4 Multicenter, Multinational, Prospective, Randomized, Placebo-Controlled, Double-Blinded Parallel Group Study to Assess Efficacy of Eluxadoline in the Treatment of Irritable Bowel Syndrome with Diarrhea (IBS-D) in Patients Who Report Inadequate Control of IBS-D Symptoms with Prior Loperamide Use (RELIEF)

Protocol Number CMO-US-GI-0429

Protocol Date 12 August 2016

Protocol accepted and approved by:

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Phase 4 Multicenter, Multinational, Prospective, Randomized, Placebo-Controlled, Double-Blinded Parallel Group Study to Assess Efficacy of Eluxadoline in the Treatment of Irritable Bowel Syndrome with Diarrhea (IBS-D) in Patients Who Report Inadequate Control of IBS-D Symptoms with Prior Loperamide Use (RELIEF)" and the accompanying eluxadoline Investigator's Brochure (see Investigator's Brochure signature page for version number and date).

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 1.0, dated 12 August 2016, the International Council for Harmonisation (ICH) harmonised tripartite guideline E6(R1): Good Clinical Practice (GCP), and all applicable government regulations. I will not make changes to the protocol before consulting with Allergan or implement protocol changes without Independent Ethics Committee (IEC) approval except to eliminate an immediate risk to patients. I agree to administer study treatment only to patients under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Allergan.

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

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Protocol Synopsis

Protocol Number: CMO-US-GI-0429

Title: A Phase 4 Multicenter, Multinational, Prospective, Randomized, Placebo-Controlled, Double-Blinded Parallel Group Study to Assess Efficacy of Eluxadoline in the Treatment of Irritable Bowel Syndrome with Diarrhea (IBS-D) in Patients Who Report Inadequate Control of IBS-D Symptoms with Prior Loperamide Use (RELIEF)

Sponsor: Allergan
Harborside Financial Center
Plaza 5, Suite 1900
Jersey City, NJ 07311, USA
[redacted]

Study Phase: Phase 4

Study Sites: The study will be conducted at approximately 75 sites in the United States, and approximately 10 sites in Canada.

Indication: Treatment of patients with IBS-D.

Rationale: In the Phase 3 studies that established the efficacy and safety of eluxadoline in the treatment of IBS-D, patients were prospectively asked about loperamide use in the prior 12 months for IBS-D and whether treatment with loperamide had adequately controlled their symptoms; 36% (N=873) of patients reported using loperamide in the prior 12 months for their IBS-D symptoms. Of these, approximately 65% reported that use of loperamide failed to provide adequate control of their symptoms of IBS-D (N=538). Similar to the results in the overall intent-to-treat population, in patients who reported that loperamide did not provide adequate relief of their IBS-D symptoms, the proportion of composite responders was significantly greater in the eluxadoline treatment groups as compared with placebo ($p < 0.05$) for both eluxadoline 75 mg and 100 mg after 12 weeks of treatment. This prospective study is being conducted to further study the efficacy and safety of eluxadoline 100 mg twice daily (BID) in patients who self-report that loperamide failed to adequately control their IBS-D symptoms in the prior 12 months.

The data from this study will enable Allergan to meet additional needs to understand the appropriate patient population for treatment of IBS-D symptoms with eluxadoline.

Objectives:

The objectives of the study are:

- To evaluate the efficacy of eluxadoline 100 mg BID versus placebo BID over 12 weeks of treatment in patients with IBS-D who report that use of loperamide in the prior 12 months failed to provide adequate control of their IBS-D symptoms.
- To evaluate the safety and tolerability of eluxadoline 100 mg BID versus placebo BID over 12 weeks of treatment in patients with IBS-D who report that use of loperamide in the prior 12 months failed to provide adequate control of their IBS-D symptoms.

Patient Population:

Key Inclusion Criteria:

- Patient is an adult aged 18 to 80 years (male or female), inclusive, at screening.
- Patient has a diagnosis of IBS-D, defined by the Rome III criteria as loose (mushy) or watery stools ≥25% and hard or lumpy stools ≤25% of bowel movements.
- [redacted]
- [redacted]
- Patient reports use of loperamide in the 12 months prior to screening for IBS-D symptoms and that loperamide did not provide adequate control of IBS-D symptoms.
- [redacted] prior to randomization. Patients have 3 weeks to meet these criteria.
- Patient has not used any loperamide rescue medication within 14 days prior to randomization.

Key Exclusion Criteria

- [redacted]
- [redacted]
- Patient has a history or current evidence of laxative abuse within 5 years prior to screening.
- Patient has documented evidence of cirrhosis (Child-Pugh classification A, B, or C).

- [redacted]
- [redacted]
- Patient has used aspirin or aspirin-containing medications (>325 mg of aspirin per day) or nonsteroidal anti-inflammatory drugs, when taken specifically for the symptoms of IBS, within 14 days of randomization.
- Patient has surgical history of cholecystectomy or previously documented agenesis of gallbladder.
- Patient has a history of cholecystitis within 6 months before Screening.
- Patient has a history of pancreatitis or structural diseases of the pancreas, including known or suspected pancreatic duct obstruction.
- Patient has a history of known or suspected biliary duct obstruction or sphincter of Oddi disease or dysfunction, excluding a history of gallstones.
- Patient has a history of alcohol abuse, alcohol addiction, and alcoholism or drinks more than 3 alcoholic beverages per day.

Study Design: This is a Phase 4, multicenter, multinational, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy, safety, and tolerability of eluxadoline 100 mg BID in patients with IBS-D who report that use of loperamide to treat their IBS-D symptoms in the prior 12 months failed to adequately control their symptoms of IBS-D.

Approximately 340 patients will be randomly assigned (in a 1:1 ratio) to 1 of 2 treatment groups:

- Group 1: Eluxadoline 100 mg oral tablets BID with food
- Group 2: Matching placebo oral tablets BID with food

After screening procedures have been performed (up to 1 week), eligible patients will enter a pretreatment period of up to 3 weeks. At the beginning of the pretreatment period, patients will receive instructions for completing an ePRO diary to collect daily information related to their IBS-D symptoms and use of loperamide rescue medication. At the conclusion of the pretreatment period, patients who meet the study entry criteria related to ePRO diary compliance, stool

consistency (BSS), average WAP, and use of loperamide rescue medication will be randomized to a 12-week double-blind treatment period via central randomization. Patients randomized into the study will continue to record their IBS-D symptoms on a daily basis including WAP, stool consistency (BSS), abdominal discomfort, abdominal bloating, number of bowel movements, urgency, episodes of fecal incontinence, and use of loperamide rescue medication via an ePRO diary. A mandatory posttreatment visit will be performed 14 days after the last dose of study drug.

Estimated Study Duration:

The total duration of the study is up to 18 weeks, which includes a screening period (up to 1 week), pretreatment period (up to 3 weeks), 12-week double-blind treatment period, and 2-week posttreatment follow-up period. A total of 7 study visits are planned for each patient:

- Screening, week -4 (visit 1)
- Pretreatment, week -3 to day 1 (visit 2)
- Day 1 (visit 3; randomization and first administration of study drug)
- Week 4 (visit 4)
- Week 8 (visit 5)
- Week 12 (visit 6; end of treatment)
- Week 14 (visit 7; Posttreatment follow-up/exit)

Efficacy Assessments:

Daily IBS Symptoms: Patients will be required to access the ePRO diary each evening, preferably at the same time each day, to record their: stool consistency, WAP, abdominal discomfort, abdominal bloating, and information related to their bowel functioning (number of bowel movements, episodes of urgency and incontinence) over the past 24 hours.

[redacted]

Degree of Relief of IBS Symptoms: Patients will be asked to rate their overall degree of relief of IBS symptoms during the past 7 days compared with before they started this study on a weekly basis in the ePRO diary.

[redacted]

[redacted]

Safety Assessments:

[redacted]

Study Drug, Dosage, and Route of Administration:

Eluxadoline will be supplied as 100-mg, immediate release, film-coated (Opadry II) tablets. The excipients included in the formulation are microcrystalline cellulose, silicon dioxide, crospovidone, mannitol, and magnesium stearate. Placebo tablets of matching tablet image contain the same excipients.

Eluxadoline 100 mg and placebo are taken orally BID with food.

