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Study ID: 3030-401-002

Title: An Open-Label Pilot Study of Eluxadoline in Participants with Irritable Bowel Syndrome with Diarrhea (IBS-D) Who Have Evidence of Bile Acid Malabsorption (BAM)

Protocol Date: April 17, 2019

Title Page

Protocol Title: 3030-401-002: An Open-Label Pilot Study of Eluxadoline in Participants with Irritable Bowel Syndrome with Diarrhea (IBS-D) Who Have Evidence of Bile Acid Malabsorption (BAM)

Amendment Number: 2

Brief Protocol Title: 3030-401-002 ELX BAM Study

Product: Eluxadoline

Sponsor Name and Legal Registered Address: Allergan Sales, 5 Giralda Farms, Madison, NJ 07940, United States; Allergan Limited, 1st Floor Marlow International, The Parkway, Marlow, Buckinghamshire SL7, 1YL Allergan Sales, 5 Giralda Farms, Madison, NJ 07940, United States

Regulatory Agency Identifying Number(s): IND 79,2014

Emergency Telephone Number: Refer to the study contacts page

SAE Reporting Fax Number/Email:

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Allergan Pharmaceuticals	[redacted]	[redacted]

Approval Date: 17 April 2019

Amendment 1 Date: 05 June 2018

Original Protocol Date: 19 October 2017

Sponsor Signatory:

Signatures of the sponsor signatories are collected on the protocol approval form.

[redacted]

VP, Clinical Development – GI

Therapy Area Head

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	**17 April 2019**
Amendment 1	05 June 2018
Original Protocol	19 October 2017

Purpose of Amendment

The purpose of Protocol Amendment 2 for 3030-401-002 (dated 17 April 2019) is to reflect the definition of BAM based on the most recent literature.

The following is a summary of content-oriented changes that were made. Strikethrough text denotes text removed and bolded text denotes added text. Additional administrative edits were also made, but not specifically noted (eg, corrected spelling, punctuation, grammar, abbreviation, and style errors) including global edits required for consistency.

Table 1–1 Summary of Changes in Protocol Amendment 2

Section No. and Name	Description of Change	Rationale
Title Page	Added Allergan UK, Marlow Sponsor Address to facilitate inclusion of ex-US sites in the study	Update to align with current Allergan standard
Section 5.4 Scientific Rationale for Study Design	Updated with rationale for use of both serum 7αC4 testing and measurement of fecal bile acids to determine BAM status.	To update definition of BAM based on the most recent literature
Synopsis and Section 6.1 Inclusion Criteria	Amended IC 1.01: Participant is a man or woman aged 18 to ~~65~~ **75** years, inclusive, at screening.	Approximately 25% of participants with chronic diarrhea or diarrhea predominant irritable bowel syndrome are found to have bile acid malabsorption. As there is not age restriction in developing bile acid malabsorption, Allergan believe it is critical to understand how this medication will affect this participant population.
Synopsis and Section 6.1 Inclusion Criteria	Amended IC 2.03: Participants with evidence of BAM Participants must have **at least one of the following** ~~results from fasting serum 7αC4 level ≥ 52.5 ng/mL~~ at screening or within 1 calendar year prior to screening. • **fasting serum 7a-hydroxy-4-cholesten-3-one (7αC4) level ≥ 52.5 ng/mL** • **total fecal bile acids > 2337 micromoles/48 hours** • **primary bile acids (fecal CA and CDCA) ≥ 10% in a 48h fecal collection** • **primary bile acids (fecal CA and CDCA) ≥ 4% with total fecal bile acid ≥ 1,000 micromoles/48hr** ~~Note: Participants may be enrolled as BAM positive without serum 7αC4 test results if they have positive results from 48 hour measurement of total fecal bile acids within 1 calendar year prior to~~	To update definition of BAM based on the most recent literature

Section No. and Name	Description of Change	Rationale
	~~screening, defined by total fecal BA > 2337 micromoles/48 hours.~~	
Synopsis and Section 6.1 Inclusion Criteria	Amended IC 2.04: Participants without BAM Participants must have **at least one of the following** ~~results from fasting serum 7αC4 level ≤ 47.1 ng/mL~~ at screening or within 1 calendar year prior to screening. • **fasting serum 7αC4 level ≤ 47.1 ng/mL** • **fasting serum 7αC4 levels > 47.1 ng/mL but < 52.5 ng/mL with fecal bile acids that are negative for bile acid malabsorption (i.e. do not meet criteria 2.03 based on fecal bile acids level)** • **total fecal bile acids (BA) ≤2337 micromoles/48 hours** • **primary bile acids (fecal CA and CDCA) < 10% in a 48h fecal collection** • **primary bile acids (fecal CA and CDCA)< 4% with total fecal bile acid <1,000 micromoles /48hr** ~~Note: Participants may be enrolled as BAM negative without serum 7αC4 test results if they have negative results from 48-hour measurement of total fecal BA within 1 calendar year prior to screening, defined by total fecal BA < 2200 micromoles/48 hours. Participants with fasting serum 7αC4 levels > 47.1 ng/mL but < 52.5 ng/mL may be enrolled as participants without BAM if within 1 calendar year prior to screening visit they had negative results from 48-hour measurements of total fecal BA.~~	

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1. Synopsis

Protocol Title: 3030-401-002: An Open-Label Pilot Study of Eluxadoline in Participants with Irritable Bowel Syndrome with Diarrhea (IBS-D) Who Have Evidence of Bile Acid Malabsorption (BAM)

Protocol Number: 3030-401-002

Brief Title: 3030-401-002 ELX BAM Study

Study Phase: Phase IV

Study Rationale:

Eluxadoline was approved for the treatment of adult patients with IBS-D by the FDA and EMA in 2015 and 2016, respectively. Because the Phase 3 confirmatory studies of eluxadoline for IBS-D were conducted prior to the issuance of the latest version of the Rome criteria (Rome IV) and prior to the publication of the final EMA guideline on irritable bowel syndrome (IBS), these studies did not prospectively exclude patients with evidence of BAM. Baseline characteristics of the Phase 3 IBS-D patient population demonstrated a high prevalence of both obesity and prior cholecystectomy. Given the known association of higher body mass index (BMI) with BAM and that cholecystectomy is a known risk factor for BAM it is conceivable that some portion of participants enrolled in those studies may have had evidence of BAM. Since the eluxadoline Phase 3 IBS-D studies did not evaluate participant's bile acid absorption status, it is unknown whether the effectiveness of eluxadoline may be different in patients with evidence of BAM. It is possible that the overall effects of eluxadoline could have been diluted by a subset of non-responsive participants suffering from BAM for whom a bile acid sequestrant might have been a more appropriate treatment option.

The goal of the present study is therefore to evaluate the possibility of a differential effect of eluxadoline on altered bowel function in IBS-D participants with and without evidence of BAM. The overall hypothesis of this study is that the efficacy of eluxadoline is greater in participants without evidence of BAM compared to those with evidence of BAM.

Objectives and Endpoints

The primary and secondary study objectives and their corresponding endpoints are listed in the table below.

Objectives	Endpoints
Primary	
• To evaluate the efficacy of eluxadoline 100 mg BID in IBS-D participants with evidence of BAM compared to IBS-D participants without evidence of BAM	• Change from baseline in average BSFS score over 4 weeks of treatment period
• To evaluate the safety and tolerability of eluxadoline 100 mg BID in IBS-D participants with evidence of BAM and in IBS-D participants without evidence of BAM	• Evaluation of adverse events, clinical laboratory tests, vital signs, physical examinations
Secondary	
• To further evaluate the efficacy of eluxadoline 100 mg BID in IBS-D participants with evidence of BAM compared to IBS-D participants without evidence of BAM	• Change from baseline in the 4-week average of daily bowel movement frequency during the treatment period • Change from baseline in the 4-week average of daily worst abdominal pain scores during the treatment period • Change from baseline in the 4-week average of daily bloating during the treatment period • Change from baseline in the 4-week average of number of daily urgent bowel movements during the treatment period • The proportion of participants with any fecal incontinence during the treatment period • Change from baseline in IBS-QOL score at the end of the treatment period • Change from baseline in serum 7αC4 levels at the end of the treatment period
• To evaluate the population PK of eluxadoline in IBS-D patients with and without evidence of BAM	• Population pharmacokinetic parameters of eluxadoline determined from plasma concentration data extrapolated from dried blood sample analysis

7αC4 = 7a-hydroxy-4-cholesten-3-one; BAM = bile acid malabsorption; BID = twice daily; BSFS = Bristol Stool Form Scale; IBS-D = irritable bowel syndrome with diarrhea; IBS-QOL = irritable bowel syndrome-quality of life; PK = pharmacokinetics.

Overall Study Design:

This Phase IV study will use an open-label, parallel-group, cohort-controlled design in participants meeting the Rome IV criteria for IBS-D with and without evidence of BAM. Participants will be assigned to 1 of 2 cohorts based on their BAM status. As far as possible the 2 cohorts will be matched by age, gender and severity of symptoms.

1. Cohort 1: IBS-D participants with evidence of BAM treated with eluxadoline 100 mg oral tablets twice daily (BID) with food.

2. Cohort 2: IBS-D participants without evidence of BAM treated with eluxadoline 100 mg oral tablets BID with food.

Study Design

Period	Screening[a]	Pretreatment[a]	Open-Label Treatment			Post-Treatment
Duration	0-2 weeks	2-3 weeks	4 weeks			2 weeks
Week	Screening	Pretreatment	Baseline	Week 2[b]	Week 4 (EOT/ET)	Week 6[b] (Follow-up)
Study Visit	1	2	3	4	5	6
Study Day			1	15 (±2)	29 (±2)	Visit 5 + 14 days (±7)

7αC4 = 7a-hydroxy-4-cholesten-3-one; BA = bile acid

[a] Screening and pretreatment periods may be combined. if results of fasting serum 7αC4 test or 48-hour fecal BA collection conducted within 1 calendar year from screening are available at the time of the combined visit or results from fasting serum 7αC4 test are available prior to the start of study treatment..

[b] May be done over the phone.

The total duration of study participation for each participant will be up to 11 weeks.

