Allergan

Biostatistics

Analysis Plan – Clinical Study Report

Study ID: CMO-US-GI-0429

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

Study Phase:	IV
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Version:	1.0
Issue Date:	October 18, 2017

List of Abbreviations

Abbreviation	Definition
AE	adverse event
BID	twice daily
BSS	Bristol Stool Scale
CDS-HRQOL-4	Healthy Days Core Module
eCRF	electronic case report form
ePRO	electronic patient-reported outcome
EQ-5D	EuroQoL-5 Dimension
GI	gastrointestinal
HADS	Hospital Anxiety and Depression Scale
HEOR	health economics and outcomes research
IBS	irritable bowel syndrome
IBS-AR	irritable bowel syndrome adequate relief
IBS-D	irritable bowel syndrome with diarrhea
ICF	informed consent form
ITT	intent-to-treat
IxRS	interactive response system
MedDRA	Medical Dictionary for Regulatory Activities
SAE	serious adverse event

US	United States
WAP	worst abdominal pain
WPAI: IBS-D	Work Productivity and Activity Impairment questionnaire: Irritable Bowel Syndrome with Diarrhea

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1. Introduction

The analyses described in the SAP are based upon the final protocol dated 12 August 2016. Where differences exist between analyses specified in the protocol and this SAP, the SAP will be followed.

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

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

• Group 1: eluxadoline 100 mg oral tablets BID with food

• Group 2: matching placebo oral tablets BID with food

During the screening period (up to 1 week), screening procedures, including Prior Symptoms Management Questionnaire (refer to Appendix 10.7), will be performed. After that, eligible patients will enter a pretreatment period (up to 3 weeks). At the beginning of the pretreatment period, patients will receive instructions for completing an electronic patient-reported outcome (ePRO) diary to collect daily information related to their IBS-D symptoms and use of loperamide rescue medication. At the end of the pretreatment period, patients who meet the study inclusion criteria related to ePRO diary compliance, stool consistency (Bristol Stool Scale [BSS]) , average worst abdominal pain (WAP) score , and use of loperamide rescue medication will be randomized into a 12-week double-blind treatment period via central randomization.

Patients randomized into the study will return to the clinic for study visits at week 4, week 8, week 12 (end-of-treatment study visit), and for a post-treatment follow-up visit at week 14. A complete schedule of events is provided in Appendix 10.1, Table 10–1 and Table 10–2. Patients who discontinue from the study before the week 12 visit should return to the study site to complete the early withdrawal assessments as soon as possible after stopping the study drug.

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

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

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

• Screening, week -4 (visit 1)

• Pretreatment, week -3 to day 1 (visit 2)

• Day 1 (visit 3; randomization and first administration of study drug)

• Week 4 (visit 4)

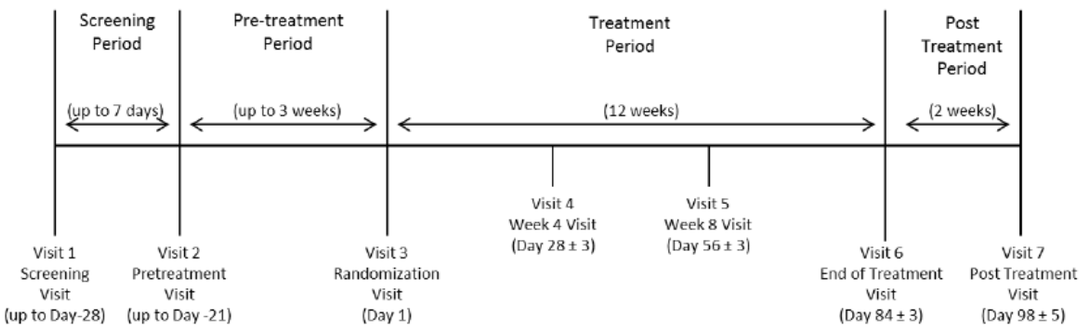
• Week 8 (visit 5)

• Week 12 (visit 6; end of treatment)

• Week 14 (visit 7; post-treatment follow-up/exit)

A diagram representing patient participation in the study is presented in Figure 1–1.

Figure 1-1 Patient Participation



1.1 Primary Study Objective

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

1.2 Secondary Objectives

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

2. Analysis Populations and Data Conventions

2.1 Analysis Populations

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

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

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

2.2 Baseline Definition and Visit Window for Analysis

For the score of BSS, WAP, abdominal discomfort, and abdominal bloating, the baseline value is defined as the weekly average in the week prior to randomization.

For bowel movement, urgency episodes, and episodes of fecal incontinence, the baseline value is defined as the average number per day in the week prior to randomization.

For HADS, EQ-5D, WPAI, and CDC HRQOL-4, the score on Day 1 will be the baseline value.

For all other variables, the baseline value is the last observation prior to receiving the first dose of study medication as usual.

Visit	Target Day of the Visit	Visit Window
1 (Screening Visit)	Up to 1 week	Up to Day -28
2 (Pretreatment Visit)	Up to 3 weeks	Day -1-- up to Day - 21
3 (Randomization Visit)	Day 1	Day 1
4 (Week 4 Visit)	Day 29	Day 26 -- Day 32
5 (Week 8 Visit)	Day 57	Day 54 -- Day 60
6 (Week 12; End of Treatment Visit)	Day 85	Day 82 -- Day 88
7 (Week 14; Post Treatment Visit)	Day 99	Day 94 -- Day 104

For weekly assessment such as treatment satisfaction and degree of relief of IBS symptoms, the visit window is defined as target day ± 3 days. For example, the treatment satisfaction assessment is collected weekly, starting from end of Week 1, the visit window will be day 4 (- 3 days) -- day 7 (target day) -- day 10 (+ 3 days).

2.3 Data Conventions

Based upon interactive voice response compliance data from the completed Phase 3 trials in patients with IBS-D, we are anticipating 15% to 20% missed ePRO diary entry days for those patients who were not discontinued. For this study, missed daily ePRO diary entries will not be considered as protocol violations. The minimum of the non-missing diary entries for each study endpoint will be specified in corresponding sections and the method of handling missing data for each endpoint is described in corresponding sections. Only observed data (i.e., no imputation) will be used for analyses except for the second definition of weekly composite responder (details are described in Section 6.5.1 14)).

If there is more than one visit within a visit window (e.g., unscheduled visits), the visit closest to the target date of the visit will be used for analyses. If two visits are equidistant from the target date, then the data from the later visit will be used for analyses.
If the date of a visit is out of the visit window, the data will only be displayed in listings.
All data collected will be displayed in listings.

3. Disposition and Exit Status

3.1 Screening Log Data

A summary table will be provided for the number of screen failures for study enrollment and the break-down of screen failures by failure reasons.

3.2 Disposition and Exit Status

The number of patients in ITT population and Safety population in each treatment group will be summarized for overall and by site. Another table will summarize the number of completers and non-completers with sub-categorization of reason for discontinuation and p-value for comparison between treatment groups.
A listing for patients who prematurely discontinued during double-blind treatment period will be provided.

4. Demographics and Other Baseline Characteristics

4.1 Demographics and Baseline Characteristics

A demographic and baseline disease characteristic table will be provided with p-values for testing differences between treatment groups.

4.2 Medical History

Medical history will be coded by MedDRA 20.0. The medical history data will be summarized by SOC and preferred term in MedDRA and by treatment groups.

4.3 Prior Medications

Prior medications are defined as any medication taken between Day -14 to Day -1.
Medications are to be coded by WHO DDE B2. The prior medication records will be summarized by preferred drug name under ATC level 2 classification and by treatment groups.