Sample Size:

Assuming a placebo response for the primary efficacy endpoint (primary composite response in pain and stool consistency) of 13% and an approximate 14% treatment effect over placebo, a sample size of 340 patients with 1:1 randomization ratio (eluxadoline: placebo, 170 patients per arm) is required. This sample size will have approximately 90% power to detect the difference of the primary efficacy endpoint response proportion between eluxadoline and placebo

	using a 2-sided chi-square test at significance level of 0.05.
Statistical Methods:	The comparison of proportion of primary composite responders in pain and stool consistency and the proportion in pain or stool consistency alone over 12 weeks between the eluxadoline and placebo groups will be performed using the chi-square test at a significance level of 0.05. Safety endpoint will be summarized descriptively.
Date of Protocol:	12 August 2016

List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
BSS	Bristol Stool Scale
CFR	Code of Federal Regulations
CV	curriculum vitae
CDS-HRQOL-4	Healthy Days Core Module
δOR	delta-opioid receptor
eCRF	electronic case report form
EDC	electronic data capture
ePRO	electronic patient-reported outcome
EQ-5D	EuroQoL-5 Dimension
FCS	Fisher Clinical Services
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HADS	Hospital Anxiety and Depression Scale
HEOR	health economics and outcomes research
IBS	irritable bowel syndrome
IBS-AR	irritable bowel syndrome adequate relief
IBS-D	irritable bowel syndrome with diarrhea
IBS-M	irritable bowel syndrome with diarrhea and constipation (mixed)
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IxRS	interactive response system
κOR	kappa-opioid receptor
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
μOR	mu-opioid receptor
PI	package insert
SAE	serious adverse event
ULN	upper limit of normal
US	United States
WAP	worst abdominal pain
WPAI: IBS-D	Work Productivity and Activity Impairment questionnaire: Irritable Bowel Syndrome with Diarrhea

1 Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder characterized by symptoms of abdominal discomfort or pain associated with altered bowel habits (Drossman 2006). The 3 primary subtypes of IBS are characterized by predominant bowel habits: diarrhea (IBS-D), constipation (IBS-C), or mixed constipation and diarrhea (IBS-M). All forms of IBS have symptoms of abdominal pain or discomfort that may be linked to local reflexes within the bowel and visceral hypersensitivity (Drossman 2006). A recent meta-analysis of population-based studies yielded an international IBS prevalence of 11.2% (95% confidence interval, 9.8%–12.8%) in adults (≥15 years old). The prevalence varied according to country (from 1.1% to 45.0%), and was dependent on criteria used to define IBS (Lovell and Ford 2012). Irritable bowel syndrome is not life threatening but because of its chronic recurring course, often overlapping with other functional GI disorders, quality of life can be impaired. Irritable bowel syndrome is associated with high direct and indirect medical expenses (Thompson et al 1999).

Pharmacologic options for treatment of IBS-D are limited. Alosetron, a selective serotonin 5-HT_3 receptor antagonist, is approved for severe IBS-D for female patients in the United States (US) (Talley 2003). The non-systemic antibiotic rifaximin was approved by US Food and Drug Administration (FDA) in May 2015 for treatment of IBS-D, and although effective in some patients, has shown high rates of symptom recurrence (Xifaxan® package insert [PI] 2015). Loperamide, a peripherally restricted mu-opioid receptor (μOR) agonist, is widely used as an antidiarrheal, both over-the-counter and via prescription; however, loperamide is not indicated for chronic use, can result in constipation, and has not been shown to effectively treat the abdominal pain of IBS-D (Efskind et al 1996, Talley 2003, Loperamide PI 2015). Thus, there is a need for new agents with favorable safety and tolerability profiles that are effective in providing sustained relief of IBS-D.

Eluxadoline is a locally active mixed μOR agonist, kappa-opioid receptor (κOR) agonist, and delta-opioid receptor (δOR) antagonist approved by FDA on 27 May 2015 for the treatment of IBS-D. Eluxadoline has GI transit-inhibiting activity that is consistent with its primary pharmacological profile as a μOR agonist. The additional δOR antagonist activity may mitigate against the constipating effects of unopposed peripherally acting μOR agonists (e.g., loperamide or diphenoxylate).

Eluxadoline was generally well tolerated in single- and multiple-dose animal studies. Across the Phase 1 studies and Phase 2 study, eluxadoline demonstrated an acceptable safety profile marked by the infrequent incidence of adverse events (AEs) (Eluxadoline Investigator's Brochure).

Efficacy and safety in IBS-D patients was demonstrated in 2 randomized, multicenter, multi-national, double-blind, placebo-controlled Phase 3 studies in a total of 2426 patients (studies IBS-3001 and IBS-3002; Lembo et al 2016 and VIBERZI™ PI 2015). The primary endpoint of the Phase 3 trials was defined by the simultaneous improvement in the daily worst abdominal pain (WAP) score by ≥30% compared with baseline weekly average and a reduction in the Bristol Stool Scale (BSS) to <5 on at least 50% of days within a 12-week treatment period (FDA endpoint) and a 26-week treatment period (European Medicines Agency endpoint). Eluxadoline 100 mg twice daily (BID) demonstrated significantly greater composite responder rates as compared with placebo over 12 weeks and 26 weeks of treatment. Eluxadoline 75 mg BID demonstrated significantly greater responder rates than placebo over 12 weeks in both studies, and greater responder rates than placebo over 26 weeks of treatment in study IBS-3002, but not in study IBS-3001 (Lembo et al 2016, VIBERZI PI 2015). The treatment effect of eluxadoline over placebo was observed within the first week and was maintained throughout the 26-week assessment period. Based on efficacy of both eluxadoline 75 mg and 100 mg at 12 weeks of treatment, both doses were approved by FDA for treatment of adults with IBS-D.

Other abdominal symptoms and measures of bowel function were also significantly improved with eluxadoline treatment as compared with placebo. Longitudinal analyses demonstrated that daily abdominal discomfort scores were significantly lower than placebo for both the 75-mg and 100-mg eluxadoline groups through week 26. Daily bloating scores were significantly lower than placebo with eluxadoline 100 mg after week 12 (weeks 16, 20, 24, and 26). Risks for frequency of bowel movements and urgency episodes were also significantly lower than placebo for both eluxadoline doses through week 26 of treatment. Additionally, both doses of eluxadoline were significantly superior to placebo with respect to the endpoints of adequate relief of IBS symptoms, scores for global symptoms, and scores on the IBS-Quality of Life questionnaire. Eluxadoline was significantly superior to placebo in all subpopulations explored (Lembo et al 2016).

Overall, the clinical experience suggests that eluxadoline is a promising treatment for the symptoms of IBS-D, providing clinically important improvements in both abdominal pain and diarrhea.

2 Study Objectives

The objectives of this study are:

- To evaluate the efficacy of eluxadoline 100 mg BID versus placebo BID over 12 weeks of treatment in patients with IBS-D who report that use of loperamide in the prior 12 months failed to provide adequate control of their IBS-D symptoms.

- To evaluate the safety and tolerability of eluxadoline 100 mg BID versus placebo BID over 12 weeks of treatment in patients with IBS-D who report that use of loperamide in the prior 12 months failed to provide adequate control of their IBS-D symptoms.

3 Investigational Plan

3.1 Study Design

This is a Phase 4, multicenter, multinational, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy, safety, and tolerability of eluxadoline 100 mg BID in patients with IBS-D who report that use of loperamide to treat their IBS-D symptoms in the prior 12 months failed to adequately control their symptoms of IBS-D.

Approximately 340 patients will be randomly assigned (in a 1:1 ratio) to 1 of 2 treatment groups:

- Group 1: eluxadoline 100 mg oral tablets BID with food
- Group 2: matching placebo oral tablets BID with food

After screening procedures have been performed (up to 1 week), eligible patients will enter a Pretreatment period of up to 3 weeks. At the beginning of the pretreatment period, patients will receive instructions for completing an electronic patient-reported outcome (ePRO) diary to collect daily information related to their IBS-D symptoms and use of loperamide rescue medication. At the conclusion of the pretreatment period, patients who meet the study entry criteria related to ePRO diary compliance, stool consistency (BSS), average WAP, and use of loperamide rescue medication (refer to Section 4.1.1 for details) will be randomized to a 12-week double-blind treatment period via central randomization.