Key inclusion criteria:

1. Adult men or women aged 18 to 75 years inclusive with a diagnosis of IBS-D per Rome IV criteria.
2. Participants with evidence of BAM must have at least one of the following at screening or within 1 calendar year prior to screening:
   - fasting serum 7a-hydroxy-4-cholesten-3-one (7αC4) level ≥ 52.5 ng/mL
   - total fecal bile acids > 2337 micromoles/48 hours
   - primary bile acids (fecal CA and CDCA) ≥ 10% in a 48h fecal collection
   - primary bile acids (fecal CA and CDCA) ≥ 4% with total fecal bile acid ≥ 1,000 micromoles/48hr
3. .Participants without BAM must have at least one of the following at screening or within 1 calendar year prior to screening:
   - fasting serum 7αC4 level ≤ 47.1 ng/mL
   - fasting serum 7αC4 levels > 47.1 ng/mL but < 52.5 ng/mL with fecal bile acids that are negative for bile acid malabsorption (i.e. do not meet criteria 2.03 based on fecal bile acids level)
   - total fecal bile acids (BA) ≤2337 micromoles/48 hours

- primary bile acids (fecal CA and CDCA) < 10% in a 48h fecal collection
- primary bile acids (fecal CA and CDCA)< 4% with total fecal bile acid <1,000 micromoles /48hr

4. An average daily Bristol Stool Form Scale (BSFS) score ≥ 5.0 or ≥ 25% of diary entry days with a BSFS score of 6 or 7 during the 14 days prior to Day 1.
5. Women of childbearing potential must use hormonal or double barrier contraception or maintain a monogamous relationship with a vasectomized male partner from the date of informed consent until 24 hours after final dose of study drug.
6. Completed the electronic diary (eDiary) on ≥ 10 of the 14 days prior to Day 1.
7. Has not used loperamide rescue medication on > 3 of the 14 days prior to Day 1.

Key exclusion criteria:

1. A diagnosis of IBS with a subtype of irritable bowel syndrome with constipation (IBS-C), mixed IBS, or unsubtyped IBS per Rome IV criteria.
2. Does not have a gallbladder.
3. Known or suspected biliary duct obstruction, or sphincter of Oddi disease or dysfunction. (Participants with a history of gallstones may be enrolled).
4. History of alcoholism, alcohol abuse or alcohol addiction, or drinks more than 3 alcoholic beverages per day.
5. History of pancreatitis; structural diseases of the pancreas, including known or suspected pancreatic duct obstruction.
6. History of mild, moderate, or severe hepatic impairment according to Child-Pugh classification. History or current diagnosis of inflammatory or immune-mediated gastrointestinal (GI) disorders.
7. Celiac disease or a positive serological test for celiac disease.
8. Known lactose or fructose intolerance associated with diarrhea, abdominal pain or discomfort, that could confound assessments in the study.
9. Women who are currently pregnant or nursing, or plan to become pregnant or nurse during the study.
10. Known allergies or hypersensitivity to opioids.

Number of Participants:

There will be 24 participants enrolled in the study, 12 participants with evidence of BAM and 12 participants without evidence of BAM.

Number of Sites:

The study will be conducted at 1 study site in the United States.

Treatment Groups and Study Duration:

The total duration of the study is up to 11 weeks, which includes: screening period (0-2 weeks), pretreatment period (2-3 weeks), 4-week open-label treatment period, and 2-week post-treatment safety follow-up period.

2. Schedule of Activities (SoA)

[redacted]

[redacted]

[redacted]

3. Introduction

Irritable bowel syndrome (IBS) is one of the most common and most widely studied functional gastrointestinal disorders (FGID; Longstreth 2006; Chey 2015). IBS is characterized by abdominal pain associated with altered bowel movement symptoms and is subcategorized based on stool patterns (Drossman 2006). Four different subtypes are defined which include IBS with: diarrhea (IBS-D), constipation (IBS-C), both constipation and diarrhea (IBS-M), or unspecified (IBS-U). As an FGID, IBS lacks an underlying organic cause (such as a structural, inflammatory, or biochemical abnormality) and is diagnosed primarily based on patients' symptom reports per the Rome Diagnostic Criteria for Functional Gastrointestinal Disorders (Rome). The global prevalence of IBS is estimated to be 11.2% (Lovell 2012; Chey 2015). IBS is associated with significant impairment in quality of life and high rates of comorbid conditions (Gralnek 2000), which imposes a significant socioeconomic burden to society (Hulisz 2004; Paré 2006).

The pathophysiology of IBS is not completely understood but is thought to be multifactorial, with genetics, abnormal gut motility, visceral hypersensitivity, psychosocial distress, altered gut microbiome, and brain-gut interaction playing important roles in its development (Camilleri 2012; Chey 2015). Important to the diarrheal subtype of IBS, it is increasingly recognized that bile acid malabsorption (BAM) may be a potential cause of chronic diarrhea (Aziz 2015; Bajor 2015; Camilleri 2015; Valentin 2016). In BAM, the failure to adequately reabsorb conjugated bile salts in the terminal ileum leads to excess bile acids entering the colon where they stimulate colonic secretion and motility (Camilleri 2014). Symptoms of BAM present as watery diarrhea, bloating, fecal urgency and fecal incontinence, which closely overlap the symptoms of functional diarrhea and IBS-D (Islam 2012). Recent evidence suggests that up to 1/3 of patients who meet the Rome criteria for IBS-D have evidence of BAM based primarily on ^{75}Selenium-homocholic acid taurine (SeHCAT) retention testing (Wedlake 2009; Aziz 2015; Bajor 2015). Overall, IBS-D patients with and without evidence of BAM appear highly similar in demographic characteristics and assessments of well-being, except that patients with BAM tend to have higher BMIs (Camilleri 2014a; Aziz 2015).

The potential overlap of IBS-D and BAM may have important implications for clinical practice, especially if an altered treatment course would be considered. Recognizing this, the most recent version of the Rome diagnostic criteria for IBS-D issued in 2016 (Rome IV) now recommends an assessment of BAM status as a potential cause of chronic, watery diarrhea (Lacy 2016). For patients with evidence of BAM, a bile acid sequestrant may be an appropriate treatment option, at least for the diarrheal symptoms, though poor tolerability and compliance can be problematic for the most economical bile acid binding agent cholestyramine (Camilleri 2014). The potential IBS-D/BAM overlap also has implications for clinical research, particularly if a product being developed for IBS-D has a different benefit-risk profile in patients with evidence of BAM. Such a situation could lead to an underestimate of a product's real effectiveness in IBS-D, especially if a large proportion of patients in a study have overlapping BAM and are unresponsive to treatment. To eliminate this possibility, the September 2014 EMA guideline (CPMP/EWP/785/97/Rev. 1) on the development of drugs for IBS recommends excluding patients with BAM from IBS-D studies.

3.1. Study Rationale

Eluxadoline was approved for the treatment of adult patients with IBS-D by the FDA and EMA in 2015 and 2016, respectively. Because the Phase 3 confirmatory studies of eluxadoline for IBS-D were conducted prior to the issuance of the latest version of the Rome criteria (Rome IV) and prior to the publication of the final EMA guideline on IBS, these studies did not prospectively exclude patients with evidence of BAM. Baseline characteristics of the Phase 3 IBS-D patient population demonstrated a high prevalence of both obesity and prior cholecystectomy. Given the known association of higher BMI with BAM (Camilleri 2014a; Aziz 2015) and that cholecystectomy is a known risk factor for BAM (Walters 2010), it is conceivable that some portion of participants enrolled in those studies may have had evidence of BAM. Since the eluxadoline Phase 3 IBS-D studies did not evaluate participant's bile acid absorption status, it is unknown whether the effectiveness of eluxadoline may be different in patients with evidence of BAM. It is possible that the overall effects of eluxadoline could have been diluted by a subset of non-responsive patients suffering from BAM for whom a bile acid sequestrant might have been a more appropriate treatment option.

The goal of the present study is therefore to evaluate the possibility of a differential effect of eluxadoline on altered bowel function in IBS-D participants with and without evidence of BAM. The overall hypothesis of this study is that the efficacy of eluxadoline is greater in participants without evidence of BAM compared to those with evidence of BAM.

3.2. Background

Eluxadoline is a locally active mixed mu-opioid receptor (μOR) agonist, kappa-opioid receptor (κOR) agonist, and delta-opioid receptor (δOR) antagonist with low oral bioavailability. Eluxadoline has been approved for the treatment of adult patients with IBS-D in the United States, the European Union, and Canada, among other regions. Eluxadoline has gastrointestinal (GI) transit inhibiting activity that is consistent with its primary pharmacological profile as a μOR agonist. The mixed pharmacological profile of eluxadoline may mitigate the risk of constipation effects through unopposed μOR agonism as seen with agents such as loperamide, through antagonism of the δOR (Wade 2012).

Eluxadoline has been demonstrated to be effective in treating the abdominal pain and diarrheal symptoms of patients with IBS-D with an acceptable risk profile (Eluxadoline Investigator's Brochure). The efficacy and safety in IBS-D patients was confirmed in 2 randomized, multicenter, multinational, double-blind, placebo-controlled Phase 3 studies in a total of 2426 patients meeting the Rome III criteria for IBS-D (studies IBS-3001 and IBS-3002; Lembo 2016 and VIBERZI™ PI 2017). The primary endpoint of the Phase 3 studies was defined by the simultaneous improvement in the daily worst abdominal pain score by ≥30% compared with baseline weekly average and a reduction in the Bristol Stool Form Scale (BSFS) to < 5 on at least 50% of days within a 12-week treatment period (FDA endpoint) and a 26-week treatment period (EMA endpoint).

3.3. Benefit/Risk Assessment

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 2016, VIBERZI PI 2017). The treatment effect of eluxadoline over placebo was observed within the first week and was maintained throughout the 26-week assessment period.

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 2016).

In clinical studies, eluxadoline had a favorable tolerability profile with low rates of predominantly GI AEs. The most commonly reported AEs were constipation, nausea, and abdominal pain. Approximately 50% of constipation events occurred within the first 2 weeks of treatment, with most cases being of mild to moderate intensity.

Infrequent, medically important risks reported with eluxadoline in clinical studies were (1) mild transient pancreatitis or rapidly reversible elevation of transaminases associated with abdominal pain, both consistent with sphincter of Oddi (SO) spasm or biliary sludge, and (2) pancreatitis associated with heavy alcohol consumption. Some of these events led to brief hospitalizations, but all had favorable outcomes with no sequelae. There were 13 cases that were adjudicated as SO spasm with an overall occurrence rate of 0.58%. Cholecystectomy status was known in 12 of the 13 patients, and all 12 patients where status was known had no gall bladder. In the postmarketing setting, severe cases of acute pancreatitis, sometimes fatal, were observed following the use of eluxadoline in patients without a gallbladder. Because of this, use of eluxadoline in patients without a gallbladder is contraindicated.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of eluxadoline may be found in the Investigator's Brochure (IB) and/or package insert.

4. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of eluxadoline 100 mg BID in IBS-D participants with evidence of BAM compared to IBS-D participants without evidence of BAM	• Change from baseline in average BSFS score over 4 weeks of treatment period
• To evaluate the safety and tolerability of eluxadoline 100 mg BID in IBS-D participants with evidence of BAM and in IBS-D participants without evidence of BAM	• Evaluation of adverse events, clinical laboratory tests, vital signs, physical examinations
Secondary	
• To further evaluate the efficacy of eluxadoline 100 mg BID in IBS-D participants with evidence of BAM compared to IBS-D participants without evidence of BAM	• Change from baseline in the 4-week average of daily bowel movement frequency during the treatment period • Change from baseline in the 4-week average of daily worst abdominal pain scores during the treatment period • Change from baseline in the 4-week average of daily bloating during the treatment period • Change from baseline in the 4-week average of number of daily urgent bowel movements during the treatment period • The proportion of participants with any fecal incontinence during the treatment period • Change from baseline in IBS-QOL score at the end of the treatment period • Change from baseline in serum 7αC4 levels at the end of the treatment period
• To evaluate the population PK of eluxadoline in IBS-D patients with and without evidence of BAM.	• Population pharmacokinetic parameters of eluxadoline determined from plasma concentration data extrapolated from dried blood sample analysis

7αC4 = 7a-hydroxy-4-cholesten-3-one; BAM = bile acid malabsorption; BID = twice daily; BSFS = Bristol Stool Form Scale; IBS-D = irritable bowel syndrome with diarrhea; IBS-QOL = irritable bowel syndrome-quality of life; PK = pharmacokinetics

Clinical Hypotheses

The potential inclusion of participants with evidence of BAM in the eluxadoline Phase 3 studies of IBS-D could have led to an underestimation of eluxadoline's effects on IBS-D, especially if the participants' BAM represented the primary cause of their diarrheal symptoms. However, given its mechanism of action as a mixed μOR/κOR agonist and δOR antagonist, eluxadoline should result in reduced intestinal motility and secretions irrespective of any underlying etiology (such as unabsorbed luminal bile acids due to BAM). It is therefore hypothesized that

eluxadoline will have similar pharmacodynamic effects to increase stool consistency in IBS-D participants with and without evidence of BAM.

5. Study Design

5.1. Overall Design

This is a Phase 4, open-label, parallel-group, cohort controlled study to evaluate the efficacy, safety, tolerability and pharmacokinetics of eluxadoline in participants meeting the Rome IV criteria for IBS-D with and without evidence of BAM. This study will be comprised of a 0 to 2-week screening period, a 2 to 3-week pretreatment period, a 4-week open-label treatment period during which time participants will receive eluxadoline 100 mg BID, and a 2-week post-treatment safety follow-up.

There will be 24 participants enrolled in the study, 12 with evidence of BAM and 12 without evidence of BAM.

- Cohort 1: IBS-D participants with evidence of BAM treated with eluxadoline 100 mg oral tablets BID with food
- Cohort 2: IBS-D participants without evidence of BAM treated with eluxadoline 100 mg oral tablets BID with food

As far as possible, the 2 cohorts will be matched by age, gender and severity of historic symptoms based on the investigator's discretion. Evaluation of IBS-D symptoms during the pretreatment period will establish the baseline of IBS-D severity and will continue for the duration of the study. Measurements of stool consistency scores and other IBS-D signs and symptoms will be measured daily using an electronic diary (eDiary).

After screening procedures have been performed (up to 2 weeks), eligible participants will enter a pretreatment period of 2 to 3 weeks. At the beginning of the pretreatment period participants will receive instructions for completing the eDiary to collect daily information related to their IBS-D symptoms including stool consistency (BSFS), worst abdominal pain, abdominal bloating, bowel movement frequency, rescue medication usage, number of episodes of urgency in a day, and number of episodes of fecal incontinence, if any. At the conclusion of the pretreatment period, participants who meet the study entry criteria related to stool consistency, eDiary compliance, and rescue loperamide use will be enrolled to receive a 4-week open-label eluxadoline 100 mg BID treatment.

Participants enrolled in the treatment period will return to the study site for study visits at Week 2, Week 4 (end-of-treatment study visit), and for a post-treatment follow-up study visit at Week 6. Telephone contacts may be made to participants in lieu of an on-site visit at Week 2. A complete schedule of activities (SoA) is provided in Section 2. Participants who discontinue from the study before the Week 4 visit should return to the study site to complete the early termination assessments as soon as possible after stopping the study drug.

During the open-label treatment period, participants will record via the eDiary their daily IBS-D symptoms including stool consistency (BSFS), worst abdominal pain, abdominal bloating, bowel movement frequency, rescue medication usage, number of episodes of urgency in a day, and number of episodes of fecal incontinence, if any.

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

The total duration of the study is up to 11 weeks, which includes: screening period (0-2 weeks), pretreatment period (2-3 weeks), 4-week open-label treatment period, and 2-week post-treatment follow-up period. A total of 6 study visits are planned for each participant:

- Screening, Week -3 to -5 (Visit 1) prior to Baseline visit
- Pretreatment, Week -3 to -2 (Visit 2) prior to Baseline visit
- Day 1 (Visit 3; first administration of study drug)
- Week 2 (Visit 4; Week 2 of treatment), may be done by telephone
- Week 4 (Visit 5; end of treatment/early termination)
- Week 6 (Visit 6; post-treatment follow-up)

The study design is presented in Table 5–1.

Table 5–1 Study Design

Period	**Screening[a]**	**Pretreatment[a]**	**Open-Label Treatment**			**Post-Treatment**
Duration	0-2 weeks	2-3 weeks	4 weeks			2 weeks
Week	Screening	Pretreatment	Baseline	Week 2[b]	Week 4 (EOT/ET)	Week 6[b] (Follow-up)
Study Visit	1	2	3	4	5	6
Study Day			1	15 (±2)	29 (±2)	Visit 5 + 14 days (±7)

7αC4 = 7a-hydroxy-4-cholesten-3-one; BA = bile acid

[a] Screening and pretreatment periods may be combined if results of fasting serum 7αC4 test or 48-hour fecal BA collection conducted within 1 calendar year from screening are available at the time of the combined visit or results from fasting serum 7αC4 test are available prior to the start of study treatment.

[b] May be done over the phone.

5.2. Participant and Study Completion

A maximum of 24 participants, 12 participants with evidence of BAM and 12 participants without evidence of BAM will receive study treatment such that approximately 24 evaluable participants complete the study.

5.3. End of Study Definition

The end of the study is defined as the date of Visit 6 (post-treatment follow-up visit).

A participant is considered to have completed the study if he/she has completed all periods of the study including post-treatment follow-up visit.

5.4. Scientific Rationale for Study Design

This is an open-label, cohort controlled study designed to evaluate the comparative effects of eluxadoline on the altered bowel function in IBS-D participants with and without evidence of BAM. This non-randomized design is considered most appropriate since the cohort assignment will be based on the determination of BAM status.

A primary factor in the design of this study is the mechanism by which evidence of BAM will be established and documented in the patient population. Both the Rome IV criteria and EMA guideline for IBS suggest that the results from a therapeutic study with a bile acid binding agent can be an appropriate surrogate given that these agents have been shown to improve stool passage and stool consistency in patients with BAM (Wong 2012; Bajor 2015). While empiric studies of sequestrants such as cholestyramine or colesevelam have the advantage of being clinically applicable, they provide only indirect evidence of BAM since these agents can have nonspecific effects to ameliorate diarrhea of other causes (Camilleri 2015). Additionally, therapeutic studies of cholestyramine are hampered by tolerability and compliance issues owing to its poor palatability and potential side effects, while studies of the newer agent colesevelam are hampered by its expense (Camilleri 2014).

Most potentially direct diagnostic tests of BAM are limited in their availability and/or clinical practicality. The most definitive test is the measurement of fecal bile acids in a 48-hour stool collection. Measurement of fecal bile acids is a direct measure of excess bile acids entering the colon. Primary fecal bile acids [Chenodeoxycholic acid (CDCA) and cholic acid (CA)] are significantly higher in patients with BAM and correlate with stool frequency and consistency (Shin 2013, Wong 2012). A potential alternative, the nuclear medicine SeHCAT test which measures bile acid retention is more clinically practical but does require 2 separate clinical visits to determine SeHCAT retention after a week. While SeHCAT testing has been the primary measure by which the overlap of BAM and IBS-D has been identified, it is not approved for use in the United States and is not widely available in the rest of the world (Islam 2012). Total fecal bile acids $\geq$ 2337 µmol/48 hr is the gold standard for BAM diagnosis in countries where SeHCAT retention is not available (Shin 2013).

The typical proportion of primary fecal bile acids in healthy volunteers is ~0.2%. Patients with BAM have higher stool weight compared to those with chronic diarrhea without BAM or healthy volunteers (Vijayvargiya 2018). The sensitivity and specificity of the fecal biomarkers of BAM are listed in Table 5-2. Therefore, elevated primary BA alone or in combination with total fecal bile acids of $\geq$ 1000 µmol/48 hr have a similar diagnostic accuracy as total fecal BA alone of $>$ 2337 µmol/48 hr in detecting elevated fecal weight in patients with BAM. Statistical analysis has demonstrated no significant difference between the ROC curve to estimate elevated fecal weight for either total BA or elevated primary fecal BA (p=0.13). After increasing the primary

BA cutoff to 10% or higher with total fecal BA ≥1000 µmol/48 hr , there was no significant gain in either sensitivity (41%) or specificity (97%) compared to the lower cutoff of primary BA ≥ 4% with total fecal BA ≥ 1,000 µmol/48 hr (Vijayvargiya 2018).

Therefore, even at the lower cutoff values of ≥4%, primary fecal bile acids are indicative of BAD even though the total fecal BA may be only 1000 µmol/48 hr.

However, in an analysis of 986 patients who underwent 48 hour fecal BA evaluation for chronic diarrhea, 26% of patients had elevated total fecal bile acids whereas 46% of patients had fecal primary bile acids ≥10%, indicating that measuring total fecal bile acids alone will miss a subgroup of patients who have features of BAM (Vijayvargiya 2018).

