Title Page

Protocol Title: A Phase 3, Multicenter, Randomized, Double-blind, Parallel-group, Safety and Efficacy Study of Linaclotide in Pediatric Participants, Ages 6 to 17 Years, With Irritable Bowel Syndrome with Constipation (IBS-C) and of Linaclotide versus Placebo in Pediatric Participants with Functional Constipation (FC)

Protocol Number: LIN-MD-64

Amendment Number: 1

Product: Linaclotide

Brief Protocol Title: Linaclotide Safety and Efficacy in Pediatric Participants, 6 to 17 Years of Age, with IBS-C or FC

Development Phase: 3

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

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	*Jun 2020*
Original Protocol	*Apr 2019*

Amendment 1 (June 2020)

The purpose of Global Protocol Amendment 1 is to include enrollment of pediatric participants ages 7 – 17 years with IBS-C, to include a plan for a potential interim analysis to assess futility for FC participants, and to provide additional clarification and updates to the LIN-MD-64 protocol (dated 17 April 2019).

The following is a summary of changes made in Global Protocol Amendment 1. 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.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Protocol Section(s)	Description of Changes	Rationale for Changes
Title Page	• Updated title to include IBS-C participants. • Added the EudraCT number.	• To align with changes in the protocol • To reflect current information
Section 1.1 Synopsis	• All relevant changes made below in subsequent sections in the body of the protocol have been carried up to the synopsis.	• To align with the body of the protocol
Section 1.3 Schedule of Activities (SoA)	• Table 1-1 was edited to include IBS-C participants. • An assessment of Rome III criteria at EOT was added for all participants. • The following text was added to footnote 'e': 'Prior to dosing, the investigator or appropriate site staff member will assess if Rome IV criteria for Child/Adolescent FC **(FC and IBS-C participants) or Rome IV criteria for Child/Adolescent IBS (IBS-C participants)** was met and record the outcome in the eCRF.' • A fecal impaction assessment at Randomization (Visit 3) was added for all participants. The footnotes have been updated accordingly. • Footnote 'l' has been updated for clarity. • Footnote 'u' has been added: 'Additional unscheduled visits may be allowed at the discretion of the investigator with approval from the sponsor'.	• For clarification and update to include IBS-C participants in the study • To assess participants for fulfilling Rome criteria at both screening and at end of treatment as an 'other' efficacy endpoint. • To update to include IBS-C participants in the study • To ensure participants didn't have fecal impaction prior to receiving study intervention • For clarification • To allow additional visits for participants if needed
Section 2 Introduction	• Text added to include the pediatric Phase 2 study LIN-MD-63 results in the introduction.	• To reflect current information
Section 2.1 Study Rationale	• Text added to describe the IBS disease and prevalence and the lack of any approved therapy for IBS-C in pediatric patients. • Added a summary of results for Phase 2 dose ranging study LIN-MD-63 evaluating linaclotide in pediatric IBS-C participants. • Added the primary objective of LIN-MD-64 for IBS-C participants.	• Updated to include IBS-C participants in the study

Protocol Section(s)	Description of Changes	Rationale for Changes
Section 2.2.1 Adult Linaclotide Program	• Text added to include the recently completed Phase 3b study MCP-103-312.	• To reflect current information
Section 2.2.2 Pediatric Linaclotide Program	• A summary of results for the recently completed LIN-MD-63 study in pediatric IBS-C participants was added.	• To reflect current information
Section 2.2.3.2 GC-C mRNA Expression	• Corrected the study number for Study MCP-103-311.	• Correction of typo
Section 2.3 Benefit/Risk	• Text added to include the IBS-C population.	• Updated to include IBS-C participants in the study
Section 3 Objectives and Endpoints	• Added the objective and primary and secondary endpoints for IBS-C participants.	• Updated to include IBS-C participants in the study
Section 4.1 Overall Design	• Added the study design for IBS-C participants. • Added text regarding the addition of an optional interim analysis for futility in FC participants.	• Updated to include IBS-C participants in the study • To address potential enrollment issues with the pediatric FC population
Section 4.1.1 Clinical Hypotheses	• Added a clinical hypothesis for treatment of IBS-C participants with linaclotide.	• Updated to include IBS-C participants in the study
Section 4.2 Scientific Rationale for Study Design	• Added a scientific rationale for the study design for IBS-C participants.	• Updated to include IBS-C participants in the study
Section 4.3 Justification for Dose	• Added a justification for the doses chosen for IBS-C participants.	• Updated to include IBS-C participants in the study
Sections 5.1 Inclusion Criteria	• Edits were made to inclusion criteria 1.01, 1.02, 2.01, and 4.02 to add IBS-C participants and/or to add clarity. • Inclusion criteria 2.011 and 2.012 for IBS-C participants were added.	• For clarification and to include IBS-C participants • Updated to include IBS-C participants in the study

Protocol Section(s)	Description of Changes	Rationale for Changes
Section 5.2 Exclusion Criteria	• Edits were made to exclusion criteria 1.01, 1.05, and 1.11 to add IBS-C participants and/or to add clarity. • Exclusion criterion 1.04 was revised to add a fecal impaction assessment at Visit 3. • '**Vital sign assessment**' was included in exclusion criteria 1.07. • Criterion 1.13 was removed.	• For clarification and to include IBS-C participants • To ensure participants didn't have fecal impaction prior to dosing • For clarification • Updated eligibility criteria to be more inclusive for enrollment
Section 5.3 Lifestyle Considerations	• Added lifestyle considerations for IBS-C participants. • Reorganized habits by all participants, FC participants, and IBS-C participants.	• For clarification and update to include IBS-C participants in the study
Section 6 Study Intervention	• Added text on the randomization and dosing of IBS-C participants.	• Updated to include IBS-C participants in the study
Section 6.1 Study Intervention Administered	• Added text on the study intervention administered to IBS-C participants.	• Updated to include IBS-C participants in the study
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	• Added text on the randomization of FC and IBS-C participants being carried out separately. • Revised the study number from 301 to 364. • Revised the site number from 00001-99999 to 10001-19999.	• Update to include IBS-C participants in the study • To reflect what's being used in the study
Section 6.3.1.2 Unblinding	• Added text on the separate database locks and unblinding procedures for FC and IBS-C participants.	• Updated to include IBS-C participants in the study
Section 6.5.1 Prohibited Interventions	• Added linaclotide to the list of prohibited medicines with a 14-day washout period.	• To provide additional clarity
Section 6.5.2 Rescue Medication	• Added a statement clarifying the use of rescue medication with regard to Visit 3 (Randomization Visit).	• For clarification
Section 6.6 Dose Modification	• Added the dose modifications permitted for IBS-C participants.	• Updated to include IBS-C participants

Protocol Section(s)	Description of Changes	Rationale for Changes
Section 7.1.1 Removal of Individual Participants from Therapy or Assessment	• Two criteria have been moved from 'participant may be discontinued' to 'participant must be discontinued'. • Text referring to signs of drug-induced liver injury was moved to newly added Appendix 9: Liver Safety: Suggested Actions and Follow-up Assessments.	• To further ensure participant safety • To align with the liver appendix template
Section 8 Study Assessments and Procedures	• The following text was added: '**Additional details regarding study conduct during the novel coronavirus pandemic are provided in Appendix 11**.'	• To add a reference to newly added Appendix 11
Section 8.1 Efficacy Assessments	• Information regarding the efficacy assessments for IBS-C participants has been added and changes made to clarify what pertains to FC participants versus IBS-C participants. • The following text was deleted: '~~The relationship of the caregiver to the participant should be recorded in the eCRF~~.'	• For clarification and update to include IBS-C participants in the study • To reflect current information
Section 8.1.1 Efficacy Assessments in FC Participants	• Replaced 'parameter' with 'endpoint' as needed.	• For clarification
Section 8.1.1.2 Secondary Efficacy Assessment	• Revised text to reflect the text in the current eDiary.	• To align with the current eDiary
Section 8.1.1.3 Additional Efficacy Assessments	• Added an assessment of modified Rome III criteria at the end of the study intervention period.	• To assess FC participants for fulfilling modified Rome III criteria at both screening and at end of treatment as an 'other' efficacy endpoint
Section 8.1.2 Efficacy Assessments in IBS-C Participants	• Added the efficacy assessments that will be performed for IBS-C participants.	• Updated to include IBS-C participants.
Section 8.2.1 Physical Examinations	• The following text was removed: A complete physical examination will be done at screening and at the EOT Visit ~~by a professionally trained physician or health professional listed on Form FDA 1572 or the Delegation of Authority log and licensed to perform physical examinations~~. • Added a fecal impaction assessment at randomization (Visit 3) prior to dosing for all participants.	• To align with current Allergan template • To ensure participants don't have fecal impaction prior to receiving study intervention
Section 8.2.2 Vital Signs	• Removed bullet 2 from the procedure for obtaining vital signs.	• For clarification