Patients randomized into the study will return to the clinic for study visits at week 4, week 8, week 12 (end-of-treatment study visit), and for a posttreatment follow-up study visit at week 14. A complete schedule of events is provided in Appendix 12.1, Table 12–1 and Table 12–2. Patients who discontinue from the study before the week 12 visit should return to the study site to complete the early withdrawal assessments as soon as possible after stopping the study drug.

During the double-blind Treatment period, patients will record via the ePRO diary their daily IBS-D symptoms including stool consistency (BSS), WAP, abdominal discomfort, abdominal bloating, bowel movement frequency, number of episodes of urgency in a day, if any, number of episodes of fecal incontinence, and use of loperamide rescue medication.

The actual ePRO data entered by the patients will not be provided to the investigative site staff at the time of randomization or during the study to prevent any potential bias in subsequent patient entries. However, periodic notifications will be generated to inform the investigator of patients' ongoing compliance with ePRO diary entries and to alert investigators if patients have experienced episodes of constipation or have required excessive loperamide rescue medication for acute treatment of uncontrolled diarrhea.

3.1.1 Rationale of Study Design

In the Phase 3 studies that established the efficacy and safety of eluxadoline in the treatment of IBS-D, patients were prospectively asked about loperamide use in the prior 12 months for IBS-D and whether treatment with loperamide had adequately controlled their symptoms; 36% (N=872) of patients reported using loperamide in the prior 12 months for their IBS-D symptoms. Of these, approximately 65% reported that use of loperamide failed to provide adequate control of their IBS-D symptoms (N=538). Similar to the results in the overall intent-to-treat (ITT) population, in patients who reported that loperamide did not provide adequate relief of IBS-D symptoms, the proportion of composite responders was significantly greater in the eluxadoline treatment groups as compared with placebo ($p < 0.05$) for both eluxadoline 75 mg and 100 mg after 12 weeks of treatment. This prospective study is being conducted to further study the efficacy and safety of eluxadoline 100 mg BID in patients who self-report that loperamide failed to adequately control their IBS-D symptoms in the prior 12 months.

To be included in the trial, patients must have an average daily stool consistency score (BSS) of ≥5.5 and at least 5 days with a BSS score ≥5 on a 1-7 scale over the week prior to randomization and an average WAP score in the past 24 hours of >3.0 on a 0 to 10 scale over the week prior to randomization. Patients must report that use of loperamide in the 12 months to treat IBS symptoms prior to screening had failed to provide adequate control of their IBS-D symptoms. Additionally patients must have completed the ePRO diary on at least 5 of the 7 days during the week prior to randomization AND at least 10 of 14 days during the 2 weeks prior to randomization. The patient population under study is considered as appropriate for achieving the study objectives.

The screening and pretreatment periods permit evaluation of inclusion and exclusion criteria data (e.g., laboratory assessments, physical examination) and enables confirmation of eligibility of patients for inclusion in the study. Patients will be randomized to 1 of 2 treatment groups (eluxadoline 100 mg or matching placebo BID with food). In order to ensure patient safety, a mandatory posttreatment visit will be performed 14 days after the last dose of study drug. Any ongoing AEs at the posttreatment visit must be followed until resolution, until the AE stabilizes, until it is determined to be non-clinically significant, or until the patient is lost to follow-up.

The 100-mg BID dose of eluxadoline to be administered in the present study is a marketed dose in the US and was shown to be generally well tolerated in prior studies with no evidence of a need for drug titration. Therefore, a fixed-dose design will be employed in this study. The placebo-control group has been included to establish the efficacy and safety of eluxadoline in this subset of patients.

The treatment duration of 12 weeks has been chosen because this is considered an acceptable period to demonstrate efficacy and safety in this patient population.

The data from this study will enable the sponsor to meet additional needs to understand the appropriate patient population for treatment of IBS-D symptoms with eluxadoline.

4 Patient Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 340 patients will be enrolled at approximately 75 sites in the US and approximately10 sites in Canada. Patients will be assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1.1 Inclusion Criteria

To be eligible for enrollment in this study, each of the following criteria must be satisfied with a "YES" answer (unless not applicable):

1. Patient is an adult aged 18 to 80 years (male or female), inclusive, at Screening.
2. Patient has a diagnosis of IBS-D, defined by the Rome III criteria as loose (mushy) or watery stools ≥25% and hard or lumpy stools ≤25% of bowel movements.
3. Patient has had a colonoscopy performed within 5 years prior to Screening if they are at least 50 years of age, OR if they meet any of the following alarm features:
    a) Patient has documented weight loss within the past 6 months; or
    b) Patient has nocturnal symptoms; or
    c) Patient has a familial history of colon cancer; or
    d) Patient has blood mixed with their stool (excluding any blood from hemorrhoids)

[redacted]

[redacted]

6. Patient reports use of loperamide in the 12 months prior to Screening for IBS-D symptoms and that loperamide did not provide adequate control of IBS-D symptoms.

[redacted]

9. Patient has not used any loperamide rescue medication within 14 days prior to randomization.

[redacted]

[redacted]

4.1.2 Exclusion Criteria

To be eligible for this study, each of the following criteria must be satisfied with a "NO" answer:

1. Patient has a diagnosis of IBS with a subtype of constipation IBS, mixed IBS, or unsubtyped IBS by the Rome III criteria (refer to Appendix 12.2 for details).

2. Patient has a history of inflammatory or immune-mediated GI disorders including inflammatory bowel disease (i.e., Crohn's disease, ulcerative colitis), microscopic colitis, or celiac disease.

3. Patient has a history of diverticulitis within 3 months prior to screening.

4. Patient has a documented history of lactose intolerance.

5. Patient has a documented history of bile-acid malabsorption.

6. Patient has a history of chronic or severe constipation or intestinal obstruction, stricture, toxic megacolon, GI perforation, fecal impaction, gastric banding, bariatric surgery, adhesions, ischemic colitis, or impaired intestinal circulation (e.g., aortoiliac disease).

7. Patient has any of the following surgical history:

a) Cholecystectomy or previously documented agenesis of gallbladder; or

b) Any abdominal surgery within the 3 months prior to screening; or

c) Major gastric, hepatic, pancreatic, or intestinal surgery (appendectomy, hemorrhoidectomy, or polypectomy greater than 3 months post-surgery are allowed).
Note: For the purposes of this study, laparoscopic surgeries without complication are considered minor and non-exclusionary, provided the condition for which the surgery was performed was not exclusionary.

8. Patient has a history of cholecystitis within 6 months before screening.

9. Patient has a history of pancreatitis or structural diseases of the pancreas, including known or suspected pancreatic duct obstruction.

10. Patient has a history of known or suspected biliary duct obstruction or sphincter of Oddi disease or dysfunction, excluding a history of gallstones.

[redacted]

12. Patient has a history or current evidence of laxative abuse within 5 years prior to screening.

13. Patient has documented evidence of cirrhosis (Child-Pugh classification A, B, or C).

[redacted]

15. Patient has a history of cardiovascular events, including stroke, myocardial infarction, congestive heart failure, or transient ischemic attack within 6 months prior to screening.

16. Patient has an unstable renal, hepatic, metabolic, or hematologic condition.

17. Patient has a history of malignancy within 5 years before screening (except squamous and basal cell carcinomas and cervical carcinoma in situ).

18. Patient has a history of human immunodeficiency virus infection.

19. Patient has a history of Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision-defined substance dependency, excluding nicotine and caffeine, within 2 years prior to screening.

20. Patient has a history of alcohol abuse, alcohol addiction, and alcoholism or drinks more than 3 alcoholic beverages per day.

[redacted]

25. Patient has used aspirin or aspirin-containing medications (>325 mg of aspirin per day) or nonsteroidal anti-inflammatory drugs, when taken specifically for the symptoms of IBS, within 14 days of randomization.

26. Patient has current (within 14 days of randomization) or expected use of any narcotic or opioid-containing agents, tramadol, docusate, enemas, GI preparations (including antacids containing aluminum or magnesium, antidiarrheal agents [except loperamide rescue medication after randomization]), antinausea agents, antispasmodic agents, bismuth, or prokinetic agents.