Evidence has suggested that measurement of serum 7α-hydroxy-4-cholesten-3-one (7αC4 test) may also be an effective indicator of BAM. Serum 7αC4 is a surrogate for hepatic BA synthesis rate and has been demonstrated to be elevated in patients with BAM (Eusufzai 1993) and in some patients with IBS-D (Odunsi-Shiyanbade 2010; Wong 2012). The use of serum 7αC4 to diagnose BAM has been validated against SeHCAT testing and was demonstrated to have approximately 90% sensitivity and 79% specificity (Sauter 1999). The fasting (6-10 am) serum 7αC4 test is considered most ideal because of its simplicity, as collection of blood for 7αC4 analysis can occur as part of the routine screening process for the study. The analysis of serum 7αC4 levels requires a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method which is currently available (Camilleri 2009; Camilleri 2014a). Further, serum 7αC4 was demonstrated to have high positive and negative predictive values making it attractive as a diagnostic test of BAM. Therefore, in this study, BAM status will be determined by the presence of at least one of the parameters listed in Table 5-2.

The sample size is based primarily on clinical considerations, including the desire to minimize the number of potential clinical sites given the possible need to utilize a research laboratory for analysis of screening serum 7αC4 samples. While not statistically powered, the study sample is considered sufficient to characterize the effects of eluxadoline on the altered bowel function of IBS-D patients with BAM and to qualitatively evaluate whether these patients respond differently to eluxadoline treatment.

The duration of treatment was chosen to be consistent with clinical practice in IBS, where a 1-month therapeutic study of a new agent is common and is supported by results of the Phase 3 studies which showed that a patient's response to eluxadoline treatment over the first month is reasonably predictive of responsiveness over longer durations. The post-treatment period is intended to allow for an off-treatment assessment of safety.

The study will enroll an IBS-D population similar to that enrolled in the Phase 3 studies of eluxadoline. Participants will meet the Rome IV criteria for IBS-D, which differs from the Rome III criteria used in the Phase 3 studies primarily in eliminating abdominal discomfort as a distinct entity from abdominal pain in the definition of IBS-D (Lacy 2016). Evidence of BAM will be determined by a screening serum 7αC4 value ≥ 52.5 ng/mL, which has previously been utilized as a diagnostic cutoff for BAM based on this value being greater than the 95th percentile of serum 7αC4 values from 184 healthy controls (Vijayvargiya 2017).

In order to have comparable treatment groups, the cohorts will be matched to the highest extent possible by age, gender and severity of historic symptoms based on the investigator's discretion.

Improvements in bowel symptoms will be measured during the study. Stool consistency is a highly sensitive efficacy marker, making it ideally suitable to detect potential differences in responsiveness to treatment among participants with and without evidence of BAM. The primary outcome measure for this study will therefore be changes from baseline in stool consistency scores over the 4-week treatment period. Changes from baseline are considered more appropriate than monthly responder definitions given the small pilot nature of this study.

Table 5-2 Current and future and bile acid diarrhea (BAD) diagnostic tests

Diagnostic Test	Fasting serum C4	Total fecal BA	Primary BA >4% + total fecal BA	Fecal primary BA >10%
What does it measure	Hepatic bile acid synthesis	Total fecal bile acid excreted from the colon	Amount of bile acids with secretory potential with total fecal BA excretion	Amount of bile acids that are directly synthesized from the liver with secretory potential
Diagnostic Cutoffs	$\geq$52.5 ng/mL	$\geq$ 2,337 µmol/48h	Primary BA $\geq$ 4% + total fecal BA $\geq$ 1,000 µmol/48h	$\geq$ 10% Primary BA
Sensitivity relative to fecal weight >400g/48h	15%	59%	46%	49%
Specificity relative to fecal weight >400g/48h	86%	92%	97%	91%

Source: Vijayvargiya 2018

5.5. Justification for Dose

The 100 mg BID dose selected for this study is consistent with US and global labeling for eluxadoline in IBS-D.

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1.	**Age/Sex**
1.01	Participant is a man or woman aged 18 to 75 years, inclusive, at screening.
2.	**Type of Participant and Disease Characteristics**
[redacted]	
2.02	Participant has a diagnosis of IBS with predominant diarrhea (IBS-D) defined by the Rome IV criteria as > ¼ (25%) of bowel movements with BSFS score of 6 or 7 and < ¼ (25%) of bowel movements with BSFS score of 1 or 2.
2.03	Participants with evidence of BAM: Participants must have at least one of the following at screening or within 1 calendar year prior to screening. • fasting serum 7a-hydroxy-4-cholesten-3-one (7αC4) level ≥ 52.5 ng/mL • total fecal bile acids > 2337 micromoles/48 hours • primary bile acids (fecal CA and CDCA) ≥ 10% in a 48h fecal collection • primary bile acids (fecal CA and CDCA) ≥ 4% with total fecal bile acid ≥ 1,000 micromoles/48hr

2.04	Participants without BAM: Participants must have at least one of the following at screening or within 1 calendar year prior to screening. • fasting serum 7αC4 level ≤ 47.1 ng/mL • fasting serum 7αC4 levels > 47.1 ng/mL but < 52.5 ng/mL with fecal bile acids that are negative for bile acid malabsorption (i.e. do not meet criteria 2.03 based on fecal bile acids level) • total fecal bile acids (BA) ≤2337 micromoles/48 hours • primary bile acids (fecal CA and CDCA) < 10% in a 48h fecal collection • primary bile acids (fecal CA and CDCA)< 4% with total fecal bile acid <1,000 micromoles /48hr
2.05	Participant meets the colonoscopy requirements defined in Appendix 10 Section 12.10, which are modified from the Summary of the US-Multi-Society Task Force on Colorectal Cancer and other Colonoscopy Requirements
2.06	Participant has an average daily BSFS score ≥ 5.0 or at least 25% of days of diary entry with a BSFS score of 6 or 7 during the 14 days prior to Day 1 of study treatment
3.	**Contraceptives**
3.01	A sexually active woman of childbearing potential (WOCBP), as defined in Appendix 5, Section 12.5 must agree to follow the contraceptive guidance given in Appendix 5, Section 12.5 from the date she provides informed consent until 24 hours after her final dose of study drug.
4.	**Informed Consent**
4.01	Participant must sign an informed consent form (ICF) before the initiation of any study-related procedures indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.
5.	**Other**
5.01	Participant has completed the eDiary on at least 10 of the 14 days prior to Day 1 of study treatment.
5.02	Participant has not used loperamide rescue medication on more than 3 days in the 14 days prior to Day 1 of study treatment (see Section 7.7.3).

[redacted]

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1.	**Medical Conditions**
1.01	Participant has a diagnosis of IBS with a subtype of IBS with constipation, mixed IBS, or unsubtyped IBS by the Rome IV criteria.
1.02	Participant does not have a gallbladder.
1.03	Participants with known or suspected biliary duct obstruction, or sphincter of Oddi disease or dysfunction. Participants with a history of gallstones may be enrolled.
1.04	Participant has a history of alcoholism, alcohol abuse or alcohol addiction, or drinks more than 3 alcoholic beverages per day.
1.05	Participant has a history of pancreatitis; structural diseases of the pancreas, including known or suspected pancreatic duct obstruction.
[redacted]	
1.09	Participant has documented history of mild, moderate, or severe hepatic impairment according to Child-Pugh classification.

1.10	Participant has a history or current diagnosis of inflammatory or immune-mediated GI disorders including inflammatory bowel disease (ie, Crohn's disease, ulcerative colitis, microscopic colitis).
[redacted]	
1.13	Participant has celiac disease or a positive serological test for celiac disease, and the condition has not been ruled out by endoscopic biopsy.
[redacted]	
1.15	Participant has a history of a microbiologically documented (ie, stool culture or medical history) GI infection within 3 months prior to screening.
[redacted]	
2.	**Prior/Concomitant Therapy**
2.01	Participant used a protocol-specified prohibited medication or failed to meet the stable-dose requirements of certain medications (see Section 7.7.1)
2.02	Participant has previously received eluxadoline.
[redacted]	
4.	**Other**
4.01	Female participants who are currently pregnant or nursing, or plan to become pregnant or nurse during the clinical study.

4.02	Participant has known allergies or hypersensitivity to opioids. Nausea and vomiting in response to opioid treatment are not hypersensitivity reactions. Participants who have had prior mild, opioid-induced pruritus in the absence of demonstrable allergic dermatitis, angioedema, and laryngeal edema are eligible for the study.

[redacted]

Rationale for Inclusion and Exclusion Criteria

The eligibility criteria defined in the protocol are intended to ensure enrollment of an IBS-D participant population consistent with the approved global labeling of eluxadoline as well as allowing for the selective inclusion of participants with overlapping BAM based on standard diagnostic methodology. The eligibility criteria and specific diagnostic screening procedures are intended to exclude other potential etiologies of the participant's IBS-D symptoms and, consistent with global labeling, to exclude participants who may be at increased risk of experiencing certain AEs associated with eluxadoline, such as constipation, SO spasm, or pancreatitis. The inclusion criteria related to eDiary entries are intended to ensure participants have sufficient baseline diary data and diarrheal symptoms of a sufficient intensity to detect a treatment difference with eluxadoline.

6.3. Lifestyle Restrictions

No lifestyle restrictions are required.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study to receive study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened.

7. Treatments

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1. Treatments Administered

Table 7–1 Treatments Administered

Study Treatment Name	Eluxadoline
Dosage Formulation	film-coated tablet
Unit Dose Strength(s)/Dosage Level(s)	100 mg BID
Route of Administration	Oral
Dosing Instructions	One tablet twice a day to be taken with food
[redacted]	
Manufacturer	Allergan

7.2. Dose Modification

No dose modification will be allowed.

Retreatment Criteria

No retreatment will be allowed.

7.3. Method of Treatment Assignment

This is an open-label, parallel-group study. Eluxadoline 100 mg BID will be administered to all participants in the study after they are qualified based on meeting all eligibility criteria. Participants will be stratified into 2 cohorts: IBS-D participants with evidence of BAM and IBS-D participants without evidence of BAM. As far as possible, the 2 cohorts will be matched by age, gender and severity of historic symptoms based on the investigator's discretion. Study participants who have discontinued the study may not be replaced.

[redacted]

7.4. Blinding/Masking

Open-label, No Blinding at Site Level	This is an open-label study; potential bias will be reduced by the following steps: matching non-BAM participants to BAM participants by eligibility criteria fulfilled during baseline period

7.5. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

1. Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment.

[redacted]

7.6. Treatment Compliance

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

7.7. Concomitant Therapy

All prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications taken within 30 days prior to the open-label treatment period will be recorded as prior medications. It will also be determined which prior medications were prescribed or taken over-the-counter by participants for the treatment of IBS-D.