4.4 Concomitant Medications

Concomitant medications are defined as any medication that are ongoing or start after the first dose of study drug has been administrated and through the early termination or follow-up visit.
Medications are to be coded by WHO DDE B2. The concomitant medication records will be summarized by preferred drug name under ATC level 2 classification and by treatment groups.

4.5 Prior IBS-D Symptom Management Questionnaire

The number and percentage of patient's taking each category of medication (Loperamide, Antidiarrheals (other than loperamide), Antidepressants, Anticholinergics/Antispasmodics) will be summarized with p-values for testing differences between treatment groups. Furthermore, the responses to follow-up questions will be summarized by each category of medication and by questions.

Further text answers will be provided in a listing.

5. Duration to Study Treatment(s) and Compliance of Treatment

Duration of treatment is defined as: [(last dose date - first dose date) + 1].

The duration of treatment will be summarized by descriptive statistics. A listing will present the first dose date and the last dose date, the dates and days of interruption, and the overall days of exposure.

The total dose for a patient is defined as the sum of the patient reported dose on each day with dosing information (i.e., without any imputation) during 12-week treatment period. The total dose will be summarized by descriptive statistics.

Study drug compliance will be calculated as the number of tablets taken divided by the target number of tablets to be taken during 12-week treatment period.

$$\text{Overall Compliance (\%)} = \frac{\text{(Number of tablets taken) x 100 \%}}{\text{Target number of tablets to be taken}}$$

The target number of tablets to be taken is calculated as: (last dose date – first dose date + 1) x 2, since the dose is 1 tablet BID. The number of tablets taken is obtained by: (no. dispensed – no. returned).
If the drug is not returned at one visit for a patient, the compliance for the patient will be set to missing and the patient will be excluded from the analysis.

Treatment compliance will be summarized by descriptive statistics and also as frequency counts and percentages for the following categories (<80 % vs ≥80%).

The diary entry compliance will be summarized by compliance days categories (< 60 days vs > = 60 days) during the 12-week treatment period (84 days). For partial diary entry, the diary entry compliance is defined as if a patient's diary entry has EITHER WAP score and BSS score OR WAP score and bowel movement frequency data for a day, this patient will be considered as diary entry compliance for the day.

A listing will be provided for drug administration data, including number of tablets dispensed, returned, and the number not returned also not taken, etc.

6. Efficacy Analyses

6.1 Efficacy Measurement(s)

6.1.1 Daily IBS Symptoms

Patients will be required to access the ePRO diary each evening, preferably at the same time each day, to record daily IBS symptoms throughout the 12-week double-blind treatment period as follows:

- Stool Consistency: Patients will be asked to rate their stool consistency during the past 24 hours based on the BSS. The patient-reported BSS is a 1 to 7 scale where 1 corresponds to a hard stool and 7 corresponds to watery stool (refer to Appendix 10.2):

  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: Patients will be asked to rate their WAP in the past 24 hours on a 0 to 10 scale, where 0 corresponds to no pain and 10 corresponds to worst imaginable pain.

- Abdominal Discomfort: Patients will be asked to rate their worst abdominal discomfort in the past 24 hours on a 0 to 10 scale, where 0 corresponds to no discomfort and 10 corresponds to worst imaginable discomfort.

- Abdominal Bloating: Patients will be asked to rate their worst abdominal bloating in the past 24 hours on a 0 to 10 scale, where 0 corresponds to no bloating and 10 corresponds to worst imaginable bloating.

- Frequency, Urgency and Incontinence: Patients will be asked to record number of bowel movements (and characteristics, where applicable), number of urgency episodes, and number of episodes of fecal incontinence, over the past 24 hours.

6.1.2 Use of Loperamide Rescue Medication

During their daily ePRO diary entry, patients will be asked to record the use of loperamide rescue medication over the past 24 hours for the acute treatment of uncontrolled diarrhea, and total amount used.

6.1.3 Degree of Relief of IBS Symptoms

The ePRO diary will prompt patients to rate their overall IBS-D symptoms during the past 7 days based on the following:
Compared to before you started this study, how would you rate your IBS symptoms during the past 7 days?

1 = Completely relieved;
2 = Considerably relieved;
3 = Somewhat relieved;
4 = Unchanged;
5 = Somewhat worse;
6 = Considerably worse;
7 = As bad as I can imagine

6.1.4 Treatment Satisfaction

The ePRO diary will prompt patients to rate their satisfaction weekly with the study drug's ability to relieve their IBS symptoms based on the following:
Overall, how satisfied are you with the study drug's ability to relieve your IBS symptoms?

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

6.1.5 IBS Adequate Relief (IBS-AR)

The ePRO diary will prompt patients to evaluate whether they have experienced adequate relief of their IBS symptoms based on the following:

Over the past week, have you had adequate relief of your IBS symptoms?

- Yes
- No

6.1.6 Hospital Anxiety and Depression Scale (HADS)

The HADS will be used to determine the levels of anxiety and depression that a patient is experiencing. The HADS is a 14 item scale that generates ordinal data. Seven of the items relate to anxiety and 7 relate to depression (Zigmond and Snaith 1983; refer to Appendix 10.3). Patients will be asked to complete the HADS at the study site at baseline (day 1) prior to receiving study drug, and week 4, and 12 (or early withdrawal visit).

6.2 HEOR Assessments

6.2.1 Work Productivity and Activity Impairment Questionnaire: IBS-D (WPAI: IBS-D)

The WPAI: IBS-D is a tool for quantifying the effects of IBS-D symptoms on absenteeism, presenteeism, work productivity loss, and activity impairment (Reilly et al 2004; refer to Appendix 10.4). Patients will be asked to complete the WPAI-IBS-D questionnaire at the study site at baseline (day 1) prior to receiving study drug, and at week 4, 8, and 12 (or early withdrawal visit).

6.2.2 EuroQoL-5 Dimension (EQ-5D) Health Questionnaire

The EQ-5D health questionnaire is a generic measure of health status (EuroQoL group 1990; refer to Appendix 10.5). The descriptive system consists of 5 questions assessing the following dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Responses to the 5 questions define a health state for which a utility index can be derived from published algorithms. The second component of the EQ-5D is the visual analogue scale, asking patients to rate their health from 0 to 100 (0 represents worst imaginable health state and 100 represents best imaginable health). Patients will be asked to complete the EQ-5D health questionnaire at the study site at baseline (day 1) prior to receiving study drug, and at week 4, 8, and 12 (or early withdrawal visit).

6.2.3 CDC Healthy Days Core Module (CDC HRQOL-4)

The CDC HRQOL-4 assess a person's perceived health status and activity limitation through 4 questions on that assess self-rated health, numbers of recent days when physical health or mental health was not good and number of recent days with limitations due to poor physical or mental health (US Department of Health and Human Services, 2000). For the Core Healthy Days Measures, *recent* is defined as during the past 30 days. The CDC HRQOL-4 (refer to Appendix 10.6) will be completed at the study site at baseline (day 1) prior to receiving study drug, and at week 4, 8, and 12 (or early withdrawal visit).

6.3 Primary Efficacy Analyses

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

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

- Daily pain response: WAP score in the past 24 hours improved by ≥40% compared to baseline pain (average of daily WAP in the week prior to randomization).

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

To be eligible to be a primary composite responder, a patient must have a minimum of 60 days of diary entries, including partial entries, over the interval of week 1-12. A partial diary entry should consist of EITHER WAP score and BSS score OR WAP score and bowel movement frequency equals 0 to determine whether a patient is a daily responder. Any patient with fewer than 60 days of diary entry will be considered as a non-responder.