27. Patient has current (within 28 days of randomization) use of rifaximin or other antibiotics (with the exception of topical antibiotics or a 1-day course with an antibiotic). Expected use of rifaximin or other antibiotics during the course of the study that is known at the time of randomization (e.g., for planned elective surgery) is also prohibited. However, a patient will be allowed to remain in the study should unplanned used of antibiotics other than rifaximin occur after the patient has been randomly assigned to study drug.

[redacted]

31. Patient has an elective surgery planned or expects to need elective surgery at any time during the study. An elective procedure scheduled after the patient has been randomly assigned to study drug will not be considered a protocol violation.

[redacted]

4.2 Duration of Study

The duration of the study is defined for each patient as the date signed written informed consent is provided through the posttreatment visit (visit 7) on day 126.

4.2.1 Withdrawal of Patients from the Study

All patients have the right to withdraw from the study at any time, for any reason, without prejudice. At any point, the investigator may discontinue the patient's study participation at his/her discretion and ensure the patient receives appropriate medical care; the investigator may also consult the medical monitor to discuss out-of-range test results. The patient may also be withdrawn or terminated at the request of the sponsor. Additionally, although Allergan has every intention of completing the study, Allergan reserves the right to discontinue the study at any time for clinical or administrative reasons.

As part of the clinical laboratory assessments, liver enzymes (ALT, AST, alkaline phosphatase), and total bilirubin values will be evaluated for all patients. In the event that a patient's bilirubin level is elevated after the first dose of study drug, a fractionated bilirubin test should be performed if possible. In general, an increase in serum aminotransferases to greater than 3 times ULN after the first dose in patients who entered the study with normal baseline values should be followed by repeat testing within 48 to 72 hours of all 4 of the usual serum measures (ALT, AST, alkaline phosphatase, and total bilirubin) to confirm the abnormalities and to determine if they are increasing or decreasing. There also should be an inquiry made about symptoms. Patients should be observed for other possible causes of elevated liver function test results including acute viral hepatitis, alcoholic and autoimmune hepatitis, hepatobiliary disorders, nonalcoholic steatohepatitis, cardiovascular causes, or concomitant treatments. If baseline transaminases are found to be elevated above the ULN, the preceding guidance should be considered in patients who double their baseline value(s). If the repeat value for ALT or total bilirubin is unchanged or indicates decreasing activity, monitoring should continue at weekly intervals until the results are acceptable or normalized. If any value has increased further, immediate close observation is required. If close monitoring is not possible, the drug should be discontinued.

Withdrawal from the study should be considered if any of the following occurs:

- ALT or AST >8 × the ULN
- ALT or AST >5 × ULN for more than 2 weeks
- ALT or AST >3 × ULN and (total bilirubin >2 × ULN or international normalized ratio >1.5)

- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

For complete information regarding withdrawal from the study in the event of a marked elevation of liver enzymes, refer to Pages 9-10 of Guidance for Industry – Drug-Induced Liver Injury: Premarketing Clinical Evaluation (US Department of health and Human Services 2009).

4.2.2 Handling of Withdrawals

Patients who discontinue study treatment or active participation in the study will no longer receive study drug.

When a patient withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the electronic case report form (eCRF). Whenever possible, for all patients who discontinue study treatment or withdraw from the study prematurely will undergo all end-of-treatment/early withdrawal visit assessments. Patients who fail to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol. For patients that are considered to be lost to follow-up, the site should make every attempt possible to contact the patient (e.g., via documented phone call attempts and if necessary, a certified letter to the patient).

It is vital to obtain follow-up data on any patient withdrawn because of an AE or serious AE (SAE). In every case, efforts must be made to undertake protocol-specified safety follow-up procedures until resolution or stabilization.

4.2.3 Replacements

Patients who discontinue participation in the study for any reason after randomization will not be replaced.

5 Study Treatments

5.1 Method of Assigning Patients to Treatment Groups

Approximately 340 patients will be randomly assigned (in a 1:1 ratio) to 1 of 2 treatment groups (eluxadoline 100 mg BID or matching placebo).

The randomization schedule will be sequestered until the study is unblinded after database lock. It will also use an appropriate block size, which will not be revealed to the study sites.

The randomization mechanism for the study will be deployed within an interactive response system (IxRS) and accessible 24 hours a day to authorized users. Study sites will access the IxRS to execute each randomization after a patient has met all prerequisites for randomization and has completed all scheduled procedures for day 1. Study site personnel, who are all blinded to treatment assignment, will receive a randomization notification indicating only the unique patient identifier and the date and time of randomization for each patient.

All patients will be assigned a unique patient number by the randomization system. After a patient number has been assigned, the number will not be reused even if the patient withdraws before receiving any study drug.

5.2 Treatments Administered

Patients will be randomly assigned to 1 of 2 treatment groups as follows:

- Group 1: Eluxadoline 100 mg oral tablets BID with food
- Group 2: Matching placebo oral tablets BID with food

The study drug must be swallowed whole with liquid and not chewed, divided, dissolved, or crushed.

In addition, patients will receive instructions for use of loperamide rescue medication for acute treatment of uncontrolled diarrhea (refer to Section 5.9 for details).

5.3 Identity of Study Drug

Eluxadoline will be supplied as 100-mg, immediate release, film-coated (Opadry II) tablets. The excipients included in the formulation are microcrystalline cellulose, silicon dioxide, crospovidone, mannitol, and magnesium stearate. Placebo tablets of matching tablet image contain the same excipients. [redacted], on behalf of the sponsor, will provide adequate supplies of eluxadoline and matching placebo tablets of identical size and shape to study sites.

The following drug supplies will be used in the study:

Product	Supplied as:
Eluxadoline	100-mg tablets
Placebo	100-mg tablets

Patients in each treatment group will receive a bottle containing 4-weeks' worth of study drug at randomization (visit 3), week 4 (visit 4), and week 8 (visit 5). Patients will be instructed to take 1 tablet BID with food.

5.4 Management of Clinical Supplies

5.4.1 Study Drug Packaging and Storage

The study drug will be packaged and labeled according to current Good Manufacturing Practices and local regulations.

The study drug will be packaged in child-resistant 70-count bottles by [redacted] on behalf of the sponsor. The bottles will be labeled with double-blinded labels.

Each bottle will contain a (randomized) dosage for 1 patient for 4 weeks of the 12-week double-blind treatment period and will be distributed at each of the scheduled visits during the treatment period: randomization (visit 3), week 4 (visit 4), and week 8 (visit 5).

Recommended storage conditions for study drug are as per the commercial product. The study drug will be stored in controlled temperatures ranging from [redacted] The storage conditions will be indicated on the label. Expiry dates will

be provided directly on the label or communicated to the sites with an expiry memo and/or managed electronically if drug distribution for the study is managed by IxRS.

5.4.2 Test Article Accountability

The investigator will maintain accurate records of receipt of all test articles, including dates of receipt. In addition, accurate records will be kept regarding when and how much test article is dispensed and used by each patient in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drugs will be reconciled and retained or destroyed according to applicable regulations.

5.4.3 Other Supplies

Patients will be provided with instructions on how to enter their diary data into the ePRO. Laboratory kits for assessments will be provided to the sites centrally.

5.5 Overdose Management

An overdose is any dose of study treatment given to a patient or taken by a patient that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly reported to the medical monitor. Overdoses without signs or symptoms do not need to be recorded as AEs; in case of any AEs associated with the overdose, these should be reported on relevant AE/SAE sections in the eCRF.

5.5.1 Treatment of Overdose

No reports of overdosage with eluxadoline have been reported.

In the event of acute overdose, the stomach should be emptied and adequate hydration maintained. The patient should be carefully observed and given standard supportive treatment as required. Given eluxadoline's action at opioid receptors, administration of a narcotic mu-opioid antagonist, such as naloxone, should be considered. Considering the short half-life of naloxone, repeated administration may be necessary. In the event of naloxone administration, patients should be monitored closely for the return of overdose symptoms, which may indicate need for repeated naloxone injection (VIBERZI PI 2015).