All medications taken after beginning open-label treatment and through the early termination or follow-up visit will be recorded as concomitant therapy. The use of all prior and concomitant medications is to be recorded on the participant's electronic case report form (eCRF) at each visit along with the reason the medication was taken. Any changes in concomitant medications will also be recorded on the participant's eCRF. The minimum requirement is that drug name and the dates of administration are to be recorded.

Any concomitant medication deemed necessary for the welfare of the participant 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.

7.7.1. Prohibited Treatments Before and During the Study

Participants must discontinue any of the medications listed in the table below for the specified period prior to Day 1. These medications are prohibited for the duration of the study. Other medications being used at screening may be continued.

[redacted]

7.7.2. Permitted Treatments

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Indication
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Therapy considered necessary for the participant's welfare may be given at the discretion of the investigator. If the permissibility of a specific medication/treatment is in question, please contact the sponsor.

The sponsor or designee should be contacted if there are any questions regarding concomitant or prior therapy.

[redacted]

7.7.3. Rescue Medicine

Loperamide hydrochloride may be used as rescue medication for acute treatment of diarrhea during the pretreatment and open-label treatment periods. Loperamide rescue medication use will be recorded by the participant in the eDiary.

[redacted]

7.8. Treatment after the End of the Study

Not applicable.

8. Discontinuation/Withdrawal Criteria

Premature discontinuation of the study will occur when a participant ceases participation in the study, regardless of circumstances, before the completion of the study visits and procedures. Notification of early participant discontinuation from the study and the reason for study discontinuation will be sent to the sponsor and will be clearly documented on the eCRF.

Reasons for premature discontinuation from the study treatment and/or the study may include the following:

- Adverse event
- Death
- Lack of efficacy
- Lost to follow-up
- Non-compliance with study drug
- Other
- Physician decision
- Pregnancy
- Protocol deviation
- Site terminated by sponsor
- Withdrawal by subject

When a participant discontinues study treatment, the reason(s) for treatment discontinuation shall be recorded by the investigator on the relevant page of the eCRF. Whenever possible, all enrolled participants who prematurely discontinue study treatment will undergo all EOT/ET visit assessments.

It is vital to obtain follow-up data on any participant discontinuing study treatment because of an AE or SAE. In every case, efforts must be made to undertake protocol-specified safety follow-up procedures until resolution or stabilization.

8.1. Discontinuation of Study Treatment

Participants **must** prematurely discontinue study treatment for reasons of safety including:

- an SAE considered by the investigator or the sponsor to be possibly related or related to investigational product,
- an AE of special interest (SO spasm, pancreatitis, severe constipation) see Section 9.2.8.1,
- pregnancy, see Section 9.2.7,

- signs of drug-induced liver injury (DILI), see Appendix 6, Section 12.6.

Participants may prematurely discontinue study treatment for reasons of safety including:

- the presence of intentional overdose or intentional misuse per investigator discretion,
- an AE indicative of a central nervous system (CNS) opioid effect, eg, pinpoint pupils, loss of consciousness, delirium, sedation or somnolence, euphoric, anxious or depressed mood, that in the opinion of the investigator or the sponsor is possibly related or related to the investigational product,
- a vital sign, and/or laboratory abnormality judged to be clinically significant by the investigator and that in the opinion of the investigator or the sponsor is possibly related or related to the investigational product,
- an intolerable AE (defined as an AE that subjectively would cause a participant to consider study withdrawal),
- an absence of bowel movements for ≥ 3 consecutive days, see Section 9.2.8.1, based on responses recorded via eDiary.
- the use of an excessive amount of loperamide rescue medication see Section 7.7.3.
- the occurrence of any other AE that in the opinion of the investigator or the sponsor is possibly related or related to the study treatment that represents a clinically significant safety risk to the participant.

See the schedule of activities (Section 2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

8.1.1. Temporary Discontinuation

Temporary discontinuations are not allowed.

8.1.2. Rechallenge

Rechallenge is not allowed.

8.2. Withdrawal from the Study

1. A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
2. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
3. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
4. See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

[redacted]

9. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Screening (Visit 1)

Participants will undergo a screening visit to determine eligibility to proceed in the study. This visit may be combined with the pretreatment visit if results from a fasting serum 7αC4 test or 48-hour fecal BA collection, conducted within 1 calendar year prior to screening, are available at the time of the combined visit or results from fasting serum 7αC4 test are available prior to the start of study treatment. The screening visit will occur approximately 2 to 3 weeks before the first dose of study drug (if combined with pretreatment visit) and no more than 5 weeks before the first dose of study drug, if the participant requires an additional week for each (screening and pretreatment procedures).

Before undergoing screening procedures, all potential participants will be informed of their privacy rights and will sign an ICF. Participants will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the participant. The investigator will also sign the ICF. After signing the ICF, the participant will undergo the screening assessments and procedures listed in the SoA, including fasting serum 7αC4 testing (if necessary) and clinical laboratory testing (serum chemistry, hematology), to determine eligibility. The inclusion and exclusion criteria requirements will be verified for the participant. Concomitant medication and medical history, including history specifically related to IBS-D, vital signs and weight will be recorded and a physical examination will be performed. Height will be measured only at screening.

A serum pregnancy test will also be performed for all women unless they are surgically sterile or there is a documented history of their postmenopausal status. If the pregnancy test is positive, the participant is not eligible to enter the study.

Eligible participants will be instructed to return to the study site in 1 to 2 weeks for the pretreatment visit.

Pretreatment (Visit 2)

This visit may be combined with the screening visit if results from a fasting serum 7αC4 test or 48-hour fecal BA collection, conducted within 1 calendar year prior to screening, are available at the time of the combined visit or results from fasting serum 7αC4 test are available prior to the start of study treatment. After screening procedures have been performed, eligible participants will enter the pretreatment period. Participants will undergo the pretreatment visit and procedures listed in the SoA. The pretreatment visit will occur approximately 2 to 3 weeks before the first dose of study drug.

The inclusion and exclusion criteria, medical history, concomitant medications, and AEs will be reviewed, vital signs and weight will be measured and recorded. Participants will receive instructions on the use of rescue loperamide.

Participants will be provided with the eDiary device and instructed on the use of the eDiary system to record their IBS-D symptoms and information related to their bowel functioning (eg, bowel movement frequency, urgency and episodes of incontinence) on a daily basis. Additionally, participants will be instructed to record in the eDiary their use of loperamide rescue medication for the acute treatment of uncontrolled diarrhea.

Participants will be eligible for participation in the study to receive an open-label study treatment if they meet all 3 of the following requirements:

- Compliant in completing the eDiary on at least 10 of the 14 days immediately prior to enrollment into open-label treatment period of the study; and
- Have an average daily BSFS score ≥ 5.0 or at least 25% of days of diary entry with a BSFS score of 6 or 7 during the 14 days prior to Day 1 of study treatment, and
- The use of rescue medication on no more than 3 days during the 14 days prior to enrollment in the open-label treatment period as detailed in Section 7.7.3.

[redacted]

Baseline

Day 1 (Visit 3)

On Day 1, participants who were deemed eligible during the pretreatment period will be dispensed study treatment (eluxadoline 100 mg BID).

[redacted]

Open-Label Treatment Period

During the treatment period, participants will undergo the assessments and procedures listed in the SoA.

[redacted]

Week 2 (Visit 4)

Participants will return to the study site at Week 2 (±2 days) of the study treatment. [redacted]

End-of-Treatment/Early Termination (Visit 5)

Participants will return to the study site at Week 4 (± 2 days) after the completion of the treatment period. [redacted]

Post-treatment (Visit 6)

To ensure participant safety, a mandatory post-treatment visit will be performed 14 days after the last dose of study drug for participants that complete the open-label treatment period. [redacted]

9.1. Efficacy Assessments

The efficacy of eluxadoline will be based on eDiary measures related to improvements in IBS-D signs and symptoms. Participants will be required to access the eDiary each evening, preferably at the same time each day, to record daily IBS symptoms. At the start of the pretreatment period, participants will receive full training in the use and completion of the daily eDiary.

9.1.1. Daily IBS Symptoms

Participants will record the following IBS-D signs and symptoms during their daily eDiary entry during the pretreatment period and throughout the 4 weeks of the open-label treatment period:

- Stool Consistency: Participants will be asked to use the BSFS to rate their stool consistency most representative of the past 24 hours. The participant-reported BSFS is a 1 to 7 scale where 1 corresponds to a hard stool and 7 corresponds to watery stool (Appendix 11, Section 12.11; O'Donnell 1988):

  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: Participants will be asked to rate their worst abdominal pain in the past 24 hours. The participant-reported worst abdominal pain 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 Bloating: Participants will be asked to rate their abdominal bloating in the past 24 hours. The participant-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: Participants will be asked to record the number of bowel movements, number of urgent bowel movements, and number of episodes of fecal incontinence, over the past 24 hours.

9.1.2. Irritable Bowel Syndrome-Quality of Life Questionnaire

The impact of IBS on participants' quality of life will be assessed using the IBS-Quality of Life (IBS-QoL) questionnaire (Drossman 2000; Patrick 1998; Appendix 12, Section 12.12). The IBS-QoL questionnaire will be completed by participants at the study site at Baseline (Day 1) prior to the administration of study drug, and Week 4 (or ET visit). The questionnaire will be completed at the beginning of the applicable study visits before all other evaluations, especially discussion of AEs or the participant's medical condition.

[redacted]

[redacted]

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4, Section 12.4.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study (see Section 8).

9.2.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs/SAEs from the start of treatment until the follow-up visit will be collected at the timepoints specified in the SoA (Section 2), and as observed or reported spontaneously by study participants. Any clinically significant abnormalities persisting at the end of the study will be followed until the AE has resolved.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4, Section 12.4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4, Section 12.4.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/SAEs and non-serious AEs of special interest (as defined in Section 9.2.8) will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3).

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings including histopathology.

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Cardiovascular and Death Events

Not applicable

9.2.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable

9.2.7. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and until 30 days after the last dose.

[redacted]

9.2.8. Adverse Events of Special Interest

9.2.8.1. Adverse Events of Special Interest

AEs of special interest are defined as AEs of sphincter of Oddi spasm, pancreatitis, and severe constipation. These events must be reported to the sponsor expeditiously, as described below. Given the μ-opioid receptor agonism of eluxadoline, there is a potential for increased risk of sphincter of Oddi spasm, resulting in pancreatitis or hepatic enzyme elevation associated with acute abdominal pain (eg, biliary-type pain), especially during the first few weeks of treatment, in participants taking eluxadoline, particularly in participants without a gallbladder. Pancreatitis, with or without sphincter of Oddi spasm has been reported in patients taking eluxadoline, including serious cases resulting in hospitalization, primarily in patients without a gallbladder. Fatal cases have also been reported in patients without a gallbladder.