6.3.1 Primary Analyses for Primary Efficacy Endpoint

The primary analysis is to evaluate the proportions of primary composite responders between the eluxadoline and placebo groups. These 2 proportions are represented as $\pi_{\text{Eluxadoline}}$ and π_{Placebo}. The primary hypotheses for this study are described below:

H_0: $\pi_{\text{Eluxadoline}} - \pi_{\text{Placebo}} = 0$
vs
H_A: $\pi_{\text{Eluxadoline}} - \pi_{\text{Placebo}} \neq 0$

The number and the percentage of responders and non-responders will be summarized in a table with p-value from chi-square test to test the different response rates between treatment groups.

6.3.2 Other Analysis for Primary Efficacy Endpoint

As a supportive analysis, the primary endpoint will also be analyzed using logistic regression model with treatment group, the baseline pain score, and the baseline stool consistency score as exploratory variables.

6.4 Secondary Efficacy Analyses

The following are the secondary efficacy endpoints:

- Proportion of stool consistency responders: defined as patients who meet the daily stool consistency response criteria (BSS <5, or absence of a bowel movement) for ≥50% of days with diary entries over a certain time period. This endpoint is defined for the 12-week treatment period and for each 4-week interval (week 1 to 4, 5 to 8, and 9 to 12). For the 12-week treatment period, the ≥50% requirement is the same as specified for the primary efficacy endpoint in Section 6.3. For each of the 4-week intervals, a responder must have a minimum of 20 days of diary entries over the 4 weeks. Any patient with fewer than 60 days (for 12-week period) or with fewer than 20 days (for 4-week interval) of diary entries will be considered as a non-responder.

- Proportion of pain responders: defined as patients who meet the daily pain response criteria (as defined in Section 6.3) for ≥50% of days with diary entries over a certain time period. This endpoint is defined for the 12-week treatment period and for each 4-week interval (week 1 to 4, 5 to 8, and 9 to 12). For the 12-week treatment period, the ≥50% requirement is the same as specified for the primary efficacy endpoint in Section 6.3. For each of the 4-week intervals, a responder must have a minimum of 20 days of diary entries over the 4 weeks. Any patient with fewer than 60 days (for 12-week period) or with fewer than 20 days (for 4-week interval) of diary entries will be considered as a non-responder.

- Proportion of monthly composite responders: defined as patients who meet the daily composite response criteria (as defined in Section 6.3) for at least 50% of days with diary entry for each 4-week interval (week 1 to 4, 5 to 8, and 9 to 12). For each of the 4-week intervals, a responder must have a minimum of 20 days of diary entries over the 4 weeks. Any patient with fewer than 20 days of diary entries for the 4-week interval will be considered as a non-responder.

The secondary endpoints will be analyzed by the number and percentage of the corresponding responders with p-value from chi-square test to test the different response rates between treatment groups. No adjustment for the multiplicity of the endpoints will be performed.

6.5 Other Efficacy Analyses

6.5.1 Additional Endpoints

A patient much have at least 4 days of diary entries in a week in order to be considered for the weekly endpoints below unless specified.

The weekly average will be based on the actual days of available diary entries in a week. The weekly average or the weekly number will be set to missing for patients with fewer than 4 days of diary entries in a week.

For any responder definition related to a 12-week interval, a patient must have a minimum of 60 days of diary entries over the 12 weeks to be considered as a responder. Otherwise, the patient will be considered as a non-responder.

For any responder definition related to a 4-week interval, a patient must have a minimum of 20 days of diary entries over the 4 weeks to be considered as a responder. Otherwise, the patient will be considered as a non-responder.

For any responder definition related to a week, a patient must have a minimum of 4 days of diary entries in the week to be considered as a responder. Otherwise, the patient will be considered as a non-responder.

1) WAP: weekly average of the daily WAP score for each weekly interval during the 12-week treatment period.

   [Note: the average WAP in the week prior to randomization is the baseline value.]

2) Abdominal discomfort: weekly average of the daily abdominal discomfort scores for each weekly interval during the 12-week treatment period

3) Abdominal bloating: weekly average of the daily abdominal bloating scores for each weekly interval during the 12-week treatment period.

4) Bowel movement frequency: weekly average of daily number of bowel movements for each weekly interval during the 12-week treatment period

5) Urgency: weekly average of the daily number of urgency episodes for each weekly interval during the 12-week treatment period

6) Fecal incontinence: weekly average of daily number of bowel incontinence episodes for each weekly interval during the 12-week treatment period

7) Incontinence-free days: patient reported incontinence-free days for each weekly interval during the 12-week treatment period

8) Loperamide rescue medication usage: patient reported total dose for each weekly interval and for the 12-week treatment period

   [Note: For each weekly interval, there is no 'at least 4 days of diary entry' diary compliance requirement for this endpoint. The total dose for a patient will be the sum of the patient reported dose over days with diary entry in the week, regardless of diary compliance. If a patient has no diary entry for loperamide use in the week, his total dose will be set to missing. The same rule will be applied to 12-week treatment period.]

9) HADS: total scores at baseline (day 1), week 4, and week 12 for each of the 2 domains: anxiety and depression.

   [Note: Total score = (sum of non-missing item scores / number of non-missing items) × 7, if the number of missing items is no more than 20% (that is, for each domain, only one missing item is allowed); otherwise the total score will be set to missing.]

10) Treatment satisfaction: the score at each week during the 12-week treatment period

11) Degree of relief of IBS symptoms: the score at each week during the 12-week treatment period

12) Proportion of patients with at least 50% urgency-free (number of urgency episode = 0) days for the 12-week treatment period and for each 4-week interval (week 1 to 4, 5 to 8, and 9 to 12) of the treatment period.

13) Proportion of patients with at least 75% urgency-free (number of urgency episode = 0) days for the 12-week treatment period and for each 4-week interval (week 1 to 4, 5 to 8, and 9 to 12) of the treatment period.

14) Proportion of weekly composite responders. There are two definitions for weekly responders.

- Weekly composite responders defined as daily composite responders on ≥ 4 days for each weekly interval of the 12-week treatment period.

- Weekly composite responders defined as patients with weekly average WAP improvement ≥40% from average WAP of the baseline week AND with ≥ 50% reduction in the days of BSS 6/7 comparing with the days of BSS 6/7 during the baseline week for each weekly interval of the 12-week treatment period.

[Note: For patients who met the criteria of the minimum of 4 days of diary entry, any missing diary entries will be imputed by last observation carry forward (LOCF) method. The percentage reduction calculation will use the imputed data.]
[Note: Percentage reduction = [days with BSS 6/7 during baseline week (n0) - days with BSS 6/7 in a week (n1)]/ (n0). If the percentage reduction >= 50%, then it meets the criteria of '≥ 50% reduction' above.]

15) Proportion of 6-week composite responders defined as patients who meet the weekly composite responder criteria (by each of two definitions above) for ≥ 6 weeks of the 12-week treatment period.

[Note: A patient must be a weekly composite responder on 6 or more weeks, regardless of diary compliance; otherwise, the patient will be considered as a non-responder.]

16) Proportion of pain responders with ≥30% improvement in WAP from baseline for the 12-week treatment period and for each 4-week interval (week 1 to 4, 5 to 8, and 9 to 12) of the 12-week treatment period.

17) Proportion of pain responders with ≥50% improvement in WAP from baseline for the 12-week treatment period and for each 4-week interval (week 1 to 4, 5 to 8, and 9 to 12) of the 12-week treatment period.

18) Proportion of IBS adequate relief (IBS-AR) responders over 12 weeks: defined as patients with a weekly response of "Yes" to adequate relief of their IBS symptoms for ≥ 6 weeks during the 12-week treatment period

[A patient must have a positive response for 6 or more weeks, regardless of diary compliance; otherwise, the patient will be considered as a non-responder.]