5.5.2 Medication Errors

Dispensing study treatment to be taken by patients in an outpatient study increases risk for medication errors. All errors in medication dispensing or administration must be carefully documented. These errors may include but are not limited to providing the wrong dose, losing medication, or administration at the wrong time of day. Medication adherence will be emphasized at every study visit. Additional adherence procedures and/or technology, such as a mobile device application, may be implemented.

5.5.3 Treatment of Medication Errors

The treatment of medication errors should be discussed with the medical monitor on a case by case basis. In the case of overdose, refer to Section 5.5.1.

5.6 Blinding

Patients will be randomly assigned to double-blind treatment of eluxadoline at a dose of 100 mg BID or placebo BID. Blinding of the placebo tablets and eluxadoline tablets will be maintained throughout the study by using active and placebo tablets that are identical in appearance. The randomization schedules and treatment assignments will remain sequestered until the study blind is broken.

5.6.1 Breaking the Blind

When necessary for the safety and proper treatment of the patient, the investigator can unblind the patient's treatment assignment to determine which treatment has been assigned and institute appropriate follow-up care. When possible, the sponsor (Allergan Medical Safety Physician) should be notified prior to unblinding study drug. The investigator should inform the sponsor (Allergan Medical Safety Physician) of the unblinding if there is no notification prior to the unblinding.

The treatment assignment for the patient can be determined by designated site personnel in the IxRS system via password protected access. The reason for breaking the code must be recorded in the patient's source documents.

5.7 Treatment Compliance

Treatment compliance will be assessed at the study site by pill counts. This review will be documented in the source documents.

5.8 Prior and Concomitant Therapy

All prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications taken within 2 weeks prior to randomization will be recorded as prior medications. All medications taken after randomization and through the early termination or follow-up visit will be recorded as concomitant therapy. Use of all concomitant medications will be recorded in the patient's eCRF. Any changes in concomitant medications will also be recorded in the patient's eCRF. The minimum requirement is that drug name and the dates of administration are to be recorded. It will also be determined which prior medications were prescribed or taken over-the-counter by patients for the treatment of IBS-D.

The following medications are prohibited before and during the study, as indicated:

- 5-HT_3 antagonists (e.g., alosetron or ondansetron); prohibition begins within 14 days of screening.
- Aspirin or aspirin-containing medications (>325 mg of aspirin per day) or nonsteroidal anti-inflammatory drugs, when taken specifically for the symptoms of IBS; prohibition begins within 14 days of randomization.
- Investigational drug or investigational medical device within 30 days prior to randomization.
- Narcotics or opioid-containing agents, tramadol, docusate, enemas, or GI preparations (including antacids containing aluminum or magnesium, antidiarrheal agents [except loperamide rescue medication after randomization], antinausea agents, antispasmodic agents, bismuth, or prokinetic agents); prohibition begins within 14 days of randomization.
- Rifaximin or other antibiotics (with the exception of topical antibiotics or a 1-day course with an antibiotic); prohibition begins within 28 days of randomization (see exclusion criteria number 27 for details).

Stable doses of antidepressants (i.e., for the 3 months prior to screening) can be taken during the study. Additionally, medications taken for the treatment of allergies, chronic medical conditions, and migraine headaches can be taken during this study (with the exception of opioids for acute treatment of migraines). Patients must be on a stable dose of medication for chronic migraines or preventive therapy for at least 1 month at screening. As-needed use of benzodiazepines for anxiety is permitted during the study.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the source documents as well as in the eCRF.

5.9 Acute Loperamide Rescue Medication for Uncontrolled Diarrhea

Use of loperamide rescue medication for the acute treatment of uncontrolled diarrhea will not be allowed within 14 days prior to randomization.

During the double-blind Treatment period and the Posttreatment period of the study, patients will be allowed to take loperamide rescue medication for the acute treatment of uncontrolled diarrhea. Loperamide at a unit dose of 2 mg may be taken once approximately every 6 hours with the following guidelines:

- No more than 4 unit doses over a continuous 24-hour time period (8 mg/day)
- No more than 7 unit doses over a continuous 48-hour time period (14 mg over 2 days)
- No more than 11 unit doses over a continuous 7-day time period

The use of loperamide rescue medication should be recorded by the patient in the ePRO diary. If a patient uses more than the allowed amount of loperamide rescue medication the ePRO system will generate a notification to alert the investigator. Excessive use of loperamide rescue medication may be cause for study discontinuation but will not be considered a protocol violation.

6 Study Assessments and Procedures

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.2 Efficacy Assessments

6.2.1 Daily IBS Symptoms

Patients will be required to access the ePRO diary each evening, preferably at the same time each day, to record daily IBS symptoms:

- Stool Consistency: During their daily ePRO entry throughout the 12 weeks of double-blind treatment period, patients will be asked to rate the BSS most representative of the past 24 hours. The patient-reported BSS is a 1 to 7 scale where 1 corresponds to a hard stool and 7 corresponds to watery stool (Appendix 12.3):

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

  2=Sausage shaped but lumpy

  3=Like a sausage but with cracks on surface

  4=Like a sausage or snake, smooth and soft

5=Soft blobs with clear-cut edges (passed easily)

6=Fluffy pieces with ragged edges, a mushy stool

7=Watery, no solid pieces (entirely liquid)

- Worst Abdominal Pain: During their daily ePRO entry throughout the 12 weeks of double-blind treatment period, patients will be asked to rate their WAP in the past 24 hours. The patient-reported WAP in the past 24 hours will be recorded on a 0 to 10 scale, where 0 corresponds to no pain and 10 corresponds to worst imaginable pain.

- Abdominal Discomfort: During their daily ePRO entry throughout the 12 weeks of double-blind treatment period, patients will be asked to rate their abdominal discomfort in the past 24 hours. The patient-reported worst abdominal discomfort in the past 24 hours will be recorded on a 0 to 10 scale, where 0 corresponds to no discomfort and 10 corresponds to worst imaginable discomfort.

- Abdominal Bloating: During their daily ePRO entry throughout the 12 weeks of double blind treatment period, patients will be asked to rate their abdominal bloating in the past 24 hours. The patient-reported worst abdominal bloating in the past 24 hours will be recorded on a 0 to 10 scale, where 0 corresponds to no bloating and 10 corresponds to worst imaginable bloating.

- Frequency, Urgency and Incontinence: During their daily ePRO entry throughout the 12 weeks of double-blind treatment period, patients will be asked to record the number of bowel movements (and characteristics, where applicable), number of urgency episodes, and number of episodes of fecal incontinence, over the past 24 hours.

[redacted]

[redacted]

[redacted]

[redacted]

6.3.1 Adverse Events

Adverse events occurring during the study will be recorded in an AE eCRF. If AEs occur, the first concern will be the safety of the study participants.

6.3.1.1 Definitions of Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. In addition, during the screening period, AEs will be assessed regardless of the administration of a pharmaceutical product.

Note: Adverse events must be collected once informed consent has been obtained, regardless of whether or not the patient has been administered study drug. Progression of treatment

indication including new or worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variables and assessed as unequivocally associated with the disease progression and/or lack of efficacy, should NOT be reported as AEs unless the disease progression is greater than anticipated in the natural course of the disease.

Adverse events will be assessed, documented, and recorded in the eCRF throughout the study (i.e., after informed consent has been obtained). At each visit, after the study assessments have been completed, the investigator will begin by querying for AEs by asking each subject a general, non-directed question such as "How have you been feeling since the last visit?" Directed questioning and examination will then be done as appropriate. All reported AEs will be documented in the appropriate eCRF.

Any abnormal laboratory test results (hematology, serum chemistry, or serum lipase) or other safety assessments (e.g., vital sign measurements), including those that worsen from baseline, felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs. See Section 4.2.1 for specific instructions for monitoring patients with abnormal liver function tests.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition, are **not** to be reported as AEs or SAEs.

6.3.1.2 Serious Adverse Event:

An SAE is any AE occurring at any dose that results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (See Section 6.3.1.4 for procedures for reporting an SAE).

Allergan considers all cancer AEs as SAEs. In addition, Allergan considers any abortion (spontaneous or nonspontaneous) as an SAE.