Participants must be instructed to stop the study treatment and seek medical attention if they experience symptoms suggestive of sphincter of Oddi spasm such as acute worsening of abdominal pain (eg, acute epigastric or biliary [ie, right upper quadrant] pain) that may radiate to the back or shoulder, with or without nausea and vomiting and/or if they experience symptoms suggestive of pancreatitis such as acute abdominal or epigastric pain radiating to the back.

Constipation was the most frequent AE reported in studies of eluxadoline for IBS-D. Per the US Prescribing Information, eluxadoline is to be discontinued in participants who develop severe constipation. To ensure the investigator is made aware of severe constipation (ie, the participant is experiencing severe discomfort that severely limits or prevents his/her performance of normal activities, or represents a definite hazard to health that has or could result in hospitalization and prescription drug therapy) episodes, an alert will be sent to the investigator if a participant fails to record a bowel movement for 3 consecutive days in his/her eDiary. Once notified, the investigator must contact the participant to review the participant's status as soon as possible to assess the severity of his/her constipation or the presence of any sequelae of constipation. Every attempt should be made to reach the study participant within 24 hours. An unscheduled visit to

further evaluate the participant's status should be arranged if deemed warranted by the investigator. The study treatment must be discontinued if the investigator determines that severe constipation is present.

If a participant is suspected of experiencing pancreatitis, sphincter of Oddi spasm, or severe constipation, the AE must be reported to the sponsor's SAE mailbox: IR-Clinical-SAE@allergan.com within 24 hours on an SAE Form for Clinical Trials; in the absence of scanning or emailing, the SAE form may be faxed to +1-714-796-9504.

[redacted]

9.2.9. Medication Errors

Medication error refers to any unintended error in the dosing and/or administration of the study treatment as per instructions in the protocol. Medication errors generally fall into 4 categories as follows:

- Wrong study drug/device
- Wrong dose (including dosing regimen, strength, form, concentration, amount)
- Wrong route of administration
- Wrong participant (ie, not administered to the intended participant)

9.3. Treatment of Overdose

Please refer to the US prescribing information (VIBERZI PI 2017) for the treatment to be given in case of overdose.

[redacted]

9.4. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

9.4.1. Physical Examinations

- A physical examination will consist of a full review of all body systems (excluding rectal and pelvic examinations) systems.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

- Pulse, respiratory rate, and blood pressure will be assessed.

- Blood pressure and pulse measurements will be assessed in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Vital signs will be measured after at least 5 minutes rest for the participant in a quiet setting without distractions (eg, television, cell phones). One reading each of pulse, respiratory rate, and blood pressure will be taken.
- Height and weight will also be measured and recorded as specified in the SoA.

9.4.3. Clinical Safety Laboratory Assessments

- See Appendix 2, Section 12.2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 2 weeks after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2, Section 12.2, must be conducted in accordance with the SoA.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

9.4.4. Suicidal Risk Monitoring

Suicidal Risk Monitoring is not applicable to this study.

9.5. Pharmacokinetics

[redacted]

[redacted]

9.6. Pharmacodynamics

The pharmacodynamic effects of eluxadoline on the altered bowel habits of IBS-D will be assessed via efficacy assessments previously described.

9.7. Genetics

Genetics are not evaluated in this study.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

9.9. Health Economics or Medical Resource Utilization and Health Economics

Health economics/Medical resource utilization and health economics parameters are not evaluated in this study.

10. Statistical Considerations

10.1. Sample Size Determination

The total sample size for this study is 24 participants (12 participants with BAM and 12 participants without BAM). No formal sample size estimation will be calculated because the sample size for this study is not based on statistical consideration.

10.2. Populations for Analyses

The analysis populations will consist of participants as defined in Table 10–1.

Table 10–1 Analysis Populations

Population	Definition	Study Treatment
Screened	All screened participants who sign informed consent	—
Enrolled	All participants in Screened Population who meet the eligibility criteria and enter the open-label treatment period	Assignment
Modified intent-to-treat (mITT)	All participants in Enrolled Population with ≥ 1 postbaseline assessment for BSFS	Assignment
Safety	All participants who received ≥ 1 administration of study treatment	Actual received

BSFS = Bristol Stool Form Scale

10.3. Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

10.3.1. Key Statistical Methodology

The methodologies defined in Table 10–2 apply as specified to individual endpoints. All efficacy endpoints will be summarized by participant cohort (BAM or Non-BAM) descriptively.

Table 10–2 Statistical Methodology

Methodology	Description
Categorical counts	• Number of participants in individual categories ○ Participants with ≥ 1 qualifying event counted once per individual category

Categorical descriptives	• Number and percentage of participants in individual categories
	  ○ Participants with ≥ 1 qualifying event counted once per individual category
	• [Optional] N1 if percentage denominator ≠ number of participants in the population (standard percentage denominator)
	  ○ N1 = participants with nonmissing baseline value

PCS descriptives	• Number and percentage of participants meeting PCS criteria
	  ○ Participants with ≥ 1 qualifying event counted once per PCS category
	• Percentage denominator = number of participants with nonmissing baseline and ≥ 1 nonmissing postbaseline assessment
	  ○ Unevaluable assessments considered missing

Event descriptives	• Number and percentage of events in individual categories ○ Events counted individually for each instance • Percentage denominator = total number of events
Shift analysis	• Number and percentage of participants in individual baseline and postbaseline categories • Percentage denominator = number of participants in individual baseline categories • N1 = participants with nonmissing values at both baseline and the specified postbaseline analysis visit
Continuous descriptives	• N1, mean, SD, median, minimum, maximum • N1 = participants with nonmissing value
CFB descriptives	• Continuous descriptives for baseline, postbaseline, and CFB values • N1 = participants with nonmissing values at both baseline and the specified postbaseline analysis visit

CFB = change from baseline; PCS = potentially clinically significant

10.3.2. Efficacy Analyses

The following primary and secondary efficacy endpoints will be summarized by cohort (BAM or Non-BAM) for the mITT population. All other efficacy endpoints and analyses will be defined in the SAP.

Descriptions in Table 10–3 and Table 10–4 may be linked to the assessment(s) and/or objective(s).

Table 10–3 Primary Efficacy Endpoint

Endpoint	Description	Timing	Methodology
	Change from baseline in average BSFS	Treatment Period	Descriptive

Endpoint	Description	Timing	Methodology
	score over 4 weeks of treatment period		summary

Note: Analysis visits will be in the SAP.

BSFS = Bristol Stool Form Scale

Table 10–4 Secondary Efficacy Endpoints

Endpoint	Description	Timing	Methodology
	Change from baseline in the 4-week average of daily bowel movement frequency during the treatment period	Treatment Period	Descriptive summary
	Change from baseline in the 4-week average of daily worst abdominal pain scores during the treatment period	Treatment Period	Descriptive summary
	Change from baseline in the 4-week average of daily worst abdominal pain scores during the treatment period	Treatment Period	Descriptive summary
	Change from baseline in the 4-week average of urgency-free days in a week during the treatment period	Treatment Period	Descriptive summary
	Change from baseline in the 4-week average of daily bloating scores during the treatment period	Treatment Period	Descriptive summary
	Change from baseline in IBS-QOL score at the end of the treatment period	Treatment Period	Descriptive summary
	Change from baseline in serum 7αC4 levels at the end of the treatment period	Treatment Period	Descriptive summary
	Proportion of participants with any fecal incontinence during the treatment period	Treatment Period	Descriptive summary

Note: Analysis visits will be in the SAP.

7αC4 = 7a-hydroxy-4-cholesten-3-one; IBS-QOL = irritable bowel syndrome-quality of life

10.3.3. Safety Analyses

The following safety categories will be summarized as appropriate (eg, categorical or continuous descriptives, shift tables) for the safety population and will be fully defined in the SAP.

- Serious Adverse Events
- Adverse events
- Clinical laboratory assessments
- Potential Hy's law cases
- Potential Drug Induced Liver Injury Cases

- Vital signs including weight
- Physical examinations

10.3.4. Pharmacokinetic Analyses

[redacted]

10.3.5. Other Analyses

None

10.3.6. Interim Analyses

No interim analysis will be conducted.

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12. Appendices

12.1. Appendix 1: Abbreviations and Trademarks

7αC4	7a-hydroxy-4-cholesten-3-one
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{tau}	area under the plasma concentration-time curve during the dosing interval
BA	bile acid
BAM	bile acid malabsorption
BID	twice daily
BMI	body mass index
BSFS	Bristol Stool Form Scale
CDISC	Clinical Data Interchange Standards Consortium
CFB	change from baseline
CFR	Code of Federal Regulations
CL	apparent clearance
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
DBS	dried blood sample
DILI	drug induced liver injury
eCRF	electronic case report form
eDiary	electronic diary
EMA	European Medicines Agency
EOT	end of treatment
ET	early termination
FDA	US Food and Drug Administration
FGID	functional gastrointestinal disorders

FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HRT	hormonal replacement therapy
IB	Investigator's Brochure
IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome with constipation
IBS-D	irritable bowel syndrome with diarrhea
IBS-M	irritable bowel syndrome with constipation and diarrhea
IBS-QOL	irritable bowel syndrome-quality of life
IBS-U	irritable bowel syndrome (unspecified)
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
LC-MS/MS	liquid chromatography tandem-mass spectrometry
mITT	modified intent-to-treat
NCI	National Cancer Institute
NONMEM	nonlinear mixed effects modeling
PK	pharmacokinetic
PT	prothrombin time
Rome	Rome Diagnostic Criteria for Functional Gastrointestinal Disorders
SAE	serious adverse event
SAP	statistical analysis plan
SeHCAT	^{75}Selenium-homocholic acid taurine
SO	sphincter of Oddi
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
t_{max}	time to C_{max}
ULN	upper limit of normal
V	apparent volume of distribution
WOCBP	woman of childbearing potential

δOR	delta-opioid receptor
κOR	kappa-opioid receptor
μOR	mu-opioid receptor

12.2. Appendix 2: Clinical Laboratory Tests

[redacted]

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH GCP guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
    - The investigator will be responsible for the following:
        - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
        - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
        - Providing oversight of the overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, the IRB/IEC, and European regulation 536/2014 for clinical studies (if applicable)

Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of

21 CFR Part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Committees Structure

Publication Policy

- Allergan as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between the investigator and Allergan personnel. Authorship will be established prior to the writing of the manuscript.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Source documents include a participant's medical records, hospital charts, clinic charts, the investigator's participant study files, as well as the results of diagnostic tests such as ultrasound procedures and laboratory tests. The investigator's copy of the eCRF serves as part of the investigator's record of a participant's study-related data.