19) Proportion of patients who use loperamide rescue medication for each weekly interval and for the 12-week treatment period.

[Note: There is no 'at least 4 days of diary entry' diary compliance requirement for this endpoint. For each weekly interval, a patient who took any dose of loperamide rescue medication in the week will be considered as 'Yes' for that week, regardless of diary compliance. If a patient has no diary entry for loperamide use in the week, he will be considered as 'No'. The same rule will be applied to 12-week treatment period.]

Continuous endpoints will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for baseline values, and values and change-from-baseline values for assessment intervals or at time points, whenever available.
Proportion endpoints will be analyzed by the number and percentage of the corresponding responders with p-value from chi-square test to test the different response rates between treatment groups.

Also, proportion of patients who used loperamide will be further analyzed by primary composite response status (responders vs non-responders).

6.5.2 Health Economic and Outcomes Research (HEOR) Endpoints

- WPAI: IBS-D: four types of summary scores are defined from the responses to questionnaires and the scores are expressed in percentages (refer to Appendix 10.4.1). Higher numbers indicate greater impairment and less productivity.

    - Absenteeism (work time missed);
    - Presenteeism (productivity at work);
    - Overall Work Productivity Loss (Absenteeism plus Presenteeism);
    - Daily Activity Impairment.

  The four summary scores above will be summarized using descriptive statistics for baseline (day 1) values, and values and change-from-baseline values at week 4, week 8, and week 12.

  For each summary score, treatment differences for the change from baseline at each post-baseline visit will also be analyzed using an ANCOVA with treatment and country as fixed effects and the baseline summary score as a covariate.

- EQ-5D health questionnaire: a utility score is calculated from responses to the 5 questions by published algorithms (refer to Appendix 10.5.1); another endpoint is patient's rating on 0-100 health state scale.

  Utility scores and patient's rating on 0-100 health state scale will be summarized using descriptive statistics for baseline (day 1) values, and values and change-from-baseline values at week 4, week 8, and week 12.

  A plot for mean utility scores over time (day1, week 4, 8, and 12) by treatment groups will be presented.

- CDC HRQOL-4: The unhealthy days is estimated from responses to the questions(refer to Appendix 10.6.1)

  Patient's unhealthy days will be summarized using descriptive statistics for baseline (day 1) values, and values and change-from-baseline values by treatment groups at week 4, week 8, and week 12.

6.6 Subgroup Analyses for Efficacy Parameters

The analyses (except the logistic regression) performed on primary endpoint, key secondary endpoints (stool consistency response rates, pain response rates), and IBS adequate relief rates will be performed on the following subgroups:

- Age: < 65 vs >= 65
- BMI: < 25 vs >= 25
- Gender: Male vs Female
- Country: US vs Canada

6.7 Figures for Efficacy Parameters

Line plots for percentage of daily composite responder, daily pain responder, and daily stool consistency responder over time and for daily pain score, daily stool consistency score, and daily bowel movement over time are also provided.

7. Safety Analyses

7.1 Adverse Events

Adverse events will be coded using MedDRA®, version 20.0.

An adverse event (AE) is any untoward medical occurrence in a patient administered investigational product, and which does not necessarily have a causal relationship to study medication.

For this study, during the screening period, adverse events will be collected once informed consent has been obtained, regardless of whether or not the patient has been administered study drug.

Treatment-emergent adverse event (TEAE) is defined as any AE with a start date that is on or after the start date of study medication, or any pre-existing AE worsened either in intensity or frequency after taking the first dose of the study medication.

Only TEAE will be summarized descriptively in tables. All AEs that have been reported on Case Report Forms, regardless of whether or not treatment-emergent, will be included in a data listing by patient and event, and any non-treatment-emergent AE will be marked in the listing.

An overview of TEAEs will be provided with the number and percentage of patients for each treatment group in the following categories:

- Total number of TEAEs
- Patients with at least one TEAE
- Patients with at least one study drug-related TEAE
- Patients who discontinued the study drug due to a TEAE
- Patients who discontinued the study due to a TEAE
- Patients with at least one severe TEAE
- Patients with at least one treatment-emergent serious adverse event (SAE)
- Patients with at least one study-drug related treatment-emergent SAE
- Patients who died due to TEAE

The number and percentage of patients with TEAE will be summarized by MedDRA preferred term within system organ class. Any patient reporting multiple episodes of the same TEAE (i.e., same preferred term), will be counted once.

The number and percentage of patients with Serious TEAE, study drug-related TEAE, and TEAE leading to study drug withdrawal will be summarized by MedDRA preferred term within system organ class.
Any patient reporting multiple episodes of the same drug-related TEAE (i.e., same preferred term) will be counted once.

Also, the number and percentage of patients with TEAE will be summarized by reported severity for each MedDRA preferred term within system organ class. In this summary, any patient reporting multiple episodes of the same TEAE (i.e., same preferred term) will be counted once against the most severely reported category.

All adverse event data, including screening adverse events, will be displayed in a listing. Specifically, two listings will be prepared to display serious TEAE and TEAE leading to study drug discontinuation.

7.2 Clinical Laboratory Evaluations

Descriptive statistics for hematology and serum chemistry test values and change-from-baseline values will be provided at each time point. A list of patients with positive result on pregnancy test will be presented.

Shift tables will be also provided for hematology and serum chemistry parameters.

Unscheduled lipase test results will be presented in serum chemistry listing.

7.3 Vital Signs

Vital sign assessments include blood pressure, pulse, and respiratory rate. Descriptive statistics for vital sign value and change-from-baseline values will be provided at each time point.

7.4 Physical Examination

Descriptive statistics for weight value and change from baseline will be provided at each time points whenever available.

7.5 Subgroup Analyses for Safety Variables

The TEAE categorized by SOC and preferred term table will be analyzed by the following subgroups, age (< 65 vs >= 65) and gender (male vs female).

8. Interim Analyses

There will be no interim analysis for this study.

9. Deviations from Protocol

This analysis mentioned in protocol section 7.7.3, “The mixed-effect model for repeated measures method will be used to analyze these endpoints with treatment group as the factor and baseline endpoint values as covariate.” is not performed.

10. Appendices

10.1 Schedule of Visits and Procedures

Table 10–1 Schedule of Visits and Procedures – Screening and Pretreatment

Period	Screening	Pretreatment
Week	**-4**	**-3**
Study Procedures:		
Informed consent [a]	X	
Inclusion/exclusion criteria	X	X [g]
Demographics	X	
Medical history including history related to IBS	X	X
Prior IBS-D symptom management [b]	X	
Height	X	
Vital signs [c]	X	X
Physical examination [d]	X	
Pregnancy test [e]	X	
Thyroid-stimulating hormone test	X	
Serum lipase testing	X	
Serum chemistry, hematology	X	
BSS, abdominal pain and abdominal bloating scores, bowel functioning [f]		X
Instruct patients on ePRO diary		X [h]

Abbreviations: BSS, Bristol Stool Scale; IBS, irritable bowel syndrome; IBS-D, irritable bowel syndrome with diarrhea; ePRO, electronic patient-reported outcome

a The informed consent form must be signed before any study procedure is performed.

b Any medications for treatment of IBS-D (prescription or over-the-counter) taken within 12 months, and any dietary or lifestyle modifications in the prior 12 months for management of IBS-D, will be collected.

c Vital signs will consist of pulse, respiratory rate, and blood pressure.

d Physical examination will consist of a full review of all body systems (excluding rectal and pelvic examinations). Whenever possible, assessments will be made at the same time of day by the same investigator for each patient.