Protocol Section(s)	Description of Changes	Rationale for Changes
Section 8.2.3 Electrocardiograms	• Revised text to clarify method for recording ECGs.	• To reflect current information
Section 8.3.4 Follow-up of AEs, SAEs, and AESIs	• Inserted 'etiology' in the following sentence: All AE/ SAE and non-serious AESIs will be followed until resolution, stabilization, the event**'s etiology** is otherwise explained, or the participant is lost to follow-up. • Deleted the following text as this information is presented in Appendix 3: Adverse Events: ~~If a follow-up visit is deemed necessary for appropriate safety surveillance, it will take place within 30 days of the final protocol-defined study visit .~~	• For clarification • To align with current Allergan template
Section 8.3.6 Pregnancy	• Added text regarding genetic abnormalities.	• To align with current Allergan template
Section 8.3.7 Potential Hy's Law Cases	• Details regarding liver safety assessments and follow-up for potential Hy's law cases were moved to newly added Appendix 9: Liver Safety: Suggested Actions and Follow-up Assessments.	• To align with the liver appendix template
Section 9 Statistical Considerations	• Text added to indicate that this study involves two independent parallel parts, one for FC participants and one for IBS-C participants, and that database locks will be performed separately for FC and IBS-C participants. • Section numbers were updated throughout to delineate statistical sections for each disease population, and corresponding section references were updated accordingly. • Text added throughout Section 9 to clarify what information corresponds to FC participants versus IBS-C participants.	• For clarification and update to include IBS-C participants in the study
Section 9.1.3 Sample Size Determination - FC Participants	• A brief description was added of the sample size to be targeted for FC participants if an optional interim analysis for futility is performed.	• To provide information regarding sample size for the optional interim analysis
Section 9.1.5.1.1 Efficacy Analysis Endpoints	• The other efficacy endpoint of 'Time to the first SBM after the first dose of study intervention' has been changed to 'Time to ~~the~~ first **report of** SBM after the first dose of study intervention' to more accurately reflect the endpoint. • Added the other efficacy endpoint of '**Proportion of participants who no longer fulfill modified Rome III criteria for functional constipation at the end of the study intervention period.**'	• For clarification • To assess whether participants meet Rome III criteria at the end of the 12-week study intervention period.

Protocol Section(s)	Description of Changes	Rationale for Changes
Section 9.1.5.2.2 Clinical Laboratory Assessments	• The following text was added: 'The numerator will be the total number of participants with **available non-PCS baseline values and** at least 1 PCS postbaseline value …'	• For clarification
Section 9.2 Statistical Considerations for IBS-C Participants	• Added information regarding the statistical analyses that will be performed for efficacy and safety data for IBS-C participants.	• Updated to include IBS-C participants
Section 9.3 Interim Analyses	• Details of the optional interim analysis strategy for FC participants were added.	• Updated to include an optional interim analysis for FC participants
Section 10.1.6.3 DSMB	• Added **'or ad hoc if needed'.**	• For clarification
Section 10.2 Appendix 2: Clinical Laboratory Tests	• %Reticulocytes was removed from Table 10-1. • Footnote 'a' was revised to refer to Appendix 9: Liver Safety: Suggested Actions and Follow-up Assessments for liver chemistry stopping criteria and required actions and follow-up assessments. • Footnote 'b' was moved from Routine Urinalysis to the second bullet under Other Screening Tests.	• To reflect what's being assessed in the study • To align with the liver appendix template • For clarification
Section 10.3 Appendix 3: Adverse Events	• Text regarding reporting of potential Hy's Law cases was moved to newly added Appendix 9: Liver Safety: Suggested Actions and Follow-up Assessments. • A section title was revised from 'SAE Reporting' to 'SAE Reporting **to Sponsor or Designee Within 24 Hours**'.	• For clarity and to align with the liver appendix template
Section 10.4 Appendix 4: Abbreviations	• Updated to align with new abbreviations used in the body of the protocol.	• To align with changes in the protocol
Section 10.6 Appendix 6: Study Tabular Summary	• Updated the study tabular summary to include information regarding IBS-C participants in the study.	• Updated to include IBS-C participants
Section 10.7 Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information	• The description of the pregnancy testing sensitivity was revised as shown below: 'Pregnancy testing with a sensitivity of ~~5, 10,~~ ≤ 25 mIU/mL will be performed'.	• For clarification and to reflect the sensitivity of the assay currently being used in the study

Protocol Section(s)	Description of Changes	Rationale for Changes
Section 10.9 Appendix 9: Liver Safety: Suggested Actions and Follow-up Assessments	• Appendix 9: Liver Safety: Suggested Actions and Follow-up Assessments was added. With the addition of the new Appendix 9, the subsequent Appendix has been moved to Appendix 10 and all section numbering and references have been changed accordingly.	• To provide liver safety information in a consolidated location and to align with the liver appendix template
Section 10.10.1 Screening Period (Visit 1)	• The following procedure was added to the Screening Visit: '**Complete Rome III assessment'.** • **Lumbosacral** was added to the physical exam. • Information regarding lifestyle modifications was updated to include IBS-C participants and clarify the modifications for each population.	• To assess participants for fulfilling Rome III criteria at screening • For clarification • For clarification and update to include IBS-C participants in the study
Section 10.10.2 Preintervention Period (Visit 2)	• The following text was removed: '~~If fecal impaction is documented during an optional repeat physical examination, the Study Physician must be notified'.~~ • Text regarding the use of rescue medication was added.	• For clarification
Section 10.10.3 Randomization (Visit 3, Day 1)	• A fecal impaction assessment was added to the randomization visit (Visit 3) as shown below: **'Perform a fecal impaction assessment prior to randomization. If fecal impaction is present, the participant will not be eligible for the study.'**	• To ensure participants don't have fecal impaction prior to receiving study intervention
Section 10.10.7 Week 12/EOT Visit (Visit 7)	• **Lumbosacral** was added to the physical exam. • The following procedure was added to the EOT Visit: **'Complete Rome III assessment.'**	• For clarification • To assess participants for fulfilling ROME III criteria at the end of treatment as an 'other' efficacy endpoint.
Section 10.11 Appendix 11: Study Conduct During the Novel Coronavirus Pandemic	• Appendix 11: Study Conduct During the Novel Coronavirus Pandemic was added.	• To provide information on study conduct during the novel coronavirus pandemic
Section 10.12 Supporting Information from the Adult Linaclotide Program	• Results from recently completed study MCP-103-312 were added to Table 10-3.	• To reflect current information
Section 11 References	• References for IBS and statistical analyses for the interim analysis were added.	• To reflect current information

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 3, Multicenter, Randomized, Double-blind, Parallel-group, Safety and Efficacy Study of Linaclotide in Pediatric Participants, Ages 6 to 17 Years, With Irritable Bowel Syndrome with Constipation (IBS-C) and of Linaclotide versus Placebo in Pediatric Participants with Functional Constipation (FC)

Protocol Number: LIN-MD-64

Amendment Number: 1

Brief Title: Linaclotide Safety and Efficacy in Pediatric Participants, 6 to 17 Years of Age, with IBS-C or FC

Study Phase: 3

Study Rationale:

Functional constipation (FC) is a common healthcare problem in children of all ages, with a worldwide prevalence ranging between 0.7% and 29.6% (Koppen 2018). Symptoms include infrequent, hard stools, and painful defecation and affected children may have abdominal pain and fecal incontinence, which is usually the result of fecal impaction leading to overflow incontinence. These symptoms can have a severe impact on a child's quality of life and may lead to school absenteeism and substantial costs related to healthcare utilization. Initial non-pharmacological interventions include education, behavioral modifications, and keeping a bowel diary. Despite these interventions, many children require pharmacological interventions. Treatment consists of dis-impaction (ie, removal of the rectal fecal mass), followed by maintenance treatment and eventually a weaning phase. Multiple pharmacological agents are available for the treatment of FC in children. Despite chronic pharmacological treatment, approximately 40% of children with FC referred to a pediatric gastroenterologist remain symptomatic after 5 years and 20% of children still have symptoms after 10 years. In some cases, symptoms may persist into adolescence or adulthood despite medical treatment. Potential reasons for ineffectiveness of treatment include suboptimal dosage regimens, poor compliance with treatment, or the use of drugs with action mechanisms that do not address the underlying pathophysiological etiology.

Irritable bowel syndrome (IBS) is characterized by symptoms of abdominal discomfort or pain associated with altered bowel movement characteristics (Drossman 2006). In adults, Rome III criteria has classified IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed IBS, and unsubtyped IBS, depending on the stool consistency (Longstreth 2006). In children, although IBS subtypes are encountered in clinical practice, a classification based on stool consistency had not been specified at the time the Phase 2 dose ranging study (LIN-MD-63) was originally developed.

The overall prevalence of IBS in the pediatric population is low. IBS prevalence in children across the United States, based on parental reports, ranges from 1.2% to 2.9%, while school-based studies in Colombia and Sri Lanka found a prevalence of IBS of 4.9% and 5.4%,

respectively (Hyams 2016). In adults, although not life-threatening, because of its chronic relapsing course, IBS is associated with impaired quality of life and high direct and indirect medical costs such as absenteeism from work. (Thompson 1999). In children and adolescents, IBS has been associated with significant impairment as increased rates of school absenteeism, health-care utilization and family disruption are common (Chiou and Nurko 2010).

There are no pharmacologic therapies approved in the pediatric population for the treatment of FC or IBS-C. Thus, there is a need for new agents with favorable safety and tolerability profiles that are effective in providing relief for the symptoms associated with FC and IBS-C in pediatric patients.