Study and Site Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. The study site will be closed upon study completion. The study site is considered closed when all required documents and study supplies have been collected and the study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of the study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment. **AE of Special Interest (AESI)** An AE of special interest (serious or nonserious) is one of scientific and medical concern specific to the sponsor's study drug/device or program, which warrants ongoing monitoring and rapid communication by the investigator to the sponsor. Such an event might warrant further investigation in order to characterize and understand it. The following AESIs have been identified for the study treatment in this protocol: SO spasm, pancreatitis, and severe constipation. • If a participant is suspected of experiencing an AESI (i.e. pancreatitis, SO spasm, or severe constipation), the AE must be reported to the sponsor's SAE mailbox: IR-Clinical-SAE@allergan.com within 24 hours on an SAE Form for Clinical Trials; in the absence of scanning or emailing, the SAE form may be faxed to +1-714-796-9504.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiograms [ECGs], radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease) • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition • New condition detected or diagnosed after study treatment administration even though it may have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AEs or SAEs if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition • The disease/disorder being studied or expected progression, signs, or symptoms (clearly defined) of the disease/disorder being studied, unless more severe than expected for the participant's condition • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital) • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

Definition of SAE

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life threatening The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording an AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

MILD	A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
SEVERE	A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as *serious* when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. • A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.** • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section). • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at the site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If the site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool

has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the sponsor by telephone.

- Contacts for SAE reporting can be found in the protocol title page.

SAE Reporting to the Sponsor via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the protocol title page.

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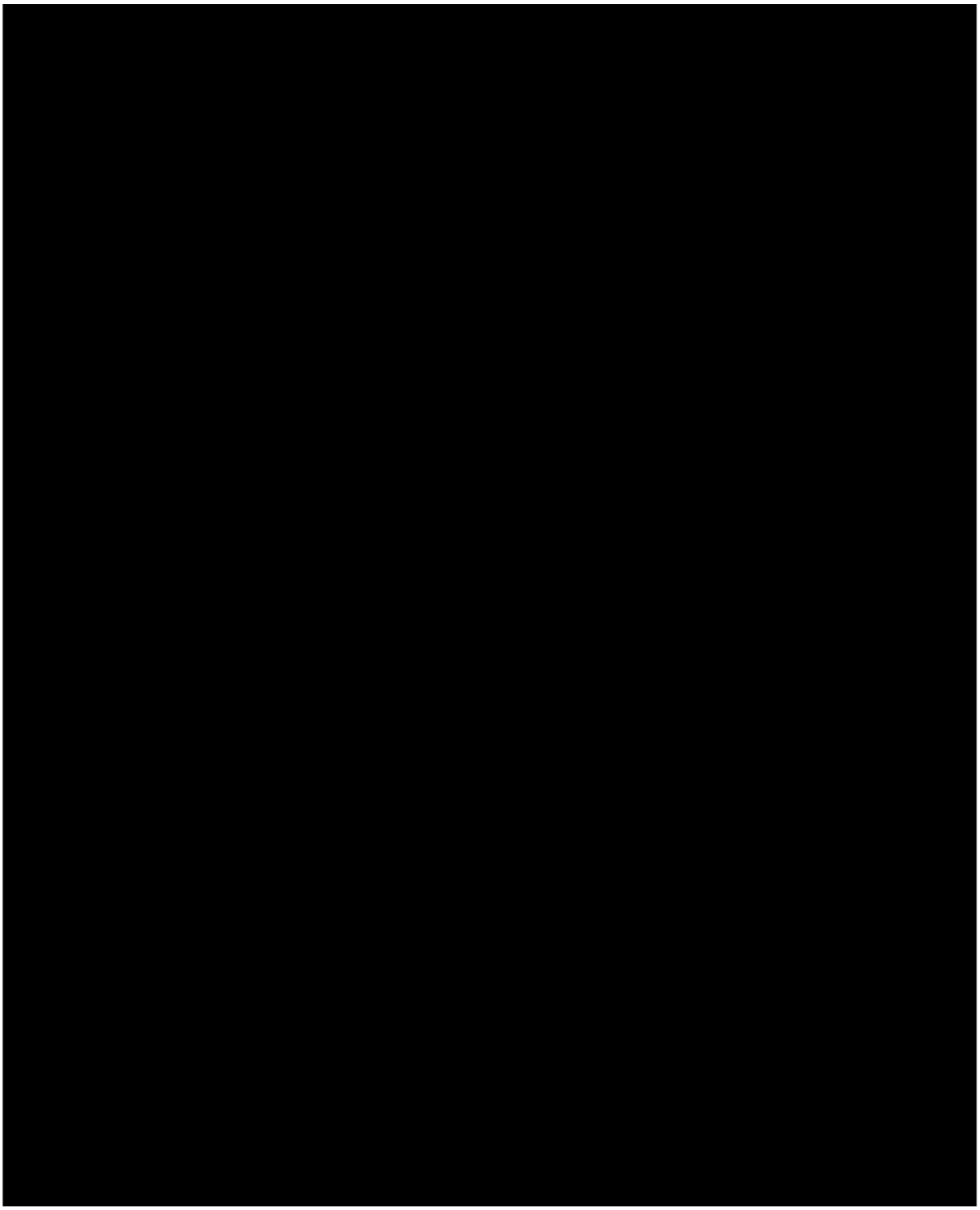

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12.7. Appendix 7: Standard Discontinuation Criteria

CDISC Submission Value	CDISC Definition
Adverse event	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any 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. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. [Modified from ICH E2A] Synonyms: side effect, adverse experience. See also serious adverse event (SAE), serious adverse experience (Clinical Data Interchange Standards Consortium [CDISC] glossary)
Completed	To possess every necessary or normal part or component or step; having come or been brought to a conclusion (National Cancer Institute [NCI])
Death	The absence of life or state of being dead (NCI)
Lack of efficacy	The lack of expected or desired effect related to a therapy (NCI)
Lost to follow-up	The loss or lack of continuation of a subject to follow-up
Non-compliance with study drug	An indication that a subject has not agreed with or followed the instructions related to the study medication (NCI)
Other	Different than the one(s) previously specified or mentioned (NCI)
Physician decision	A position, opinion or judgment reached after consideration by a physician with reference to subject (NCI)
Pregnancy	Pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth. (NCI)
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (NCI)
Screen failure	The potential subject who does not meet one or more criteria required for participation in a trial

CDISC Submission Value	CDISC Definition
Site terminated by sponsor	An indication that a clinical study was stopped at a particular site by its sponsor (NCI)
Study terminated by sponsor	An indication that a clinical study was stopped by its sponsor (NCI)
Withdrawal by subject	An indication that a study participant has removed itself from the study (NCI)

12.8. Appendix 8: Study Tabular Summary

Parameter Group	Parameter	Value
Trial information	Trial Title	3030-401-002: An Open-Label Pilot Study of Eluxadoline in Participants with Irritable Bowel Syndrome with Diarrhea (IBS-D) Who Have Evidence of Bile Acid Malabsorption (BAM)
	Clinical Study Sponsor	Allergan
	Trial Phase Classification	Phase 4
	Trial Indication	IBS-D
	Trial Indication Type	Treatment
	Trial Type	Efficacy Safety
	Trial Length	Up to 11 weeks, which includes: screening period (0-2 weeks), pretreatment period (2-3 weeks), 4-week open-label treatment period and 2-week post-treatment follow-up period.
	Planned Country of Investigational Site	United States
	Planned Number of Participants	24
	FDA-Regulated Device Study Indicator	No
	FDA-Regulated Drug Study Indicator	No
	Pediatric Study Indicator	No
Participant information	Diagnosis Group	Participants with IBS-D who have evidence of BAM
	Healthy Participant Indicator	No
	Planned Minimum Age of Participants	18
	Planned Maximum Age of Participants	65
	Sex of Participants	Both
	Stable Disease Minimum Duration	A diagnosis of IBS fulfilled for the last 3 months prior to screening with symptom onset at least 6 months before diagnosis as defined by the Rome IV criteria for IBS.
Treatments	Investigational Therapy or Treatment	Eluxadoline
	Intervention Type	Drug
	Pharmacological Class of Investigational Therapy	Locally active mixed mu-opioid receptor (μOR) agonist, kappa-opioid receptor

Parameter Group	Parameter	Value
		(κOR) agonist, and delta-opioid receptor (δOR) antagonist.
	Dose per Administration	100 mg
	Dose Units	100 mg
	Dosing Frequency	BID
	Route of Administration	Oral
	Current Therapy or Treatment	None
	Added on to Existing Treatments	No
	Control Type	N/A
	Comparative Treatment Name	N/A
Trial design	Study Type	Interventional
	Intervention Model	Open-Label, pilot
	Planned Number of Arms	1
	Planned Number of Cohorts	2
	Trial is Randomized	No
	Randomization Quotient	N/A
	Trial Blinding Schema	None
	Stratification Factor	With and without evidence of BAM
	Adaptive Design	No
	Study Stop Rules	Participants must prematurely discontinue study treatment for reasons of safety including: • an SAE considered by the investigator or the sponsor to be possibly related or related to investigational product, • an AE of special interest (SO spasm, pancreatitis, severe constipation) • pregnancy • signs of drug-induced liver injury (DILI) outlined in Appendix 6 Section 12.6, Liver Safety Participants may prematurely discontinue study treatment for reasons of safety including: • the presence of intentional overdose or intentional misuse per investigator discretion,

Parameter Group	Parameter	Value
		• an AE indicative of a CNS opioid effect, eg, pinpoint pupils, loss of consciousness, delirium, sedation or somnolence, euphoric, anxious or depressed mood, that in the opinion of the investigator or the sponsor is possibly related or related to the investigational product, • a vital sign, and/or laboratory abnormality judged to be clinically significant by the investigator and that in the opinion of the investigator or the sponsor is possibly related or related to the investigational product, • an intolerable AE (defined as an AE that subjectively would cause a participant to consider study withdrawal), • an absence of bowel movements for ≥ 3 consecutive days, based on responses recorded via eDiary, • the use of an excessive amount of loperamide rescue medication, • the occurrence of any other AE that in the opinion of the investigator or the sponsor is possibly related or related to the study treatment that represents a clinically significant safety risk to the participant.