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

f Patients will be required to access an ePRO diary each evening, preferably at the same time each day, to record their daily stool consistency score (on a 1 to 7 scale, BSS), their worst abdominal pain and abdominal bloating in the past 24 hours (both on 0 to 10 scales), and to report information related to their bowel functioning (bowel movement frequency and urgency and episodes of incontinence) and loperamide rescue medication use for acute treatment of uncontrolled diarrhea.

g Inclusion/exclusion criteria requirements will be re-verified at pretreatment. Verification of inclusion/exclusion criteria related to patient's ePRO data entries will be made by the ePRO system at the time of randomization.

h Patients will be instructed on the importance of the ePRO diary to record their IBS-D symptoms and information related to their bowel functioning (bowel movement frequency and urgency and episodes of incontinence). Additionally, patients will be instructed on recording their use of loperamide rescue medication for the acute treatment of uncontrolled diarrhea in the ePRO diary.

Table 10–2 Schedule of Visits and Procedures – Treatment Phase

Phase:	**Baseline**	**Double-Blind Treatment**			**Post- Treatment**
Week:	**Day 1**	**4**	**8**	**12 (End of Treatment/Early Withdrawal) [k]**	**14**
Visit Window:	**-**	**± 3 days**	**± 3 days**	**± 3 days**	**± 5 days**
Study Procedures:					
Study Drug Administration					
Randomization[a]	X				
Dispense study drug[b]	X	X	X		
Drug accountability		X	X	X	
Safety/Efficacy/Patient-Reported Outcomes					
IBS-D daily symptoms (BSS, WAP, abdominal discomfort, bloating, bowel symptoms[frequency, urgency, incontinence])[c]	X	X	X	X	
EQ-5D[d]	X	X	X	X	
CDC HRQOL-4[d]	X	X	X	X	
WPAI: IBS-D[d]	X	X	X	X	
HADS[d]	X	X		X	
Body weight	X			X	X
Vital signs[e]	X	X	X	X	X
Physical examination[f]	X		X	X	X
Serum lipase testing	X				
Serum chemistry, hematology	X	X	X	X	X
Pregnancy test[g]	X	X	X	X	
Ongoing Review					
Concomitant therapy[h]	X	X	X	X	X
Adverse events[i]	X	X	X	X	X
Review electronic diary notifications[j]	X	X	X	X	

Abbreviations: AE, adverse event; BID, twice daily; BSS, Bristol Stool Scale; CDC HRQOL-4- Healthy Days Core Module; ePRO, electronic patient-reported outcome; EQ-5D, EuroQoL-5 Dimension; IBS, irritable bowel syndrome; IBS-D, irritable bowel syndrome with diarrhea; IxRS, interactive response system; HADS, Hospital Anxiety and Depression Scale WAP, worst abdominal pain; WPAI: IBS-D, Work Productivity and Impairment questionnaire: Irritable Bowel Syndrome with Diarrhea.

a Patients who are compliant in completing the ePRO diary on a daily basis on at least 5 of the 7 days during the week prior to randomization AND on at least 10 of the 14 days during the 2 weeks prior to randomization, have an average of WAP score in the past 24 hours of >3.0 on a 0 to 10 scale over the week prior to randomization, have an average daily stool consistency score (BSS) of ≥5.5 and at least 5 days with a BSS score ≥5 on a 1 to 7 scale over the week prior to randomization, and who have not used any loperamide rescue medication in the 2 weeks prior to randomization will be eligible for participation and randomization into the double-blind treatment phase (i.e., all 4 diary conditions must be met to qualify for randomization).

b Eligible patients will be dispensed drug in accordance with their randomly assigned treatment (eluxadoline 100 mg BID or placebo BID). Study drug should not be dispensed at the baseline visit until all other procedures have been performed. Sufficient supplies will be distributed to ensure compliance through the next study visit.

c Patients will be required to access an ePRO diary each evening, preferably at the same time each day, to record their daily stool consistency score (on a 1 to 7 scale, BSS), their WAP and abdominal bloating in the past 24 hours (both on 0 to 10 scales), and to report information related to their bowel functioning (bowel movement frequency and urgency and episodes of incontinence) and loperamide rescue medication use. (X's on the Schedule of Visits and Procedures are intended to remind investigators that this will be an ongoing activity and does not necessarily imply actions to be taken at each visit.)

d Completed during the patient's scheduled visit at the study site and should be completed at the beginning of the study visit before all other evaluations, especially discussion of AEs or the patient's medical condition.

e Vital signs will consist of pulse, respiratory rate, and blood pressure.

f Physical examination will consist of a full review of all body systems (excluding rectal and pelvic examinations). Whenever possible, assessments will be made at the same time of day by the same investigator for each patient.

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

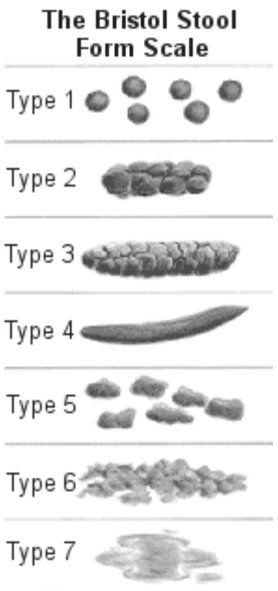
h Concomitant therapy includes all medications taken after the patient receives the first dose of study drug through the follow-up visit. Additionally, the use of loperamide rescue medication for the acute treatment of uncontrolled diarrhea should be recorded by the patient in the ePRO diary during the 12 weeks of the double-blind treatment phase.

i To be monitored throughout the study beginning from the time the patient receive the first dose of study drug through the week 14 follow-up visit (or early withdrawal visit for patients who discontinue from the study before week 12). Any clinically significant abnormalities persisting at the end of the study will be followed until the AE has resolved or until the AE is no longer considered to be of clinical significance.

j ePRO notifications will be reviewed by the investigator on an ongoing basis to assess patient compliance in completing the ePRO diary and to monitor the occurrence of diary-confirmed constipation (as defined by absence of bowel movements on 4 consecutive days) and the use of excessive loperamide rescue medication for acute treatment of uncontrolled diarrhea. In response to an ePRO notification for constipation or excessive loperamide rescue medication use, the investigator must contact the patient to review his/her status as soon as possible. An unscheduled visit to further evaluate the patient's status should be arranged if deemed warranted by the investigator.

k End-of-treatment/early withdrawal evaluations will be performed for patients who complete the study through week 12 or who are withdrawn from the study. A patient who discontinues the study drug should return to the study site to complete the early withdrawal assessments as soon as possible after stopping the study drug.

10.2 Bristol Stool Scale



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

Type 2 - Sausage shaped but lumpy

Type 3 - Like a sausage but with cracks on surface

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

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

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

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

10.3 Hospital Anxiety and Depression Scale

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

10.4 Work Productivity and Activity Impairment Questionnaire: Irritable Bowel Syndrome with Diarrhea

WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE:
IRRITABLE BOWEL SYNDROME WITH DIARRHEA (WPAI: IBS-D)

The following questions ask about the effect of your Irritable Bowel Syndrome (IBS) symptoms, e.g., abdominal discomfort, abdominal pain, bloating, diarrhea, on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1) Are you currently employed (working for pay)? ____NO ___YES
If NO, check "NO" and skip to question 6

The next questions are about the **past seven days**, not including today.