For the primary and key secondary endpoints in the Phase 2 dose ranging LIN-MD-62 study in FC participants, none of the 3 linaclotide doses (A [low dose], B [medium dose], and C [high dose]) indicated clear improvement over placebo (p-value ≥ 0.1502) based on analysis of the intent-to-treat (ITT) population. However, a numerical trend towards efficacy at the higher doses was observed for the primary endpoint of change from baseline in 4-week overall spontaneous bowel movement (SBM) frequency rate (SBMs/week). Overall, linaclotide was well tolerated across all doses in participants 6 to 17 years of age. The safety profile was consistent with prior adult linaclotide chronic idiopathic constipation (CIC) studies.

In the Phase 2 dose ranging study LIN-MD-63 in IBS-C participants, for the primary efficacy endpoint of change from baseline in 4-week overall SBM frequency rate, numerical improvement was observed with each increasing linaclotide dose compared with placebo based on analysis of the ITT population. For the key secondary efficacy endpoint of change from baseline in 4-week abdominal pain daytime symptoms, numerical improvement was observed with linaclotide 290 µg compared with placebo, while results were similar in the other linaclotide groups (Dose A, B, and C) compared with placebo. Overall, linaclotide was well tolerated across all doses in participants aged 7 to 17 years. The safety profile was consistent with prior adult linaclotide IBS-C studies and with the aforementioned pediatric Phase 2 dose-ranging FC study LIN-MD-62.

Based on the above Phase 2 results, the primary objectives of LIN-MD-64 are:

- To evaluate the safety and efficacy of 12 weeks of linaclotide therapy in comparison with placebo in pediatric participants aged 6 to 17 years who fulfill modified Rome III Criteria for Child/Adolescent FC
- To evaluate the safety and efficacy of 12 weeks of linaclotide therapy in pediatric participants aged 7 to 17 years with IBS-C (ie, fulfill Rome III Criteria for Child/Adolescent IBS and fulfill modified Rome III Criteria for Child/Adolescent FC).

Objectives and Endpoints:

Objectives for FC Participants	Efficacy Endpoints for FC Participants
Primary Objective To evaluate the safety and efficacy of 12 weeks of linaclotide therapy in comparison with placebo in pediatric participants aged 6 to 17 years who fulfill modified Rome III Criteria for Child/Adolescent FC	**Primary Endpoint** • Change from baseline in 12-week SBM frequency rate (SBMs/week) during the study intervention period
	Secondary Endpoint • Change from baseline in 12-week stool consistency during the study intervention period

Objectives for IBS-C Participants	Efficacy Endpoints for IBS-C Participants
Primary Objective To evaluate the safety and efficacy of 12 weeks of linaclotide therapy in pediatric participants aged 7 to 17 years with IBS-C (ie, fulfill Rome III Criteria for Child/Adolescent IBS and fulfill modified Rome III Criteria for Child/Adolescent FC)	**Primary Endpoint** • 6/12 weeks APS (abdominal pain and SBM) + 2 responder
	Secondary Endpoints • Change from baseline in 12-week SBM frequency rate (SBMs/week) during the study intervention period • Change from baseline in 12-week abdominal pain during the study intervention period • Change from baseline in 12-week stool consistency during the study intervention period • 6/12 weeks SBM + 2 responder • 6/12 weeks abdominal pain responder

The safety assessments will include monitoring of adverse events (AEs), clinical laboratory assessments (clinical chemistry, complete blood count [CBC], urinalysis), vital sign measurements (including postural vital signs), electrocardiograms (ECGs), physical examinations, height, and weight.

Overall Study Design:

LIN-MD-64 is a Phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel-group, confirmatory safety and efficacy study comparing linaclotide at 72 µg and placebo in pediatric participants, 6 to 17 years of age, with a diagnosis of FC based on modified Rome III Child/Adolescent Criteria (ie, who fulfill modified Rome III criteria for child/adolescent FC).

LIN-MD-64 is a Phase 3 multicenter, randomized, double-blind, parallel-group, confirmatory safety and efficacy study of linaclotide therapy (145 µg or 290 µg daily) in pediatric participants,

7 to 17 years of age, with a diagnosis of IBS-C (ie, who fulfill the Rome III criteria for child/adolescent IBS and modified Rome III criteria for child/adolescent FC).

Number of Participants:

- For FC participants, the sample size was determined based on the primary efficacy endpoint. A total of 326 FC participants are targeted to be randomized in a 1:1 ratio to receive either linaclotide 72 µg (163 participants) or placebo (163 participants). Randomization of FC participants will be stratified by age group only (6 to 11 years of age versus 12 to 17 years of age) with a minimum of 40% of participants within each age group. The study aims to enroll approximately 1/3 of the FC participants in the EU.

  An optional interim analysis (IA) for futility in the FC population may be considered based on the enrollment of FC participants in this study (ie, if the rate of enrollment is below expectations). The details related to the planned sample size with the optional IA are provided in Section 9.1.3 and Section 9.3.

- For IBS-C participants, the planned sample size is at least 50 participants per arm to inform the prescriber regarding the safe and efficacious use of this drug in this patient population. The planned sample size is not driven by any statistical consideration. A total of at least 100 IBS-C participants are planned to be randomized in a 1:1 ratio to receive either 145 µg or 290 µg linaclotide. Randomization of IBS-C participants will be stratified by age group only (7 to 11 years of age versus 12 to 17 years of age) with a minimum of 40% of participants within each age group.

The targeted participant populations will include male and female participants for both conditions.

Number of Sites:

Approximately 140 sites from the United States, Canada, Europe, and the Middle East are expected to participate in the study.

Intervention Groups and Study Duration:

The study will include a total of 8 visits and will be 17 to 20 weeks in duration (Figure 1-1): a 2-to 4-week Screening Period, a 2- to 3-week Preintervention Period, followed by a 12-week double-blind Study Intervention Period and 1-week Postintervention Period (Figure 1-1).

Participants that complete LIN-MD-64 have the option to enroll into the open-label, long-term safety study, LIN-MD-66, if they meet the eligibility criteria. Participants will be considered to have completed LIN-MD-64 if he/she has completed 12 weeks of double-blind study intervention, the end of treatment (EOT) visit (Visit 7), and the end of study (EOS) visit (Visit 8). However, the EOS visit in LIN-MD-64 is not required for participants who enroll into the open-label, long-term safety study LIN-MD-66 prior to that visit.

Participants will be randomized in a 1:1 ratio for 12 weeks during the double-blind study intervention period.

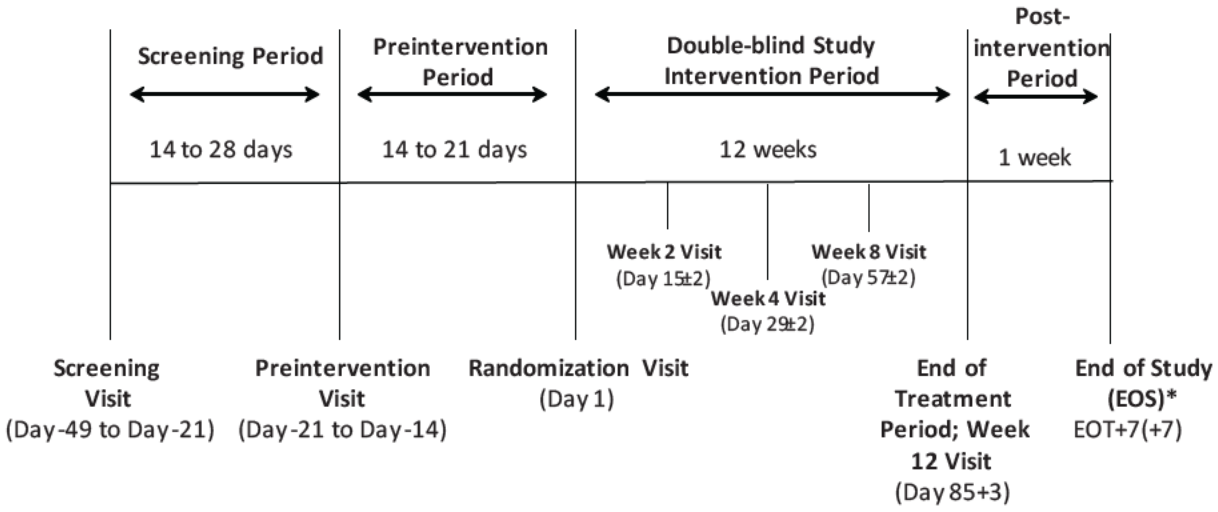
- FC participants receive either linaclotide 72 µg or placebo
- IBS-C participants receive either linaclotide 145 µg or 290 µg

Participants will be instructed to take their assigned dose orally as a single daily dose 30 minutes prior to any meal at approximately the same time each day, with the exception of the first dose at Day 1 (Randomization Visit) when participants will receive linaclotide or placebo in the clinic.

Data Monitoring Committee: Yes

1.2. Schema

Figure 1-1 LIN-MD-64 Study Schema



* Participants who rollover to the long-term safety study, LIN-MD-66, before the EOS Visit are not required to have this visit.