Pre-planned surgeries or procedures for pre-existing, known medical conditions for which a patient requires hospitalization is not reportable as an SAE. Any pre-planned surgery or procedure should be clearly documented in the site source documents by the medically qualified investigator at the time of the patient's entry into the study. If it has not been documented at the time of the patient's entry into the study, then it should be documented as an SAE and reported to Allergan.

6.3.1.3 Reporting Adverse Events

Any AE must be recorded in the appropriate eCRF.

All AEs that are drug-related and unexpected (not listed as treatment-related in the current Investigator's Brochure) must be reported to the governing Institutional Review Board/Independent Ethics Committee (IRB/IEC) as required by the IRB/IEC, local regulations, and the governing health authorities. Any AE that is marked "ongoing" at the posttreatment visit must be followed up as appropriate.

6.3.1.4 Reporting Serious Adverse Events

Any SAE occurring during the study period (beginning with informed consent) and for at least 30 days after the last dose of study drug must be immediately reported but no later than 24 hours after learning of an SAE. Serious AEs must be reported directly to Allergan in the US and Canada as listed on the Allergan Study Contacts Page and recorded on the SAE form. All subjects with an SAE must be followed up and the outcomes reported. The investigator must supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and discharge summaries).

In the event of an SAE, the investigator must:

1. Notify Allergan/[redacted] immediately by fax or email using the SAE form (contact details can be found on page 1 of the SAE form); phone numbers and relevant Allergan personnel contacts are also on the front page of protocol and Study Contacts Page.

2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject.

3. Provide Allergan/[redacted] with a complete, written description of the AE(s) on the SAE form describing the event chronologically, including any treatment given (e.g., medications administered, procedures performed) for the AE(s). Summarize relevant clinical information about the event: signs, symptoms, diagnosis, clinical course and relevant clinical laboratory tests, etc. Include any additional or alternative explanation(s) for the causality which includes a statement as to whether the event was or was not related to the use of the investigational drug.

4. Promptly inform the governing IRB/IEC of the SAE as required by the IRB/IEC, local regulations, and the governing health authorities.

6.3.1.5 Assessment of Severity

A clinical determination will be made of the intensity of an AE. The severity assessment for a clinical AE must be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated.
Moderate	Discomfort enough to cause interference with usual activity.
Severe	Incapacitating with inability to work or do usual activity.
Not applicable	In some cases, an AE may be an “all or nothing” finding which cannot be graded.

6.3.1.6 Assessment of Causality

A determination will be made of the relationship (if any) between an AE and the study drug or study procedure, as applicable. A causal relationship is present if a determination is made that there is a reasonable possibility that the AE may have been caused by the drug or study procedure.

If an AE is deemed related to study treatment, the investigator will be asked to further delineate whether the AE was related to the administration procedure (versus the study drug).

Note: a study procedure occurring during the screening/baseline period can include a washout of medication or introduction of a run-in medication or study required diagnostic procedure.

6.3.2 Investigator Required Contact to Patient

6.3.2.1 Investigator Required Contact to Patient for Diary-Confirmed Constipation

As previously noted, the ePRO system will notify the investigator if a patient reports not having a bowel movement for 4 consecutive days (i.e., diary-confirmed constipation). Once notified the investigator must contact the patient to review his/her status as soon as possible. An unscheduled visit to further evaluate the patient's status should be arranged if deemed warranted 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.

The investigator should consider permanent discontinuation of study drug should a patient not have a bowel movement for more than 7 consecutive days or have more than one episode of diary-confirmed constipation.

If a decision to permanently discontinue study drug due to diary-confirmed constipation is made, the patient should be brought in immediately for study termination procedures.

6.3.2.2 Investigator Required Contact to Patient for Frequent Use of Loperamide Rescue Medication

During the double-blind Treatment period and the posttreatment period, patients may use loperamide rescue medication for the acute treatment of uncontrolled diarrhea as described in Section 5.9. The ePRO system will notify the investigator of patients requiring >4 unit doses over a continuous 24-hour time period (8 mg/day), >7 unit doses over a continuous 48-hour time period (14 mg over 2 days), or >11 unit doses over a continuous 7-day time period. Once notified the investigator must contact the patient to review his/her status as soon as possible.

An unscheduled visit to further evaluate the patient's status should be arranged if deemed warranted by the investigator. A decision to permanently discontinue study drug due to

excessive use of loperamide rescue medication will be left to the discretion of the investigator on a patient-by-patient basis.

[redacted]

6.4 Safety Monitoring Committee

No safety monitoring committee will be used for the study.

6.5 Pregnancy

Pregnancy tests will be performed for all women according to local procedures unless they are surgically sterile or there is a documented history of their postmenopausal status. A serum pregnancy test will be performed at screening and urine pregnancy tests will be performed at all other visits through week 12 (or early withdrawal visit), unless a serum pregnancy test is preferred at the discretion of the investigator or if required by local regulations. Additional serum or urine pregnancy tests may be conducted throughout the study in sufficient number, as determined by the investigator or required by local regulation, to establish the absence of pregnancy. If positive, the patient is not eligible to enter or continue in the study.

Any pregnancy that occurs after the first dose of study drug or within 30 days of the last dose of study drug must be immediately reported, but no later than 24 hours, after learning of a pregnancy. Pregnancies must be reported directly to Allergan in the US and Canada, as listed on the Allergan Study Contacts Page and recorded on the Pregnancy Communication Form. Pregnancies in female partners of male patients occurring during the time frame described above must also be reported. The pregnancy will be followed until final outcome using the Pregnancy Notification Form and indicating that it is a follow-up report. The outcome, including any premature termination, must be reported directly to Allergan in the US and Canada. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any patient that becomes pregnant will be discontinued from the study.

If the patient agrees to have her primary care physician informed, the investigator should notify the patient's primary care physician that she was participating in a clinical study at the time that she became pregnant, and the investigator should provide the details of the treatment that the patient received (blinded or unblinded; [refer to Section 5.6.1 for information on unblinding], as applicable).

6.6 Laboratory Analyses

The contract research organization central laboratory will perform all clinical laboratory tests, except urine pregnancy tests, which will be performed locally at the study site. The details related to sample handling, blood draw amounts, tubes, shipping, address, etc. are available in a separate laboratory manual.

Blood and urine samples for hematology, serum chemistry, serum lipase, and serum and urine pregnancy tests will be prepared using standard procedures.

Hematology and serum chemistry testing will be completed at screening, baseline (day 1), week 4, and all subsequent study visits through week 14 (posttreatment follow-up visit). Serum lipase testing will be performed at screening and baseline (day 1). Unscheduled blood draws for additional serum chemistry testing (lipase specifically) should be completed when possible for any patients with confirmed or suspected AEs of pancreatitis.

In addition, pregnancy tests will be performed for all women according to local procedures unless they are surgically sterile or there is a documented history of their postmenopausal status. A serum pregnancy test will be performed at screening and urine pregnancy tests will be performed at all other study visits through week 12 (or early withdrawal study visit), unless a serum pregnancy test is preferred at the discretion of the investigator or if required by local regulations. The serum pregnancy test will be performed by the central laboratory.

The blood samples will be used for the following tests:

Hematology: white blood cell count with differential, hemoglobin, hematocrit, platelet count, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.

Serum Chemistry: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, carbon dioxide, calcium (albumin corrected), chloride, creatinine, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin*, and total protein. Serum lipase will be tested at screening and baseline (day 1) only. Thyroid-stimulating hormone will be tested at screening only.

*Note: If total bilirubin values are elevated in a patient who has received at least 1 dose of study drug, fractionated levels will also be determined if possible.

6.7 Sample Collections

The details related to sample collection are provided in a separate laboratory manual.

7 Statistical and Analytical Plan

A statistical analysis plan (SAP) will be prepared and finalized before completion of the study. The plan document will provide further details regarding the definition of analysis variables and methodologies to meet all study objectives.

7.1 Primary Efficacy Endpoints

The primary efficacy endpoint is the proportion of primary composite responders determined over the 12-week double-blind treatment period. A primary composite responder is defined as a patient who meets the daily composite response criteria for at least 50% of days with diary entry during the interval from weeks 1 to 12.