2) During the past seven days, how many hours did you miss from work because of problems associated with your IBS symptoms? *Include hours you missed on sick days, times you went in late, left early, etc. because of IBS symptoms. Do not include time you missed to participate in this study.*
_____HOURS

3) During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?
_____HOURS

4) During the past seven days, how many hours did you actually work?
_____HOURS *(If "0", skip to question 6)*

5) During the past seven days, how much did IBS symptoms affect your productivity while you were working? *Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If IBS symptoms affected your work only a little, choose a low number. Choose a high number if IBS symptoms affected your work a great deal.*

IBS symptoms had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	IBS symptoms completely prevented me from working

CIRCLE A NUMBER

6) During the past seven days, how much did IBS symptoms affect your ability to do your regular daily activities, other than work at a job? *By regular activities, we mean the usual activities you do, such as work around the house, shopping, child care, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If IBS symptoms affected your activities only a little, choose a low number. Choose a high number if IBS symptoms affected your activities a great deal.*

IBS symptoms had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	IBS symptoms completely prevented me from doing my daily activities

CIRCLE A NUMBER

10.4.1 WPAI: IBS-D Scores Definition

The 4 summary scores of the WPAI: IBS-D are defined as follows:

- Percentage of work time missed because of a problem (absenteeism):

  $100 \times \{Q2/(Q2 + Q4)\}$

- Percentage of impairment while working due to problem (presenteeism):

  $100 \times \{Q5/10\}$

- Percentage of overall work impairment due to a problem (overall work productivity loss): $100 \times \{Q2/(Q2 + Q4) + [(1 – Q2/(Q2 + Q4)) \times (Q5/10)]\}$

- Percentage of activity impairment due to a problem (daily activity impairment): $100 \times \{Q6/10\}$

If Q1 is equal to *No* or missing, absenteeism, presenteeism, and overall work productivity loss will all be set to missing. If Q1 is equal to *Yes* and Q4 is equal to 0, then, if Q2 is equal to 0, absenteeism will be set to missing; otherwise, absenteeism will be equal to 100. If Q1 is equal to *Yes* and Q4 is missing, absenteeism, presenteeism, and overall work productivity loss will all be set to missing.

10.5 EuroQoL-5 Dimension (EQ-5D) Health Questionnaire

Health Questionnaire

(English version for the US)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

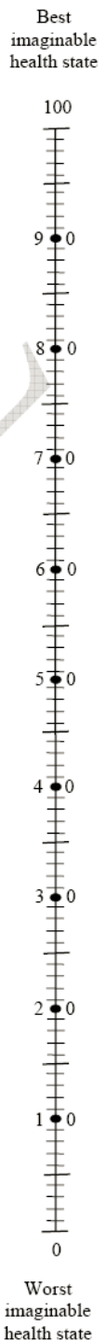
Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



10.5.1 EQ-5D Utility Index Computation Algorism

The 5-item responses of the EQ-5D define a health state that can be converted into a single summary utility index that assigns weights (i.e., value) to each level. Different weights are available. For this study, the US TTO (time trade-off) weights will be used (Shaw et al, 2005).

The EQ-5D index is computed according to the following equation as:

$$EQ_{index} = 1 - \{0.146016 \times m_1 + 0.557685 \times m_2 + 0.1753425 \times s_1 + 0.4711896 \times s_2 + 0.1397295 \times u_1 + 0.3742594 \times u_2 + 0.1728907 \times p_1 + 0.5371011 \times p_2 + 0.156223 \times a_1 + 0.4501876 \times a_2 + -0.1395949 \times d_1 + 0.0106868 \times^* i_{22} + -0.1215579 \times i_3 + -0.0147963 \times i_{32}\}$$

where the variables m_1, s_1, u_1, p_1, a_1, m_2, s_2, u_2, p_2, a_2, i_2, i_{22}, i_3, i_{32}, and d_1 are given in 11.5.1-1

Table 10.5.1-1 EuroQol Quality-of-Life Questionnaire Utility Index

EuroQoL	***Level 2***	***Level 3***	
Mobility	m_1 = 1 if Level 2 selected 0 otherwise	m_2 = 1 if Level 3 selected 0 otherwise	m_0 = 1 if m_1 = 0 & m_2 = 0 0 otherwise
Self-care	s_1 = 1 if Level 2 selected 0 otherwise	s_2 = 1 if Level 3 selected 0 otherwise	s_0 = 1 if s_1 = 0 & s_2 = 0 0 otherwise
Usual activity	u_1 = 1 if Level 2 selected 0 otherwise	u_2 = 1 if Level 3 selected 0 otherwise	u_0 = 1 if u_1 = 0 & u_2 = 0 0 otherwise
Pain/discomfort	p_1 = 1 if Level 2 selected 0 otherwise	p_2 = 1 if Level 3 selected 0 otherwise	p_0 = 1 if p_1 = 0 & p_2 = 0 0 otherwise
Anxiety/depression	a_1 = 1 if Level 2 selected 0 otherwise	a_2 = 1 if Level 3 selected 0 otherwise	a_0 = 1 if a_1 = 0 & a_2 = 0 0 otherwise
Interaction terms	$i_2 = \max\{0, (m_1 + s_1 + u_1 + p_1 + a_1) - 1\}$		
	$i_{22} = i_2 \times i_2$		
	$i_3 = \max\{0, (m_2 + s_2 + u_2 + p_2 + a_2) - 1\}$		
	$i_{32} = i_3 \times i_3$		
	$d_1 = \max\{0, 4 - (m_0 + s_0 + u_0 + p_0 + a_0)\}$		

If any dimension is missing in the EQ-5D, the EQ-5D index will not be calculated and will be set to missing.

10.6 Core Healthy Days Measures

Healthy Days Core Module (CDC HRQOL– 4)

1. Would you say that in general your health is

Please Read	
a. Excellent	1
b. Very good	2
c. Good	3
d. Fair	4
Or	
e. Poor	5
Do not read these responses	
Don't know / Not sure	7
Refused	9

2. Now thinking about your physical health, which includes physical illness and injury, for how many days during the past 30 days was your physical health not good?

a. Number of Days	_ _
b. None	8 8
Don't know / Not sure	7 7
Refused	9 9

3. Now thinking about your mental health, which includes stress, depression, and problems with emotions, for how many days during the past 30 days was your mental health not good?

a. Number of Days	_ _	
b. None	8 8	If both Q2 AND Q3="None" skip next question
Don't know / Not sure	7 7	
Refused	9 9	

4. During the past 30 days, for about how many days did poor physical or mental health keep you from doing your usual activities, such as self-care, work, or recreation?

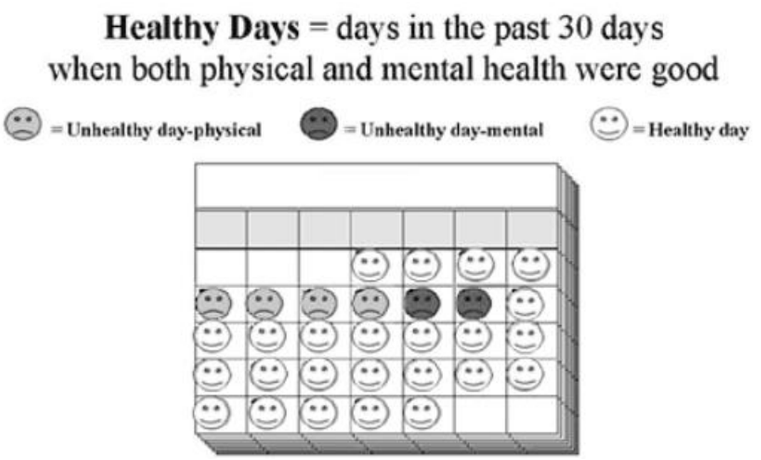
a. Number of Days	_ _
b. None	8 8
Don't know / Not sure	7 7

10.6.1 Summary Index of Unhealthy Days Calculation

Unhealthy days are an estimate of the overall number of days during the previous 30 days when the respondent felt that either his or her physical or mental health was not good. To obtain this estimate, responses to questions 2 and 3 are combined to calculate a summary index of overall unhealthy days, with a logical maximum of 30 unhealthy days. For example, a person who reports 4 physically unhealthy days and 2 mentally unhealthy days is assigned

a value of 6 unhealthy days, and someone who reports 30 physically unhealthy days and 30 mentally unhealthy days is assigned the maximum of 30 unhealthy days.