1.3. Schedule of Activities (SoA)

Table 1–1 Schedule of Activities for FC and IBS-C Participants

Study Periods (Duration)	***Screening (14-28 Days)***	***Preintervention (14-21 Days)***	***Study Intervention Period (12 weeks)***					***Postintervention (1 week)***
Study Visit[u]	***Screening***	***Preintervention***	***Randomization***	***Week 2***	***Week 4***	***Week 8***	***Week 12 Visit/ End of Treatment (EOT)[a]***	***End of Study (EOS) Visit[b]***
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study Day	**-49 to -22**	**-21 to -14**	**1**	**15 (± 2)**	**29 (± 2)**	**57 (± 2)**	**85 (+3)[c]**	**EOT +7 (+7)**
Parent/Caregiver Consent/Assent[d]	X							
Inclusion and Exclusion Criteria	X	X	X					
Rome III Assessment	X						X	
Assess Rome IV status[e]			X					
IWRS	X	X	X[f]		X	X	X	
Medical History	X							
Lifestyle Modification Information Given to Participant/Caregiver[g]	X							
Physical Examination[h]	X						X	
Fecal Impaction Assessment[i]	X	X[j]	X[k]					
Height	X						X	
Vital Signs and Postural Vital Signs[l]	X	X	X	X	X	X	X	X
ECG	X						X	
Clinical Laboratory Tests[m]	X		X				X	
Serum Pregnancy Tests[n]	X							
Urine Pregnancy Tests[o]			X		X	X	X	
Urine Drug Screen[p]	X							
AE Evaluation	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X
Rescue Medication Dispensed[q]		X	X	X	X	X	X	

Study Periods (Duration)	***Screening (14-28 Days)***	***Preintervention (14-21 Days)***	***Study Intervention Period (12 weeks)***					***Postintervention (1 week)***
Study Visit[u]	***Screening***	***Preintervention***	***Randomization***	***Week 2***	***Week 4***	***Week 8***	***Week 12 Visit/ End of Treatment (EOT)[a]***	***End of Study (EOS) Visit[b]***
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study Day	**-49 to -22**	**-21 to -14**	**1**	**15 (± 2)**	**29 (± 2)**	**57 (± 2)**	**85 (+3)[c]**	**EOT +7 (+7)**
eDiary and Instructions Given to Participant/Caregiver[r]		X						
eDiary Compliance[r]			X	X	X	X	X	X
eDiary Eligibility Report[f]			X					
Study Intervention Administered on Site[s]			X					
Study Intervention Dispensed			X		X	X		
Study Intervention and Rescue Medication Compliance and Accountability			X[s]	X	X	X	X	X[t]

AE = adverse event; ECG = electrocardiogram; eDiary = electronic diary: refers to the participant- or interviewer-administered version of the PRO diary on a handheld electronic device; IWRS = interactive Web response system; PRO = patient reported outcome.

[a] Study procedures for screening in LIN-MD-66 can be combined with End of Treatment (EOT)/Week 12 Visit (Visit 7) for Study LIN-MD-64.

[b] Participants who rollover to the long-term safety study, LIN-MD-66, before the EOS Visit (Visit 8) are not required to have this visit.

[c] Participants must complete at least 12 weeks (84 days) of study intervention before arriving at the study site for the EOT/Week 12 Visit (Visit 7). All randomized participants who prematurely discontinue from the study intervention, regardless of cause, should complete assessments at this EOT/Week 12 Visit (Visit 7).

[d] The parent/guardian/legally authorized representative must provide written informed consent and the participant must provide assent before the participant's enrollment in the study. If a parent or legal guardian is also the participant's caregiver, he or she will be asked to sign a combined parent and caregiver written informed consent**.** Caregivers other than parent or legal guardian must provide written informed consent.

[e] Prior to dosing, the investigator or appropriate site staff member will assess if Rome IV criteria for Child/Adolescent FC (FC and IBS-C participants) or Rome IV criteria for Child/Adolescent IBS (IBS-C participants) was met and record the outcome in the eCRF. Eligibility for the study is not based on this assessment.

[f] Eligibility report must be run prior to randomization.

[g] During the Screening Period, participants and their caregivers will receive information regarding lifestyle modifications (refer to Section 5.3 for details). There should be at least a 2-week interval between discussing the lifestyle modifications during the Screening Period and the participant's entry into the Preintervention Period.

[h] Physical examinations will be performed by medically qualified site personnel and may be repeated at the investigator's discretion. If fecal impaction (as defined in footnote i) is documented during an optional repeat physical examination, the Study Physician must be notified.

[i] Fecal impaction is defined as a hard mass in the lower abdomen identified on physical examination or a dilated rectum filled with a large amount of stool on rectal examination. If a rectal examination is performed, the medically qualified site personnel should assess for and document the presence of anal wink and normal anal tone.

[j] A fecal impaction assessment is only performed at the Preintervention Visit (Visit 2) if a fecal impaction was documented during the fecal impaction assessment at Screening (Visit 1). If there is no fecal impaction at the Preintervention Visit (Visit 2) (as defined in footnote i above), the participant may enter the Preintervention Period after adhering to any washout requirements. If fecal impaction is present upon re-examination, the participant will not be eligible for the study.

[k] A fecal impaction assessment is performed at the Randomization Visit (Visit 3) after eDiary eligibility is confirmed and prior to randomization. If there is no fecal impaction at the Randomization Visit (Visit 3) (as defined in footnote i above), the participant is eligible for randomization. If fecal impaction is present upon examination, the participant will not be eligible for the study.

[l] Vital signs include temperature, respiratory rate, and weight. Postural vital signs (supine and standing) include pulse rate and systolic and diastolic blood pressure. At all visits, postural vital signs must be obtained after participants have been in a supine position for at least 2 to 3 minutes, followed by a standing position for at least 1 minute. Temperature may be recorded as oral, rectal or tympanic (ear). If possible, temperature should be obtained using the same method at each visit.

[m] Clinical laboratory tests consist of clinical chemistry, hematology, and urinalysis. All laboratory tests requiring blood draws should be collected at the same time.

[n] Serum pregnancy test will be obtained for female participants of childbearing potential.

[o] Urine pregnancy test will be obtained for female participants of childbearing potential. A negative urine pregnancy test is required prior to dosing at the Randomization Visit (Visit 3) and prior to study intervention dispensing at Week 4 (Visit 5) and Week 8 (Visit 6).

[p] A urine drug screen will be obtained at Screening (Visit 1) for all participants 12 to 17 years of age and only if deemed necessary by the investigator for participants 6 to 11 years of age. Urine drug screens may be repeated at the investigator's discretion at any time during the study.

[q] Protocol-permitted rescue medication will be dispensed in IWRS where applicable. Participants may choose a different protocol-permitted rescue medication at any subsequent visit, where available. Additional protocol-permitted rescue medications may be dispensed as needed at any subsequent visit, where available.

[r] At the Preintervention Visit (Visit 2), participants and parents/caregivers will be trained on the use of the eDiary device and instructed to complete both morning and evening assessments daily. At subsequent visits, study site staff will verify participant compliance with the eDiary device and remind participants to complete their morning and evening assessments daily. The global severity items will be completed beginning at the Preintervention Period through End-of-Study, and the global change items will be completed beginning at Randomization through End-of-Study.

[s] Study intervention will be administered at the study site during the Randomization Visit (Visit 3) after running the Eligibility report and confirming the participant has fasted for at least 2 hours. IWRS will be contacted to obtain the study intervention (bottle number) to be dispensed. Participants may eat 30 minutes after dosing (the requirement for study intervention to be administered 30 minutes prior to the meal will not apply for the first dose).

[t] Protocol-permitted rescue medications only.

[u] Additional unscheduled visits may be allowed at the discretion of the investigator with approval from the sponsor.

2. Introduction

Linaclotide is a 14-amino acid peptide that acts on the apical surface of epithelial cells surrounding the intestinal lumen to stimulate the receptor guanylate cyclase subtype C (GC-C). Linaclotide is approved for the treatment of irritable bowel syndrome with constipation (IBS-C) and CIC in the United States, Canada, Australia, Japan, and Mexico; for the treatment of IBS-C in China, the EU, Hong Kong, Macau, and Switzerland; and is being studied in other regions. By activating GC- C, orally administered linaclotide has been found to increase both intestinal fluid secretion and intestinal transit and to also decrease visceral (abdominal) pain. Linaclotide has minimal oral bioavailability (≤ 0.2%) in several animal species (Bryant 2010; Eutamene 2010) and is minimally absorbed with low systemic availability in adults. Refer to the Investigator's Brochure for a more detailed description of the chemistry, pharmacology, efficacy, and safety of linaclotide, based on studies conducted in animals, healthy volunteers, and in participants with IBS-C and CIC (linaclotide IB).

Two Phase 2 dose-ranging studies have been conducted with linaclotide in pediatric participants; one in FC, 6 to 17 years of age (LIN-MD-62), and one in IBS-C, 7 to 17 years of age (LIN-MD-63). Results from these two studies are summarized in Section 2.2.2.