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12.10. Appendix 10: Summary Adapted from Guidelines of the US Multi-society Task Force on Colorectal Cancer and Other Colonoscopy Requirements

Note: Participant may be enrolled if no follow-up colonoscopy after polyp removal is due while participating in the study.

1. Participants age 50 years (40 years if African American) and older must have had a colonoscopy with negative findings within the 10 years prior to the screening visit (Visit 1).
2. If the most recent colonoscopy revealed hyperplastic polyps that were entirely removed, the participant may be enrolled, provided the colonoscopy was performed within 10 years prior to the screening visit (Visit 1).
3. If the most recent colonoscopy revealed 2 or fewer small (< 1 cm) adenomatous polyps with tubular structure with low grade dysplasia and without appreciable villous tissue, the participant may be enrolled, provided the colonoscopy was performed within 5 years prior to the screening visit (Visit 1).
4. Participants who have 1 first-degree relative with colorectal cancer or adenomatous polyps diagnosed before age 60 or 2 first-degree relatives with colorectal cancer diagnosed at any age, must have had a colonoscopy with negative findings 5 years before the screening visit (Visit 1). This applies to participants who are 40 years or older and to participants younger than 40 years, who are 10 or fewer years from the age at which their youngest relative was found to have 1 of the aforementioned conditions.
5. Participants who have 1 first-degree relative with colorectal cancer or adenomatous polyps diagnosed at age 60 or older or 2 second-degree relatives with colorectal cancer diagnosed at any age, must have had a colonoscopy with negative findings within 10 years prior to the screening visit (Visit 1). This applies to participants who are 40 years or older and to participants younger than 40 years, who are 10 or fewer years from the age at which their youngest relative was found to have 1 of the aforementioned conditions.

Other Colonoscopy Requirements:

Participants of any age who have alarm symptoms must have had a colonoscopy with negative findings after the onset of the alarm symptoms and within 5 years prior to the screening visit (Visit 1). Alarm symptoms include lower GI bleeding (rectal bleeding or heme-positive stool), iron-deficiency anemia, and weight loss. (**Note:** Current unexplained or clinically significant alarm symptoms are exclusionary.) These requirements are adapted based on recent Guidance on Colorectal Cancer Screening (Levin 2008; Lieberman 2012; Qaseem 2012).

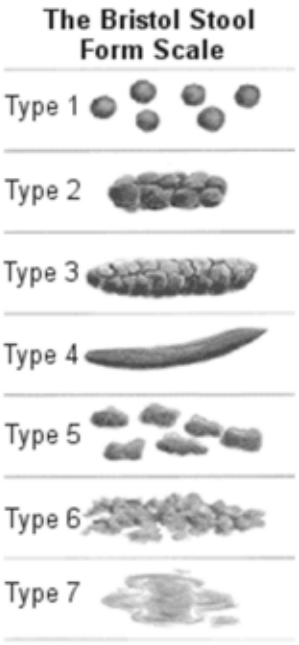
References

Levin B, Lieberman DA, McFarland B, Andrews KS, Brooks D, Bond J et al. Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps, 2008: A Joint Guideline From the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology. 2008;134:1570-1595.

Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR. Guidelines for Colonoscopy Surveillance After Screening and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2012;143:844–857.

Qaseem A, Denberg TD, Hopkins Jr RH, Humphrey LL, Levine J, Sweet DE, Shekelle P. Screening for Colorectal Cancer: A Guidance Statement From the American College of Physicians. Ann Intern Med. 2012;156:378-386.

12.11. Appendix 11: Bristol Stool Form Scale (BSFS)



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)

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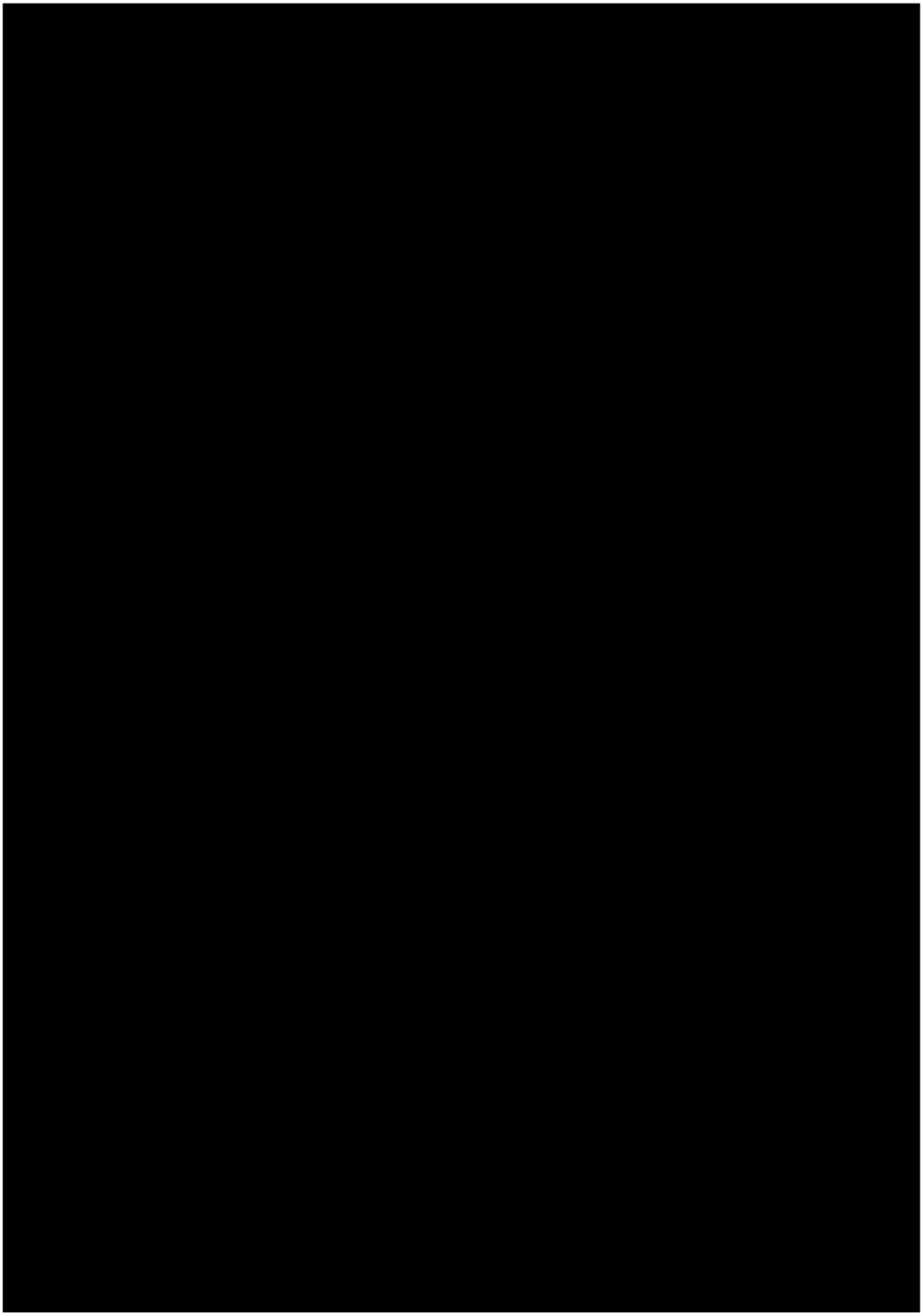

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12.13. Protocol Amendment 1 Summary

Section No. and Name	Description of Change	Brief Rationale
Section 1 Synopsis (Study design table); Section 2 SOA; Section 5.1 Table 5-1	Addition of bolded text to footnote (footnote a in synopsis and footnote b in SOA): Screening and Pretreatment periods may be combined, if results of fasting serum 7αC4 test or 48-hour fecal BA collection conducted within 1 calendar year from Screening Visit are available at the time of the combined visit **or results from fasting serum 7αC4 test are available prior to the start of study treatment**.	
Section 9 Screening Visit 1	Addition of bolded text: This visit may be combined with the pretreatment visit if results from a fasting serum 7αC4 test or 48-hour fecal BA collection, conducted within 1 calendar year prior to screening, are available at the time of the combined visit **or results from fasting serum 7αC4 test are available prior to the start of study treatment**. The screening visit will occur approximately 2 to 3 weeks before the first dose of study drug **(if combined with pretreatment visit)** and no more than 5 weeks before the first dose of study drug, if the participant requires an additional week for each, screening and pretreatment procedures).	The original protocol allowed screening and pretreatment visits to be combined for participant who had historical results of fasting serum 7αC4 test or 48-hour fecal BA collection available within 1 calendar year from screening. The turnaround for 7αC4 results used to be approximately 2-3 weeks. The 7αC4 test results are now available in approximately 1 week which was a trigger to allow combining Screening and Pretreatment for all study participants. This will allow fewer visits for some participants, decreasing the participant burden.
Section 9 Pretreatment (Visit 2)	Addition of bolded text: This visit may be combined with the screening visit if results from a fasting serum 7αC4 test or 48-hour fecal BA collection, conducted within 1 calendar year prior to screening, are available at the time of the combined visit or **results from fasting serum 7αC4 test are available prior to the start of study treatment**.	

Section No. and Name	Description of Change	Brief Rationale
Section 5.1	Duration of screening period changed to ~~1~~0-2 weeks and defined as Week - 3 to -**45 prior to Baseline Visit (V3, Study Day 1)**	To correct inaccuracy in original protocol
Section 7.5	Addition of bolded text describing destruction of test material: The study site must send any unused study treatment to the vendor specified, for destruction **or have study drug destroyed per documented institutional standards of practice that have been approved by the sponsor.**	Due to DEA handling restrictions and instiution processes the site is unableto return unused study drug to sponsor. The alternative destruction process was agreed upon and documented in Note to file
Section 9.8.2.1 AEs of Special Interest	Addition of bolded text for clarification: Once notified, the investigator must contact the participant to review the participant's status as soon as possible ~~**(eg, within 24 hours),**~~ to assess the severity of his/her constipation or the presence of any sequelae of constipation. **Every attempt should be made to reach the study participant within 24 hours**.	For clarity: Severe constipation is an adverse event of special interest and due to the potential seriousness of this condition, investigator's should attempt to reach the participant within a 24 hour period. The previous iteration of this text allow for interpretation of the phrase "as soon as possible", while the amendment makes it clear that "Every attempt should be made to reach the study participant within 24 hours".
Section 12.9 Appendix 9	The sponsor contact information was updated.	Personnel change at Allergan