Healthy days are the positive complementary form of unhealthy days. Healthy days estimate the number of recent days when a person's physical and mental health was **good** (or better) and is calculated by subtracting the number of unhealthy days from 30 days.



10.7 Prior IBS-D Symptom Management Questionnaire

Patient ID # __ __ __ __ __ **Patient initials ___ ___**

Visit Date: _____

This questionnaire is to be administered by the Study Coordinator

READ THE FOLLOWING INSTRUCTIONS ALOUD TO THE PATIENT:

The following questions inquire about medications you have taken for your irritable bowel syndrome with diarrhea (IBS-D) symptoms, including both bowel and abdominal symptoms, in the last 12 months.

I'm going to read you a list of medication categories. I will also read you some examples of types of medications in each category. For each category, please answer 'Yes' if you have taken any medications in that category to treat your IBS-D symptoms in the last 12 months. Answer 'No' if you have not taken any medications in that category to treat your IBS-D symptoms in the last 12 months.

Note to Study Coordinator: Check 'Yes' or 'No' for each medication category in the table below based on patient responses. If patient is unsure and cannot recall, please check 'No.'

Loperamide ☐ Yes ☐ No

Some examples are:

Loperamide (non-branded) / Imodium (OTC or prescription)

Antidiarrheals (other than loperamide)

Some examples are: ☐ Yes ☐ No

Colestyramine (non-branded) / Questran *(consider only if taking for diarrhea)*

Methlycellulose (non-branded) Citrucel

Psyllium (non-branded)/ Metamucil

Diphenoxylate-atropine (non-branded) / Lomotil

Codeine phosphate (non-branded)

Paregoric (non-branded)

Antidepressants ☐ Yes ☐ No

Including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)

[Note to Study Coordinator: Confirm with patient that antidepressants were prescribed for IBS symptoms, and not for depression.]

Some examples are:

Amitriptyline (non-branded) / Elavil

Clomipramine (non-branded) / Anafranil

Imipramine (non-branded) / Tofranil

Trimipramine (non-branded) / Sumontil

Nortriptyline (non-branded) / Pamelor

Paroxetine (non-branded) / Paxil

Sertraline (non-branded) / Zoloft

Citalopram (non-branded) / Celexa

Escitalopram (non-branded) / Lexapro / Cipralex

Fluoxetine (non-branded) / Prozac

Venlafaxine (non-branded)/ Effexor

Duloxetine (non-branded) / Cymbalta

Anticholinergics/Antispasmodics

☐ Yes ☐ No

Some examples are:

Dicyclomine (non-branded) / Bentyl / Bentylol

Hyoscyamine (non-branded) / Levsin

Alverine Citrate (non-branded) / Spasmonal

Hyoscine (non-branded) / Buscopan

Mebeverine (non-branded) / Colofac

Pinaverium bromide (non-branded) / Dicetel

Trimebutine maleate (non-branded) / Modulon

In addition to any medications you may be taking to treat your IBS-D symptoms, please indicate any other ways you have tried to manage your IBS-D symptoms in the last 12 months. *Please select all that apply.*

☐ Dietary changes. Please describe (e.g. FODMAP, gluten-free, dairy-free, etc.):

_____

☐ IBgard

☐ EnteraGam

☐ Probiotics

☐ Gut directed cognitive behavioral therapy

☐ Acupuncture

☐ Exercise

☐ Stress reduction techniques (e.g. yoga, meditation, etc.)

☐ Other. Please describe:

_____

☐ None

Follow-up Questions

READ THE FOLLOWING INSTRUCTIONS ALOUD TO THE PATIENT:

I am going to ask you some follow-up questions for each of the categories of medication you have taken for your IBS-D symptoms in the last 12 months.

Note to Study Coordinator: If the patient has indicated they have taken loperamide, please complete this section. For each question, please read the question and responses aloud to the patient and CIRCLE the response that matches their response.

READ THE FOLLOWING INSTRUCTIONS ALOUD TO THE PATIENT:

Please think about your experience with loperamide when answering the following questions:

Question	**Medication Category: Loperamide**

Question	Medication Category: Loperamide
1. How do (or did) you use this medication?	1 = Daily 2 = As needed 3 = Other *Note to study coordinator: If Other, ask for specific response and write below:* _____ _____

Question	Medication Category: Loperamide
2. How long have you taken (or did you take) this medication?	1 = less than 1 week
	2 = greater than 1 week but less than 1 month
	3 = greater than 1 month but less than 3 months
	4 = greater than 3 months but less than 6 months
	5 = greater than 6 months but less than 1 year
	6 = greater than 1 year

Question	Medication Category: Loperamide
3. If you stopped taking this medication, what was the reason? *(Select all that apply)* *[Note to Study Coordinator: Responses 2 and 4 for question 3 may be related as not improving abdominal symptoms may include making them worse. If response 2 includes making abdominal symptoms worse, please also include this response as a side effect under the write in option for response 4.]*	1 = Not applicable, I am currently taking this medication. 2 = It did not improve my abdominal symptoms. *If this is chosen, ask which abdominal symptoms and write below:* _____ _____ 3 = It did not improve my bowel symptoms. *If this is chosen, ask which bowel symptoms and write below:* _____ _____ 4 = I experienced side effects *(Note: A side effect is a therapeutic or adverse effect that is secondary to the medication's intended effect)*. *If this is chosen, ask which side effects and write below:* _____ _____ 5 = It costs too much

Question	Medication Category: Loperamide
4. Overall, how satisfied are (or were) you with this medication's ability to relieve your diarrhea?	1 = Not at all satisfied
	2 = A little satisfied
	3 = Moderately satisfied
	4 = Quite satisfied
	5 = Very satisfied

Question	Medication Category: Loperamide
5. Overall, how satisfied are (or were) you with this medication's ability to relieve your abdominal pain?	1 = Not at all satisfied
	2 = A little satisfied
	3 = Moderately satisfied
	4 = Quite satisfied
	5 = Very satisfied

Question	Medication Category: Loperamide
6. Overall, how satisfied are (or were) you with this medication's ability to decrease the number of times you experienced urgency in relation to your bowel movements (sudden, almost irresistible need to have a bowel movement)?	1 = Not at all satisfied 2 = A little satisfied 3 = Moderately satisfied 4 = Quite satisfied 5 = Very satisfied

Note to Study Coordinator: If the patient has indicated they have taken antidiarrheals (other than loperamide), please complete this section. For each question, please read the question and responses aloud to the patient and CIRCLE the response that matches their response.