2.1. Study Rationale

Functional constipation is a common healthcare problem in children of all ages, with a worldwide prevalence ranging between 0.7% and 29.6% (Koppen 2018). Symptoms include infrequent, hard stools and painful defecation, and affected children may have abdominal pain and fecal incontinence, which is usually the result of fecal impaction leading to overflow incontinence. These symptoms can have a severe impact on a child's quality of life and may lead to school absenteeism and substantial costs related to healthcare utilization. Initial non-pharmacological interventions include education, behavioral modifications, and keeping a bowel diary. Despite these interventions, many children require pharmacological interventions. Treatment consists of dis-impaction (ie, removal of the rectal fecal mass), followed by maintenance treatment and eventually a weaning phase. Multiple pharmacological agents are available for the treatment of FC in children. Despite chronic pharmacological treatment, approximately 40% of children with FC referred to a pediatric gastroenterologist remain symptomatic after 5 years and 20% of children still have symptoms after 10 years. In some cases, symptoms may persist into adolescence or adulthood despite medical treatment. Potential reasons for ineffectiveness of treatment include suboptimal dosage regimens, poor compliance with treatment, or the use of drugs with action mechanisms that do not address the underlying pathophysiological etiology.

Irritable bowel syndrome is characterized by symptoms of abdominal discomfort or pain associated with altered bowel movement characteristics (Drossman 2006). In adults, Rome III criteria has classified IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed IBS, and unsubtyped IBS, depending on the stool consistency (Longstreth 2006). In children, although IBS subtypes are encountered in clinical practice, a classification based on stool consistency had not been specified at the time the Phase 2 dose ranging study (LIN-MD-63) was originally developed.

The overall prevalence of IBS in the pediatric population is low. IBS prevalence in children across the United States, based on parental reports, ranges from 1.2% to 2.9%, while school-based studies in Colombia and Sri Lanka found a prevalence of IBS of 4.9% and 5.4%, respectively (Hyams 2016). In adults, although not life-threatening, because of its chronic relapsing course, IBS is associated with impaired quality of life and high direct and indirect medical costs such as absenteeism from work (Thompson 1999). In children and adolescents, IBS has been associated with significant impairment as increased rates of school absenteeism, health-care utilization and family disruption are common (Chiou and Nurko 2010).

There are no pharmacologic therapies approved in children for the treatment of FC or IBS-C in the US or the European Union (EU). Thus, effective treatments are needed to provide symptomatic relief in children and adolescents with FC or IBS-C, with the evidence for the safety and efficacy of these based on the results of adequate and well-controlled studies in children.

For the primary and key secondary endpoints in the Phase 2 dose ranging LIN-MD-62 study in FC participants, none of the 3 linaclotide doses (A [low dose], B [medium dose], and C [high dose]) indicated clear improvement over placebo (p-value ≥ 0.1502) based on the ITT population. However, a numerical trend towards efficacy at the higher doses (≥ 75 µg) was observed for the primary endpoint of change from baseline in 4-week overall SBM frequency rate (SBMs/week). In addition, the safety profile was consistent with prior adult linaclotide studies in CIC.

In the Phase 2 dose ranging study LIN-MD-63 in IBS-C participants, for the primary efficacy endpoint of change from baseline in 4-week overall SBM frequency rate, numerical improvement was observed with each increasing linaclotide dose compared with placebo based on analysis of the ITT population. For the key secondary efficacy endpoint of change from baseline in 4-week abdominal pain daytime symptoms, numerical improvement was observed with linaclotide 290 µg compared with placebo, while results were similar in the other linaclotide groups (Dose A, B, and C) compared with placebo. In addition, the safety profile was consistent with prior adult linaclotide studies in IBS-C.

Based on the above Phase 2 results, the primary objectives of LIN-MD-64 are:

- To evaluate the safety and efficacy of 12 weeks of linaclotide therapy in comparison with placebo in pediatric participants aged 6 to 17 years who fulfill modified Rome III Criteria for Child/Adolescent FC
- To evaluate the safety and efficacy of 12 weeks of linaclotide therapy in pediatric participants aged 7 to 17 years with IBS-C (ie, fulfill Rome III Criteria for Child/Adolescent IBS and fulfill modified Rome III Criteria for Child/Adolescent FC)

2.2. Background

2.2.1. Adult Linaclotide Program

Linaclotide has been developed by the sponsors, Allergan Sales, LLC and Ironwood Pharmaceuticals Inc., and is approved at 72 µg and 145 µg for the treatment of CIC and 290 µg for the treatment of IBS-C in adults. The adult clinical development program for linaclotide that culminated in FDA and EMA approvals included the following studies conducted in North America. A summary of these studies and major conclusions are provided in Section 10.12, Table 10-3.

- 4 large double-blind, placebo-controlled Phase 3 registration studies (2 IBS-C studies [LIN-MD-31 and MCP-103-302] and 2 CIC studies [LIN-MD-01 and MCP-103-303])
- 2 long-term adult safety studies (LIN-MD-02 and MCP-103-305), each with 78-week study intervention periods
- 3 randomized, double-blind, placebo-controlled, parallel-group studies (1 IBS-C study [Phase 3b study MCP-103-312] and 2 CIC studies [Phase 3b study LIN-MD-04 and Phase 3 study MCP-103-309]) have been completed.

Safety data from these adult studies showed that, except for diarrhea, the proportion of participants reporting a treatment-emergent adverse event (TEAE) was similar between placebo and each linaclotide dose group in the IBS-C and CIC studies, and the incidence of TEAEs was not dose-related.

With the exception of the gastrointestinal (GI) System Organ Class (SOC) (due to, as previously stated, the disproportionately high reporting of diarrhea in patients taking linaclotide), the occurrence of TEAEs in the CIC and IBS-C participants was balanced across study intervention groups in each SOC for the adult Phase 3 placebo-controlled studies. Diarrhea was the most frequently reported TEAE in linaclotide-treated CIC and IBS-C participants, consistent with its pharmacology; however, diarrhea was rarely associated with serious sequelae such as dehydration, fecal incontinence, or defecation urgency.

Serious adverse events (SAEs) were infrequent and balanced across study intervention groups within each indication, and there were no SAEs of diarrhea reported. An analysis of the SAEs across the entire clinical development program revealed no pattern to suggest that linaclotide causes any specific serious condition.

Minor abnormalities in laboratory, vital sign, or ECG parameters were observed rarely; overall, there were no clinically meaningful differences between linaclotide and placebo study intervention groups for any of these parameters in the Phase 3 placebo-controlled studies in adults.

Additional registration studies were conducted outside of North America, which supported the approval of linaclotide for the treatment of IBS-C and CC in Japan and IBS-C in China. Results from these studies were consistent with those studies conducted in North America (linaclotide IB).

2.2.2. Pediatric Linaclotide Program

A total of 214 pediatric participants were treated with linaclotide in two Phase 2 dose-ranging studies in the FC and IBS-C pediatric populations (LIN-MD-62 and LIN-MD-63, respectively).

LIN-MD-62 was a Phase 2 double-blind, placebo-controlled, parallel group, safety and efficacy study of a range of linaclotide doses administered to participants, 6 to 17 years of age, who fulfilled modified Rome III criteria for FC (refer to Table 2-1 for dosing information). The objective of LIN-MD-62 was to evaluate the dose response, safety, and efficacy of 4 weeks of treatment with 1 of 3 linaclotide doses (Dose A, B, and C) or 145 µg (as an exploratory objective in the adolescent participants, 12 to17 years of age, using the approved adult dose) compared with placebo in pediatric participants who fulfill modified Rome III criteria for child/adolescent FC with the goal of selecting an optimal dose of linaclotide to evaluate in this current confirmatory study.

A total of 173 participants were randomized to receive 1 of 3 proposed linaclotide doses (Dose A, B, and C) for pediatrics (n = 116 participants), the approved adult linaclotide dose (145 µg, n = 16 participants), or placebo (n = 41 participants) for 4 weeks of study intervention followed by a 1-week Postintervention Period (Table 2-1). For the primary and key secondary endpoints in the Phase 2 dose ranging LIN-MD-62 study, none of the 3 linaclotide doses (A [low dose], B [medium dose], and C [high dose]) indicated clear improvement over placebo (p-value ≥ 0.1502) based on analysis of the ITT population. However, a numerical trend toward efficacy at the higher doses was observed for the primary endpoint of change from baseline in 4-week overall SBM frequency rate (SBMs/week). Overall, linaclotide was well tolerated across all doses and both age groups. The safety profile was consistent with prior adult linaclotide studies for CIC. The most frequently reported TEAE was diarrhea, which occurred in 7.6% of linaclotide-treated participants versus 0% in the placebo group. The majority of the TEAEs of diarrhea reported were mild; none were severe. In the 12 to 17 years of age group, one participant experienced moderate diarrhea (related) leading to discontinuation in the linaclotide Dose C group.

There were no reported AESIs (ie, significant volume depletion and/or significant electrolyte abnormalities and/or ECG abnormalities that are considered by the investigator or sponsor to be related to diarrhea) or deaths. There were 2 SAEs, neither of which were diarrhea, in participants in the 12-17 years of age group, neither were considered related to study intervention. Moreover, in the younger pediatric participants, 6 to 11 years of age, no SAEs or AEs leading to discontinuation were reported.

As with adults, linaclotide is minimally absorbed with low systemic availability in this pediatric population.