A patient must meet BOTH of the following criteria on a given day to be a daily composite responder:

- Daily pain response: WAP score in the past 24 hours improved by ≥40% compared to baseline pain (average of daily WAP in the week prior to randomization).
- Daily stool consistency response: BSS score <5 (i.e., score of 1, 2, 3, or 4); or the absence of a bowel movement if accompanied by ≥40% improvement in WAP compared to baseline pain.

To be eligible to be a primary composite responder, a patient must have a minimum of 60 days of diary entries, including partial entries, over the interval from weeks 1 to 12. A partial diary entry consists of any of 3 data components: BSS score, WAP score, and bowel movement frequency. Partial entries will be used to determine whether or not a patient is a daily responder. Any patient with fewer than 60 days of diary entry will be considered a non-primary composite responder, including patients in the ITT analysis who recorded no post-baseline diary data.

7.2 Secondary Efficacy Endpoints

The following are the secondary efficacy endpoints:

- Proportion of stool consistency responders: defined as patients who meet the daily stool consistency response criteria (as defined in Section 7.1) for ≥50% of days with diary entries over a certain time period. This endpoint is defined for the 12-week treatment period, and for each 4-week interval (weeks 1 to 4, 5 to 8, and 9 to 12). For the weeks 1 to 12 time period, the ≥50% requirement is the same as specified for the primary efficacy endpoint in Section 7.1. For each of the 4-week periods, a responder must have a minimum of 20 days of diary entries over the 4 weeks.

- Proportion of pain responders: defined as patients who meet the daily pain response criteria (as defined in Section 7.1) for ≥50% of days with diary entries over a certain time period. This endpoint is defined for the 12-week treatment period, and each 4-week interval (weeks 1 to 4, 5 to 8, and 9 to 12). For the weeks 1 to 12 time period, the ≥50% requirement is the same as specified for the primary efficacy endpoint in Section 7.1. For each of the 4-week periods, a responder must have a minimum of 20 days of diary entries over the 4 weeks.

- Proportion of monthly composite responders: defined as patients who meet the daily composite response criteria (as defined in Section 7.1) for at least 50% of days with diary entry for a minimum of 20 days during each 4-week interval (weeks 1 to 4, 5 to 8, and 9 to 12).

[redacted]

[redacted]

[redacted]

7.5 Sample Size Calculations

Assuming a placebo response for the primary efficacy endpoint, composite response in pain and stool consistency rate at 12 weeks, of 13% and an approximate 14% treatment effect of eluxadoline over placebo, a sample size of 340 patients is required (1:1 randomization ratio, eluxadoline: placebo, 170 patients per arm). (From the Integrated Summary of Efficacy Report, patients refractory to loperamide in the pooled studies IBS 3001 and 3002 had 13% and 27% composite response in pain and stool consistency rates in the placebo and eluxadoline groups, respectively. This set of response rates are the same when using 40%

WAP improvement to replace the 30% in the primary efficacy composite responder criteria.) This sample size will have approximately 90% power to detect the difference of the primary efficacy endpoint response proportion between eluxadoline and placebo using a 2-sided chi-square test at a significance level of 0.05.

7.6 Analysis Sets

The following analysis sets will be used in the statistical analyses.

Intent-to-Treat Population (ITT): The ITT population will include all randomized patients. Patient disposition, demographics, and baseline characteristics and efficacy and HEOR data will be analyzed on the ITT population. Patients will be analyzed according to their randomization assignment, regardless of the actual treatment received. In this study, only randomized patients are considered as enrolled.

Safety Population: The Safety Population will include all patients enrolled who received at least 1 dose of study drug. Safety data will be analyzed using the safety population. Patients will be grouped and analyzed according to the treatment they will actually receive.

7.7 Statistical Analysis Methodology

Statistical analysis will be performed using [redacted] Continuous variables will be summarized using mean, standard deviation, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Data will be listed in patient listings.

All statistical tests will be 2-sided at significance level of 0.05.

No adjustment for the multiplicity of the endpoints will be performed since there is only a primary efficacy endpoint and no interim analyses have been planned.

Statistical analysis and methodologies will be briefly discussed in sections below. All details of the statistical analyses, methods, and missing data handling strategy will be described in the study SAP.

7.7.1 Analysis of Primary Efficacy Endpoint

The primary study analysis will be to evaluate the proportions of primary composite responders (defined in Section 7.1) over 12 weeks of treatment between the eluxadoline and placebo groups. These 2 proportions are represented as $\pi_{eluxadoline}$ and $\pi_{Placebo}$. The primary hypotheses for this study are described below:

H_0: $\pi_{eluxadoline} - \pi_{Placebo} = 0$

Vs

H_A: $\pi_{eluxadoline} - \pi_{Placebo} \neq 0$

The numbers of responder and non-responder patients and corresponding percentages will be summarized and presented in a summary table by treatment group. Treatment effect will be assessed using the chi-square test.

As supportive analysis, the primary endpoint will be analyzed using logistic regression model that will include treatment group as a factor and baseline pain score and stool consistency score as covariates.

7.7.2 Analysis of Secondary Efficacy Endpoint

The proportions of stool consistency responders and pain responders (defined in Section 7.2) over the 12-week treatment period and at each 4-week interval (weeks 1 to 4, 5 to 8, and 9 to 12) will be analyzed similar to the primary endpoint analysis.

The proportion of monthly composite responders (defined in Section 7.2) at each 4-week interval (weeks 1 to 4, 5 to 8, and 9 to 12) will be analysed similar to the primary endpoint analyses.

[redacted]

[redacted]

7.7.6 Other Analyses

Not applicable.

7.7.7 Interim Analyses

There will be no interim analysis for this study.

7.8 Handling of Missing Data

Based upon interactive voice response compliance data from the completed Phase 3 trials in patients with IBS-D, we are anticipating on the order of 15% to 20% missed ePRO diary entry days for those patients who have not discontinued. For this study, missed daily ePRO diary entries will not be considered as protocol violations. Adequacy of non-missing diary entries for each study endpoint has been defined specifically in the primary, secondary, and additional endpoints sections of this protocol; patients will be considered as non-responders for the corresponding endpoints if the adequacy criteria are not met.

Detailed missing data strategies will be defined in the study SAP.

7.9 Data Quality Assurance

To ensure compliance with Good Clinical Practice (GCP) and all applicable regulatory requirements, Allergan may conduct a quality assurance audit of the site records and regulatory agencies may conduct a regulatory inspection at any time during or after the study. In the event of an audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

7.9.1 Data Management

As part of the responsibilities assumed by participating in the study, the principal investigator or subinvestigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The investigator agrees to maintain source documentation as part of the case histories. These source documents may include patient’s medical records, hospital charts, clinic charts, the investigator’s patient study files, patient diaries, as well as diagnostics tests such as laboratory reports, etc.

Allergan/[redacted] will supply the eCRF.

The principal investigator or designee(s) must enter study data required by the protocol into an electronic data capture (EDC) system. All eCRF fields are to be filled in. If an item is not available or is not applicable, this fact should be indicated. Blank fields should not be present unless otherwise directed. The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data).

Guidelines for completion of eCRFs will be reviewed with study site personnel at the investigators' meeting/site initiation visits. The principal investigator is responsible for approval of the entered/corrected data. The eCRF responsibilities of the site personnel will be documented on the site delegation log, which will be collected at the closeout visits. Principal investigators or designees must review and approve the data before database lock.

The clinical research associate will visit each study site, at a frequency documented in the monitoring plan, to review eCRFs for completeness and accuracy. Any discrepancies found between source documents and completed eCRFs will be entered as a discrepancy in the EDC system by the clinical research associate. Appropriate study site personnel should then address those discrepancies in the EDC system. Uniform procedures for eCRF correction (queries) will be discussed at the investigators' meeting and during the study site initiation visits.

Data from eCRFs and other external data sources will be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

Computerized and manual procedures should be used to review and check data from eCRFs and data from other external sources for omissions, apparent errors, and values that may require further clarification. Data queries requiring clarification should be documented, and the study site should be requested to review and resolve the queries. Only authorized personnel can make corrections to the clinical database, and all corrections should be documented in an audit trail. A quality assurance audit should be performed before database lock.

After database lock, each study site will receive a CD-ROM containing all of their site-specific eCRF data as entered into EDC for the study, including full discrepancy and

audit history. Additionally, a CD-ROM copy of all of the study site's data from the study will be created and sent to the sponsor for storage.