READ THE FOLLOWING INSTRUCTIONS ALOUD TO THE PATIENT:

Please think about your experience with antidiarrheals (other than loperamide) when answering the following questions:

Question	**Medication Category: Antidiarrheals (other than loperamide)**
1. How do (or did) you use this medication?	1 = Daily 2 = As needed 3 = Other *Note to study coordinator: If Other, ask for specific response and write below:* _____ _____

Question	Medication Category: Antidiarrheals (other than loperamide)
2. How long have you taken (or did you take) this medication?	1 = less than 1 week
	2 = greater than 1 week but less than 1 month
	3 = greater than 1 month but less than 3 months
	4 = greater than 3 months but less than 6 months
	5 = greater than 6 months but less than 1 year
	6 = greater than 1 year

Question	Medication Category: Antidiarrheals (other than loperamide)
3. If you stopped taking this medication, what was the reason? *(Select all that apply)* *[Note to Study Coordinator: Responses 2 and 4 for question 3 may be related as not improving abdominal symptoms may include making them worse. If response 2 includes making abdominal symptoms worse, please also include this response as a side effect under the write in option for response 4.]*	1 = Not applicable, I am currently taking this medication. 2 = It did not improve my abdominal symptoms. *If this is chosen, ask which abdominal symptoms and write below:* _____ _____ 3 = It did not improve my bowel symptoms. *If this is chosen, ask which bowel symptoms and write below:* _____ _____ 4 = I experienced side effects *(Note: A side effect is a therapeutic or adverse effect that is secondary to the medication's intended effect)*. *If this is chosen, ask which side effects and write below:* _____ _____

Question	Medication Category: Antidiarrheals (other than loperamide)
4. Overall, how satisfied are (or were) you with this medication's ability to relieve your diarrhea?	1 = Not at all satisfied
	2 = A little satisfied
	3 = Moderately satisfied
	4 = Quite satisfied
	5 = Very satisfied

Question	Medication Category: Antidiarrheals (other than loperamide)
5. Overall, how satisfied are (or were) you with this medication's ability to relieve your abdominal pain?	1 = Not at all satisfied 2 = A little satisfied 3 = Moderately satisfied 4 = Quite satisfied 5 = Very satisfied

Question	Medication Category: Antidiarrheals (other than loperamide)
6. Overall, how satisfied are (or were) you with this medication's ability to decrease the number of times you experienced urgency in relation to your bowel movements (sudden, almost irresistible need to have a bowel movement)?	1 = Not at all satisfied 2 = A little satisfied 3 = Moderately satisfied 4 = Quite satisfied 5 = Very satisfied

Note to Study Coordinator: If the patient has indicated they have taken antidepressants for treatment of IBS-D symptoms, please complete this section. For each question, please read the question and responses aloud to the patient and CIRCLE the response that matches their response.

READ THE FOLLOWING INSTRUCTIONS ALOUD TO THE PATIENT:

Please think about your experience with antidepressants when answering the following questions:

Question	**Medication Category: Antidepressants**
1. How do (or did) you use this medication?	1 = Daily 2 = As needed 3 = Other *Note to study coordinator: If Other, ask for specific response and write below:* _____ _____

Question	Medication Category: Antidepressants
2. How long have you taken (or did you take) this medication?	1 = less than 1 week
	2 = greater than 1 week but less than 1 month
	3 = greater than 1 month but less than 3 months
	4 = greater than 3 months but less than 6 months
	5 = greater than 6 months but less than 1 year
	6 = greater than 1 year

Question	Medication Category: Antidepressants
3. If you stopped taking this medication, what was the reason? *(Select all that apply)* *[Note to Study Coordinator: Responses 2 and 4 for question 3 may be related as not improving abdominal symptoms may include making them worse. If response 2 includes making abdominal symptoms worse, please also include this response as a side effect under the write in option for response 4.]*	1 = Not applicable, I am currently taking this medication. 2 = It did not improve my abdominal symptoms. *If this is chosen, ask which abdominal symptoms and write below:* _____ _____ 3 = It did not improve my bowel symptoms. *If this is chosen, ask which bowel symptoms and write below:* _____ _____ 4 = I experienced side effects *(Note: A side effect is a therapeutic or adverse effect that is secondary to the medication's intended effect)*. *If this is chosen, ask which side effects and write below:* _____ _____ 5 = It costs too much

Question	Medication Category: Antidepressants
4. Overall, how satisfied are (or were) you with this medication's ability to relieve your diarrhea?	1 = Not at all satisfied
	2 = A little satisfied
	3 = Moderately satisfied
	4 = Quite satisfied
	5 = Very satisfied

Question	Medication Category: Antidepressants
5. Overall, how satisfied are (or were) you with this medication's ability to relieve your abdominal pain?	1 = Not at all satisfied 2 = A little satisfied 3 = Moderately satisfied 4 = Quite satisfied 5 = Very satisfied

Question	Medication Category: Antidepressants
6. Overall, how satisfied are (or were) you with this medication's ability to decrease the number of times you experienced urgency in relation to your bowel movements (sudden, almost irresistible need to have a bowel movement)?	1 = Not at all satisfied 2 = A little satisfied 3 = Moderately satisfied 4 = Quite satisfied 5 = Very satisfied

Note to Study Coordinator: If the patient has indicated they have taken anticholinergics, please complete this section. For each question, please read the question and responses aloud to the patient and CIRCLE the response that matches their response.

READ THE FOLLOWING INSTRUCTIONS ALOUD TO THE PATIENT:

Please think about your experience with anticholinergics/antispasmodics when answering the following questions:

Question	**Medication Category: Anticholinergics/Antispasmodics**
1. How do (or did) you use this medication?	1 = Daily 2 = As needed 3 = Other *Note to study coordinator: If Other, ask for specific response and write below:* _____ _____

Question	Medication Category: Anticholinergics/Antispasmodics
2. How long have you taken (or did you take) this medication?	1 = less than 1 week
	2 = greater than 1 week but less than 1 month
	3 = greater than 1 month but less than 3 months
	4 = greater than 3 months but less than 6 months
	5 = greater than 6 months but less than 1 year
	6 = greater than 1 year

Question	Medication Category: Anticholinergics/Antispasmodics
3. If you stopped taking this medication, what was the reason? *(Select all that apply)*	1 = Not applicable, I am currently taking this medication.
[Note to Study Coordinator: Responses 2 and 4 for question 3 may be related as not improving abdominal symptoms may include making them worse. If response 2 includes making abdominal symptoms worse, please also include this response as a side effect under the write in option for response 4.]	2 = It did not improve my abdominal symptoms. *If this is chosen, ask which abdominal symptoms and write below:* _____ _____
	3 = It did not improve my bowel symptoms. *If this is chosen, ask which bowel symptoms and write below:* _____ _____
	4 = I experienced side effects *(Note: A side effect is a therapeutic or adverse effect that is secondary to the medication's intended effect).* *If this is chosen, ask which side effects and write below:* _____ _____

Question	Medication Category: Anticholinergics/Antispasmodics
4. Overall, how satisfied are (or were) you with this medication's ability to relieve your diarrhea?	1 = Not at all satisfied
	2 = A little satisfied
	3 = Moderately satisfied
	4 = Quite satisfied
	5 = Very satisfied

Question	Medication Category: Anticholinergics/Antispasmodics
5. Overall, how satisfied are (or were) you with this medication's ability to relieve your abdominal pain?	1 = Not at all satisfied 2 = A little satisfied 3 = Moderately satisfied 4 = Quite satisfied 5 = Very satisfied

Question	Medication Category: Anticholinergics/Antispasmodics
6. Overall, how satisfied are (or were) you with this medication's ability to decrease the number of times you experienced urgency in relation to your bowel movements (sudden, almost irresistible need to have a bowel movement)?	1 = Not at all satisfied 2 = A little satisfied 3 = Moderately satisfied 4 = Quite satisfied 5 = Very satisfied

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_____

Study Coordinator Signature Date completed

11. Signature Page

Study ID: CMO-US-GI-0429

Version: 1.0

Issue Date: October 18, 2017

Issued by: DocuSigned by: Xiaoshu Xu 702F78ED68CD40A... Date: October 23, 2017

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