Table 2-1 Dose Levels (µg) by Weight in Pediatric Participants Treated with Linaclotide in LIN-MD-62

Age Group (years)	Weight (kg)	Linaclotide Dose A (µg) N = 36	Linaclotide Dose B (µg) N = 41	Linaclotide Dose C (µg) N = 39	Approved Adult Dose (µg) N = 16
6–11	18 to <35	9	18	36	–
	≥35	18	36	72	–
12–17	N/A	18	36	72	145

LIN-MD-63 was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, safety and efficacy dose-ranging study of linaclotide in children ages 7 to 17 years with IBS-C. The objectives of LIN-MD-63 were to evaluate the dose response, safety, and efficacy of 4 weeks of treatment with 1 of 3 linaclotide doses (Dose A, B, or C; refer to Table 2-2 for dosing information) or 290 µg (as an exploratory objective in the adolescent participants, 12 to 17 years of age, using the approved adult dose) compared with placebo in pediatric participants 7 to 17 years of age who fulfill the Rome III criteria for child/adolescent IBS and modified Rome III criteria for child/adolescent FC.

According to the original study design, approximately 260 participants with IBS-C were planned to be randomized in this study. However, due to slow participant enrollment, this study was terminated early based on FDA's feedback (Type C Meeting for pediatric IBS-C, June 2019). The actual sample size achieved was 101 randomized participants, which is approximately 39% of the original planned sample size. These 101 IBS-C participants were randomized to receive 1 of 3 proposed linaclotide doses (Dose A, B, and C) for pediatrics (n = 74 participants), the approved adult linaclotide dose (290 µg, n = 8 participants), or placebo (n = 19 participants) for 4 weeks of study intervention. For the primary efficacy endpoint of change from baseline in 4-week overall SBM frequency rate, numerical improvement was observed with each increasing linaclotide dose compared with placebo based on analysis of the ITT population. For the key secondary efficacy endpoint of change from baseline in 4-week abdominal pain daytime symptoms, numerical improvement was observed with linaclotide 290 µg compared with placebo, while results were similar in the other linaclotide groups (Dose A, B, and C) compared with placebo.

Overall, linaclotide was safe and well tolerated across all doses and both age groups. The safety profile was consistent with prior adult linaclotide studies for IBS-C. The most commonly reported TEAE was diarrhea. The majority of the TEAEs of diarrhea reported were mild; none were severe. In participants 12 to 17 years of age, AEs leading to discontinuation were reported in 1 participant in the linaclotide Dose B group (diarrhea [related]) and 1 participant in the placebo group (abdominal pain, anaphylactic reaction [SAE], and hematemesis; all considered not related to study treatment). There were no AESIs (ie, significant volume depletion and/or significant electrolyte abnormalities and/or ECG abnormalities that are considered by the investigator or sponsor to be related to diarrhea) or deaths reported. There were 2 SAEs reported

in participants 12-17 years of age (1 each in the placebo and linaclotide Dose A [36 µg] groups), neither of which were diarrhea, and neither were considered related to study intervention. Moreover, in pediatric participants 7 to 11 years of age, no SAEs or AEs leading to discontinuation were reported.

As with adults, linaclotide is minimally absorbed with low systemic availability in this pediatric population.

Table 2-2 Dose Levels (µg) by Weight in Pediatric IBS-C Participants Treated with Linaclotide in LIN-MD-63

Age Group (years)	Weight (kg)	Linaclotide Dose A (µg) N = 29	Linaclotide Dose B (µg) N = 21	Linaclotide Dose C (µg) N = 24	Approved Adult Dose (µg) N = 8
7–11	18 to <35	18	36	72	–
	≥35	36	72	145	–
12–17	N/A	36	72	145	290

Additional information from studies conducted with linaclotide can be found in the linaclotide IB.

2.2.3. Other Non-Clinical Information

2.2.3.1. Non-Clinical Toxicology

[redacted]

2.2.3.2. GC-C mRNA Expression

Prior research suggested GC-C receptors may be present in younger children at a greater density than in adults (Guarino 1987; Cohen 1988). Greater GC-C receptor density in childhood could result in amplification of the pharmacological effects of GC-C activation, with important clinical implications for treating children with a GC-C agonist. Study MCP-103-311 was conducted to

measure GC-C mRNA levels in duodenal and colonic mucosal tissue samples obtained from children, 0 to <18 years of age, who underwent endoscopy or colonoscopy. Four different age groups were evaluated ie, from birth to <24 months, 24 months to <6 years, 6 years to <12 years, and 12 years to <18 years.

The results showed that there was no trend toward an increase or decrease in GC-C mRNA expression based on age in either duodenal or colonic tissues. Along with results in LIN-MD-62 (Section 2.2.2), these results from study MCP-103-311 support a flat dosing approach for pediatric participants in the Phase 3 pediatric studies and not a body weight-based approach.

Refer to the linaclotide IB for additional studies on GC-C expression.

2.2.4. Post-Marketing Experience

In post-marketing experience, severe diarrhea AEs associated with dizziness, syncope, hypotension and electrolyte abnormalities (hypokalemia and hyponatremia) requiring hospitalization or IV fluid administration have been reported in adult patients treated with linaclotide.

2.3. Benefit/Risk Assessment

Although not life threatening, FC is a common healthcare problem in children of all ages, with a worldwide prevalence ranging between 0.7% and 29.6% (Koppen 2018). Symptoms include infrequent, hard stools, and painful defecation and affected children may have abdominal pain and fecal incontinence, which is usually the result of fecal impaction leading to overflow incontinence. These symptoms can have a severe impact on a child's quality of life and may lead to school absenteeism and substantial costs related to healthcare utilization.

The overall prevalence of IBS in the pediatric population is low. IBS prevalence in children across the United States, based on parental reports, ranges from 1.2% to 2.9%, while school-based studies in Colombia and Sri Lanka found a prevalence of IBS of 4.9% and 5.4%, respectively (Hyams 2016). In adults, although not life-threatening, because of its chronic relapsing course, IBS is associated with impaired quality of life and high direct and indirect medical costs such as absenteeism from work (Thompson 1999). In children and adolescents, IBS has been associated with significant impairment as increased rates of school absenteeism, health-care utilization and family disruption are common (Chiou and Nurko 2010).

Linaclotide has a safety profile that has been well established in adults with IBS-C and CIC (linaclotide IB). Moreover, the safety profiles in the first completed pediatric linaclotide studies in FC (LIN-MD-62) and IBS-C (LIN-MD-63) were consistent with prior adult linaclotide studies in CIC and IBS-C, respectively. There were no new safety signals observed in the pediatric participants and linaclotide was well tolerated across all doses and age groups. Refer to the IB for a more detailed description of the chemistry, pharmacology, efficacy, and safety of linaclotide, based on studies conducted in animals, healthy volunteers, and in participants with IBS-C and CIC.

There are no pharmacologic therapies approved in the pediatric population specifically for the treatment of FC or IBS-C. Thus, there is a need for new agents with favorable safety and

tolerability profiles that are effective in providing relief for the variety of symptoms associated with FC and IBS-C in pediatric patients.

Linaclotide provides an important treatment option for adult patients with CIC and IBS-C and may offer a therapeutic option to treat the symptoms in the pediatric population with FC and IBS-C. The sponsors consider the benefit-risk balance to be favorable and supports further clinical development of linaclotide as a treatment for FC or IBS-C in the pediatric population.

See Section 4, Study Design, for details of study procedures, dose, and study design justification.

3. Objectives and Endpoints

The objective of LIN-MD-64 is to evaluate the safety and efficacy of 12 weeks of linaclotide therapy (72 µg daily) in comparison with placebo in pediatric participants, 6 to 17 years of age, who fulfill modified Rome III Criteria for Child/Adolescent FC (Table 3-1).

The objective of LIN-MD-64 is to evaluate the safety and efficacy of 12 weeks of linaclotide therapy (145 µg or 290 µg daily) in pediatric participants, 7 to 17 years of age, who fulfill the Rome III criteria for child/adolescent IBS and modified Rome III criteria for child/adolescent FC (Table 3-1).

For FC participants, the primary efficacy endpoint will be change from baseline in 12-week SBM frequency rate (SBMs/week) during the study intervention period. An SBM is defined as a bowel movement (BM) that occurs in the absence of laxative, enema, or suppository use on the calendar day of the BM or the calendar day before the BM. Assessments of BM characteristics that determine occurrences of SBMs (ie, BM frequency and rescue medication use) will be measured by using an electronic diary (eDiary) completed twice daily (morning and evening) on a handheld, provisioned eDiary device.

For IBS-C participants, the primary efficacy endpoint will be 6/12 weeks APS (abdominal pain and SBM) + 2 responder. Assessments of abdominal pain and BM characteristics that determine occurrences of SBMs (ie, BM frequency and rescue medication use) will be measured by using an eDiary completed twice daily (morning and evening) on a handheld, provisioned eDiary device.