8 Ethics

8.1 Independent Ethics Committee or Institutional Review Board

The US federal regulations (and applicable local country regulations) and the International Council for Harmonisation (ICH) guidelines require that approval be obtained from an IRB/IEC before participation of human patients in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R1): GCP will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The principal investigator or subinvestigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The principal investigator or subinvestigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to patients.

8.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

8.3 Patient Information and Consent

A written informed consent in compliance with US Title 21 Code of Federal Regulations (CFR) Part 50 (and applicable local country regulations) shall be obtained from each patient before entering the study or performing any unusual or nonroutine procedure that involves risk to the patient. An informed consent template may be provided by the sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating patients must sign the revised form, if applicable, especially if the rights, well-being, and the safety of the patient are impacted by the revision.

Before recruitment and enrollment, each prospective patient will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing the ICF.

The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the patient.

9 Investigator's Obligations

The following administrative items are meant to guide the investigator (principal investigator or subinvestigator) in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

9.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient, except as necessary for monitoring and auditing by the sponsor, its designee, the local regulatory authorities, or ethics committees.

The principal investigator or subinvestigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.2 Study Reporting Requirements

By participating in this study, the principal investigator or subinvestigator agrees to submit reports of SAEs according to the timeline and method outlined in the protocol. In addition, the principal investigator or subinvestigator agrees to submit annual reports to his/her IRB/IEC as appropriate.

9.3 Financial Disclosure and Obligations

Principal investigators or subinvestigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54 (and applicable local country regulations). In addition, the investigator (principal investigator or any subinvestigators) must provide to

the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor [redacted] is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor [redacted] is financially responsible for further treatment of the patient's disease.

9.4 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R1) 8.2, 21 CFR (Parts 50, 54, 56, and 312), and applicable local country regulations by providing the following essential documents, including but not limited to:

- An original investigator-signed investigator agreement page of the protocol
- An IRB/IEC approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient
- IRB/IEC approval
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with 42 CFR 493
- Curriculum vitae (CV) for the principal investigator and each subinvestigator listed on Form FDA 1572. Current licensure must be noted on the CV or a copy of current licensure provided along with the CV. They will be signed and dated by the principal investigators and subinvestigators, indicating that they are accurate and current
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

9.5 Study Conduct

The principal investigator agrees that the study will be conducted according to the principles of ICH E6(R1). The principal investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins.

9.6 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R1) and all applicable guidelines and government regulations.

9.7 Adverse Events and Study Report Requirements

By participating in this study, the principal investigator or subinvestigator agrees to submit reports of SAEs according to the time line and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

9.8 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

9.9 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the principal investigator or subinvestigator/institution as to when these documents no longer need to be retained.

9.10 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

10 Study Management

10.1 Monitoring

10.1.1 External Data Monitoring Committee

There will not be an external data monitoring committee for this study.

10.1.2 Monitoring of the Study

The clinical research associate, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the clinical research associate will visit the principal investigator or subinvestigator at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the principal investigator or subinvestigator and study site personnel.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current ICH E6(R1) and current standard operating procedures.

10.1.3 Inspection of Records

Principal investigators or subinvestigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the principal investigator or subinvestigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (e.g., FDA or other regulatory agency) access to all study records.

The principal investigator or subinvestigator should promptly notify the sponsor and [redacted] of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

10.2 Management of Protocol Amendments and Deviations

10.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the principal investigator's or subinvestigator's IRB/IEC for approval before patients are enrolled into an amended protocol.

10.2.2 Protocol Violations and Deviations

The principal investigator or subinvestigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The principal investigator or subinvestigator may implement a deviation from, or a change of the protocol to eliminate an immediate hazard to study patients without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the principal investigator or subinvestigator. Deviations usually have an impact on individual patients or a small group of patients and do not involve inclusion/exclusion or primary endpoint criteria.

A protocol violation occurs when there is nonadherence to the protocol that results in a significant, additional risk to the patient, when the patient or principal investigator or subinvestigator has failed to adhere to significant protocol requirements (e.g., inclusion/exclusion criteria) and the patient was enrolled without prior sponsor approval, or when there is nonadherence to federal regulations and/or ICH E6(R1) guidelines.

Protocol violations and deviations will be documented by the clinical research associate throughout the course of monitoring visits. Principal investigators will be notified in writing by the clinical research associate of deviations. Investigators should notify their IRB/IEC of all protocol violations and deviations in a timely manner.

10.3 Study Termination

Although Allergan has every intention of completing the study, Allergan reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last patient completes the last visit (includes follow-up visit).

10.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study report is prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the clinical study report in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, the sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study patients, as appropriate. The study results will be posted on publicly available clinical trial registers.

11 Reference List

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12 Appendices

Subtyping IBS by Predominant Stool Pattern (Longstreth et al, 2006)

1. IBS with constipation (IBS-C)—hard or lumpy stools[a] ≥25% and loose (mushy) or watery stools[b] <25% of bowel movements.[c]
2. IBS with diarrhea (IBS-D)—loose (mushy) or watery stools[b] ≥25% and hard or lumpy stool[a] <25% of bowel movements.[c]
3. Mixed IBS (IBS-M)—hard or lumpy stools[a] ≥25% and loose (mushy) or watery stools[b] ≥25% of bowel movements.[c]
4. Unsubtyped IBS—insufficient abnormality of stool consistency to meet criteria for IBS-C, D, or M.[c]

Note. To subtype patients according to bowel habit for research or clinical trials, the following subclassification may be used (see Figure 1). The validity and stability of such subtypes over time is unknown and should be the subject of future research.
[a]Bristol Stool Form Scale 1–2 (separate hard lumps like nuts [difficult to pass] or sausage shaped but lumpy).
[b]Bristol Stool Form Scale 6–7 (fluffy pieces with ragged edges, a mushy stool or watery, no solid pieces, entirely liquid).
[c]In the absence of use of antidiarrheals or laxatives

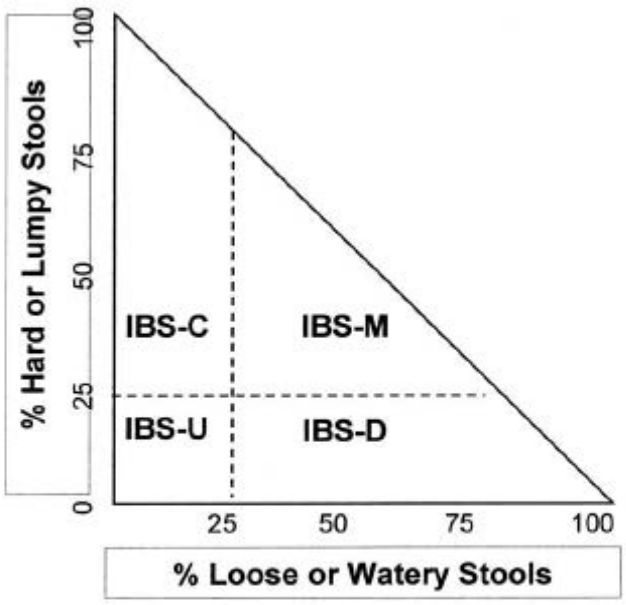
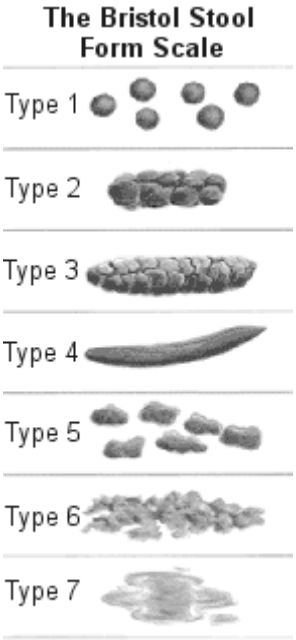


Figure 1. Two-dimensional display of the 4 possible IBS subtypes according to bowel form at a particular point in time. IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, mixed IBS; IBS-U, unsubtyped IBS.

12.3 Appendix: Bristol Stool Scale



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

Type 2 - Sausage shaped but lumpy

Type 3 - Like a sausage but with cracks on surface

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

Type 5 - Soft blobs with clear-cut edges (passed easily)

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

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