Table 3-1 Objectives and Endpoints of LIN-MD-64

Objectives for FC Participants	Efficacy Endpoints for FC Participants
Primary Objective	**Primary Endpoint**
To evaluate the safety and efficacy of 12 weeks of linaclotide therapy in comparison with placebo in pediatric participants aged 6 to 17 years who fulfill modified Rome III Criteria for Child/Adolescent FC	• Change from baseline in 12-week SBM frequency rate (SBMs/week) during the study intervention period
	Secondary Endpoint • Change from baseline in 12-week stool consistency during the study intervention period
Objectives for IBS-C Participants	**Efficacy Endpoints for IBS-C Participants**
Primary Objective	**Primary Endpoint**
To evaluate the safety and efficacy of 12 weeks of linaclotide therapy in pediatric participants aged 7 to 17 years with IBS-C (ie, fulfill Rome III Criteria for Child/Adolescent IBS and fulfill modified Rome III Criteria for Child/Adolescent FC)	• 6/12 weeks APS (abdominal pain and SBM) + 2 responder
	Secondary Endpoints • Change from baseline in 12-week SBM frequency rate (SBMs/week) during the study intervention period • Change from baseline in 12-week abdominal pain during the study intervention period • Change from baseline in 12-week stool consistency during the study intervention period • 6/12 weeks SBM + 2 responder • 6/12 weeks abdominal pain responder

The safety assessments will include monitoring of AEs, clinical laboratory assessments (clinical chemistry, CBC, urinalysis), vital sign measurements (including postural vital signs), ECGs, physical examinations, height, and weight.

4. Study Design

4.1. Overall Design

LIN-MD-64 is a Phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel-group, confirmatory safety and efficacy study comparing linaclotide at 72 µg and placebo in pediatric participants, 6 to 17 years of age, with a diagnosis of FC based on modified Rome III Child/Adolescent Criteria (ie, who fulfill modified Rome III criteria for child/adolescent FC).

LIN-MD-64 is a Phase 3 multicenter, randomized, double-blind, parallel-group, confirmatory safety and efficacy study of linaclotide therapy (145 µg or 290 µg daily) in pediatric participants, 7 to 17 years of age, with a diagnosis of IBS-C (ie, who fulfill the Rome III criteria for child/adolescent IBS and modified Rome III criteria for child/adolescent FC).

The study will include a total of 8 visits and will be approximately 17 to 20 weeks in duration (Figure 1-1): a 2 to 4-week Screening Period, a 2- to 3-week Preintervention Period, a 12-week double-blind Study Intervention Period, followed by a 1-week Postintervention Period. Participants who rollover to the long-term safety study, LIN-MD-66, before the EOS Visit are not required to have this visit. Details of each study period are provided in Appendix 10.

Number of Participants:

- A total of 326 FC participants are targeted to be randomized in a 1:1 allocation ratio to receive either linaclotide 72 µg or placebo for 12 weeks of intervention (163 participants in the linaclotide group and 163 in the placebo group). Randomization of FC participants will be stratified by age group only (6 to 11 years of age versus 12 to 17 years of age) with a minimum of 40% of participants within each age group. The study aims to enroll approximately 1/3 of the FC participants in the EU.

  An optional IA for futility in the FC population may be considered based on the enrollment of FC participants in this study (ie if the rate of enrollment is below expectations). The details related to the planned sample size with the optional IA are provided in Section 9.1.3 and Section 9.3.

- A total of at least 100 IBS-C participants are planned to be randomized in a 1:1 ratio to receive either 145 µg or 290 µg linaclotide. The planned sample size is at least 50 participants per arm to inform the prescriber regarding the safe and efficacious use of this drug in this patient population. The planned sample size is not driven by any statistical consideration. Randomization of IBS-C participants will be stratified by age group only (7 to 11 years of age versus 12 to 17 years of age) with a minimum of 40% of participants within each age group.

The targeted participant populations will include male and female participants for both conditions.

Number of Sites:

Approximately 140 sites from the United States, Canada, Europe, and the Middle East are expected to participate in the study.

4.1.1. Clinical Hypotheses

a) Once daily administration of 72 µg linaclotide for a 12-week study intervention period is safe and effective in pediatric participants, 6 to 17 years of age, with FC.

b) Once daily administration of 145 µg and 290 µg linaclotide for a 12-week study intervention period is safe and effective in pediatric participants, 7 to 17 years of age, with IBS-C.

4.2. Scientific Rationale for Study Design

The purpose of this Phase 3 study is to evaluate the safety and efficacy of 72 µg linaclotide taken daily versus placebo in pediatric participants, 6 to 17 years of age, with FC. The selected multicenter, double-blind, randomized, placebo-controlled, parallel-group design has been

endorsed by members of the Rome Foundation and a member of the Pediatric Committee of the EMA to assess the efficacy of therapeutic agents in children with FC (Koppen 2018).

The purpose of this Phase 3 study is to evaluate the safety and efficacy of 145 µg and 290 µg linaclotide taken daily in pediatric participants, 7 to 17 years of age, with IBS-C. Based on the linaclotide data that will be generated in this study, the sponsors believe that the safety and efficacy of linaclotide in the IBS-C pediatric population can be appropriately evaluated.

4.3. Justification for Dose

4.3.1. FC Participants

The dose chosen for FC participants in this study is based on results obtained from the dose range-finding study (LIN-MD-62) in pediatrics as well as results from the adult linaclotide CIC development program, which utilized the currently approved adult doses of 72 µg and 145 µg once daily. In LIN-MD-62, pediatric participants, 6 to 11 years of age, were dosed using a weight-based approach; participants received 1 of 3 linaclotide dose levels Table 2-1. Three target µg/kg dose ranges (low, medium, and high) were chosen for evaluation in pediatric participants, 6 to 11 years of age. For participants who weighed 18 to < 35 kg in the 6 to 11 years age group, the target dose ranges were approximately 0.25 to < 0.5, 0.5 to < 1, or 1 to < 2 µg/kg. For participants who weighed ≥ 35 kg in the 6 to 11 years age group, the target dose ranges were not to exceed 2 µg/kg. Pediatric participants, 12 to 17 years of age, received 1 of 4 linaclotide dose levels, irrespective of the participants' weights (ie. 18, 36, 72 µg) as well as 145 µg dose, which is equivalent to the highest approved adult dose level for CIC.

Results from LIN-MD-62 suggested a lack of body weight normalized dose response in pediatric patients of age 6 to 17 years. These data support a flat dosing approach for pediatric participants in the Phase 3 pediatric studies and not a body weight-based approach. This is also supported by the results from study MCP-103-311 that showed that there was no trend toward an increase or decrease in GC-C mRNA expression based on age in either duodenal or colonic tissues. This is consistent with the efficacy of linaclotide in adults, which is also independent of dose normalized to body weight (Studies MCP-103-201, LIN-MD-01, MCP-103-303, and MCP-103-309). The efficacy data of linaclotide from study LIN-MD-62 was explored based on fixed dosing in age groups (6 to 11 and 12 to 17 years of age) separately as well as across all enrolled participants 6 to 17 years of age. The results suggest that linaclotide efficacy was not clinically meaningful with a dose below 72 µg in the pediatric participants (6 to 17 years of age). Further, increase in dose > 72 µg (eg, 145 µg) appeared to have no additional benefit, although this should be interpreted with caution given the small sample size.

Given the safety profile of the 72 µg dose observed in participants 6 to 17 years of age, the suboptimal efficacy observed at doses < 72 µg, and the consistency in efficacy observed with linaclotide in the adult development program, the 72 µg strength was chosen for this confirmatory Phase 3 study.

4.3.2. IBS-C Participants

The doses of 145 µg or 290 µg linaclotide once daily chosen for IBS-C participants in LIN-MD-64 are based on results obtained from the dose range-finding study in pediatrics

(LIN-MD-63) as well as results from the adult IBS-C dose range-finding study MCP-103-202, which tested linaclotide dose strengths of 75, 150, 300 and 600 µg once daily (equivalent to 72, 145, 290, and 579 µg, respectively, of the current linaclotide formulation).

Results from study LIN-MD-63 indicate a lack of body weight normalized dose response in pediatric participants of age 7 to 17 years (ITT population). This flat dosing approach is consistent with the efficacy of linaclotide in adults, which is also independent of dose normalized to body weight (Study MCP-103-202). These data support a flat dosing approach for all pediatric participants in the Phase 3 pediatric study LIN-MD-64 rather than a body weight-based approach.

Results from study LIN-MD-63 indicate that a range of weight based (µg/kg) dose levels will produce a similar stool consistency response, which may be seen as a pharmacodynamic parameter related to diarrhea, the most frequently reported TEAE in linaclotide treated participants. This is consistent with results from the adult dose-finding study MCP-103-202. In addition, results from adult study MCP-103-202 and pediatric study LIN-MD-63 both suggest that diarrhea related AEs (ie, severe diarrhea, discontinuation due to diarrhea, and SAEs of diarrhea) were independent of body weight-based (µg/kg) dosing. These findings support the dosing of 7 to 11-year-old participants with 145 or 290 µg linaclotide, independent of body weight, even if these doses are higher µg/kg dose levels than what was administered in the Phase 2 study LIN-MD-63.

Additional post-hoc analyses were performed evaluating efficacy based on the individual linaclotide doses to better understand the response per dose for the purpose of dose selection for the IBS-C participants in LIN-MD-64. Change from baseline in 4-week overall SBM frequency rate (SBM/week) and change from baseline in 4-week abdominal pain daytime symptoms were evaluated at the individual linaclotide dose levels in the two individual age groups, adolescent (12 to 17 years old) and younger children (7 to 11 years old). Linaclotide showed improvement over placebo in change from baseline in 4-week overall SBM frequency rate (SBM/week) in adolescents (12 to 17-year-olds), but not in younger children (7 to 11-year-olds). Linaclotide (290 µg) showed improvement over placebo in change from baseline in 4-week abdominal pain for adolescents (12 to 17-year-olds), but improvement was not observed with any linaclotide dose in younger children (7 to 11-year-olds). These observations raise the hypothesis that linaclotide under dosing may have led to the lack of improvement in abdominal pain in linaclotide-treated subjects compared to placebo in the 7 to 11 year old age group, particularly given that, for the 12 to 17 year old age group, linaclotide 290 µg was the only dose that showed a higher numerical improvement over placebo in abdominal pain as compared to all other linaclotide doses tested.

In summary, given 1) the safety profile of the 145 and 290 µg doses observed in participants aged 7 to 17 years in LIN-MD-63 (Section 2.2.2), 2) the aforementioned data supporting a flat dosing approach as opposed to a body weight-based approach, permitting dosing of 7 to 11-year-old participants with higher µg/kg dose levels than what they received in LIN-MD-63, and 3) the apparent need for a higher dose of linaclotide to achieve symptom benefit, particularly for abdominal pain, a 290 µg dose has been selected for the entire 7 to 17 year old age group as the higher dose, while a 145 µg dose has been selected as the lower dose to evaluate whether linaclotide treatment results in a clinically meaningful benefit for both constipation and

abdominal pain in LIN-MD-64. One dose de-escalation will also be allowed to ensure safety/tolerability of the participants in the study.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the study globally.

A participant is considered to have completed the study if he/she has completed all visits of the study including the last visit.

Participants that complete LIN-MD-64 have the option to enroll into the open-label, long-term safety study, LIN-MD-66, if they meet the eligibility criteria. Participants will be considered to have completed LIN-MD-64 if he/she has completed 12 weeks of double-blind study intervention, the EOT visit (Visit 7), and the EOS visit (Visit 8). However, this EOS visit in LIN-MD-64 is not required for participants who enroll into the open-label, long-term safety study LIN-MD-66 prior to that visit.

5. Study Population

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

Where applicable for these pediatric populations, the term "participant" refers to the participant, parent, and/or caregiver.

5.1. Inclusion Criteria

The targeted participant population will include male and female participants, 6 to 17 years of age (FC participants) and 7 to 17 years of age (IBS-C participants). Randomization of FC participants will be stratified by age group only (6 to 11 years of age versus 12 to 17 years of age) with a minimum of 40% of participants within each age group. Randomization of IBS-C participants will be stratified by age group only (7 to 11 years of age versus 12 to 17 years of age) with a minimum of 40% of participants within each age group.

Participants are eligible to be included in the study only if all of the following criteria apply (unless stated otherwise, criteria apply to both FC and IBS-C participants):

1.	**Age and Weight**
1.01	Male and female participants must be ages 6 to 17 years (FC participants) or ages 7 to 17 years (IBS-C participants) (inclusive) at the time the participant provides assent for the study and parent/guardian/legally authorized representative (LAR) has provided signed consent
1.02	Participant weighs ≥18 kg at the time the participant provides assent and the parent/guardian/LAR has provided signed consent

2.	Type of Participant and Disease Characteristics
2.01	Participants who meet the modified Rome III criteria for Child/Adolescent FC. For at least 2 months before the Screening Visit, the participant has had 2 or fewer defecations (with each defecation occurring in the absence of any laxative, suppository, or enema use during the preceding 24 hours) in the toilet per week. In addition, participant meets one or more of the following criteria at least once per week for at least 2 months before the screening visit: • History of retentive posturing or excessive volitional stool retention • History of painful or hard BMs • History of large diameter stools that may obstruct the toilet • Presence of a large fecal mass in the rectum • At least 1 episode of fecal incontinence per week
2.011	For IBS-C participants only: Participant meets Rome III criteria for child/adolescent IBS: At least once per week for at least 2 months before the Screening Visit, the participant experienced abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with 2 or more of the following at least 25% of the time: • Improvement with defecation • Onset associated with a change in frequency of stool • Onset associated with a change in form (appearance) of stool
2.012	For IBS-C participants only: Participant has an average daytime abdominal pain score of ≥ 1 (at least "a tiny bit") during the 14 days before Visit 3.
2.02	Participant is willing to discontinue any laxatives used before the Preintervention Visit in favor of the protocol-permitted rescue medicine.
2.03	Participant has an average of fewer than 3 SBMs per week during the 14 days before the randomization day and up to the randomization (including the morning eDiary assessments reported before administration of first dose of double-blind study intervention on the randomization day). An SBM is defined as a BM that occurs in the absence of laxative, enema, or suppository use on the calendar day of the BM or the calendar day before the BM
2.04	Participant or parent/guardian/LAR or caregiver is compliant with eDiary requirements by completing both the morning and evening assessments for 10 out of the 14 days immediately preceding the Randomization Visit

3.	**Contraceptives**
3.01	Female participants of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at the Randomization Visit prior to dosing
3.02	Female participants who have had their first menstrual period and are sexually active must agree to use a reliable form of contraception. Reliable contraception is defined in Section 10.7 Appendix 7.
4.	**Informed Consent**
4.01	Participant must provide written or verbal informed assent and the parent/guardian/LAR and caregiver must provide written informed consent before the initiation of any study-specific procedures
4.02	Participant is able to read and/or understand the assessments in the eDiary device. If the participant is 6 to 11 years of age (FC participants) or 7 to 11 years of age (IBS-C participants) and does not meet this criterion, the interviewer-administered version of the eDiary must be used and the parent/guardian/LAR or caregiver who will be administering the interviewer-administered version of the eDiary must undergo training
5.	**Other**
5.01	Participant must have acquired toilet training skills

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply (unless stated otherwise, criteria apply to both FC and IBS-C participants):

1.	**Medical Conditions**
1.01	For FC participants only: Participant meets Rome III criteria for Child/Adolescent IBS: At least once per week for at least 2 months before the Screening Visit, the participant has experienced abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with 2 or more of the following at least 25% of the time: • Improvement with defecation • Onset associated with a change in frequency of stool • Onset associated with a change in form (appearance) of stool
1.02	Participant reports having more than 1 loose, mushy stool (eDiary-recorded stool consistency of 6 on the Pediatric Bristol Stool Form Scale [p-BSFS]) or any watery stool (eDiary-recorded stool consistency of 7 on the p-BSFS) with any SBM that occurred in the absence of laxative use on the calendar day of the BM or the calendar day before the BM during the 14 days before the randomization day and up to the randomization (including the morning eDiary assessments reported before

	administration of first dose of double-blind study intervention on the randomization day)
1.03	Participant has a history of non-retentive fecal incontinence
1.04	Participant has (a) fecal impaction at Visit 2 after failing outpatient clean-out during the Screening Period or (b) fecal impaction at Visit 3
1.05	Participant has required manual disimpaction any time prior to randomization
1.06	Participant currently has both unexplained and clinically significant alarm symptoms (lower GI bleeding [rectal bleeding or heme-positive stool], iron-deficiency anemia, or any unexplained anemia, or weight loss) and systemic signs of infection or colitis, or any neoplastic process
1.07	Participant has clinically significant findings on a physical examination, vital sign assessment, ECG, or clinical laboratory test as determined by the investigator based on consideration of whether the finding could represent a safety concern or a condition that would be exclusionary, could prevent the participant from performing any protocol assessments, or could confound study assessments.
1.08	Participant has a history of drug or alcohol abuse.
1.09	Participant has any of the following conditions: a. Celiac disease, or positive serological test for celiac disease and the condition has not been ruled out by endoscopic biopsy b. Cystic fibrosis c. Hypothyroidism that is untreated or treated with thyroid hormone at a dose that has not been stable for at least 3 months prior to the Screening Visit d. Down's syndrome or any other chromosomal disorder e. Active anal fissure (Note: History of anal fissure is not an exclusion) f. Anatomic malformations (eg, imperforate anus, anal stenosis, anterior displaced anus) g. Intestinal nerve or muscle disorders (eg, Hirschprung disease, visceral myopathies, visceral neuropathies) h. Neuropathic conditions (eg, spinal cord abnormalities, neurofibromatosis, tethered cord, spinal cord trauma) i. Lead toxicity, hypercalcemia j. Neurodevelopmental disabilities (early-onset, chronic disorders that share the essential feature of a predominant disturbance in the acquisition of cognitive, motor, language, or social skills, which has a significant and continuing impact on the developmental progress of an individual) producing a cognitive delay that precludes comprehension and completion of the daily eDiary or other study-related questionnaires (Note: Participants are excluded if the person who will be completing the daily eDiary or other study-related questionnaires meets this criterion.)

	k. Inflammatory bowel disease l. Childhood functional abdominal pain syndrome m. Childhood functional abdominal pain n. Poorly treated or poorly controlled psychiatric disorders that might influence his or her ability to participate in the study o. Lactose intolerance that is associated with abdominal pain or discomfort and could confound the assessments in this study p. History of cancer other than treated basal cell carcinoma of the skin. (Note: Participants with a history of cancer are allowed provided that the malignancy has been in a complete remission for at least 5 years before the Randomization Visit. A complete remission is defined as the disappearance of all signs of cancer in response to treatment.) q. History of diabetic neuropathy
1.10	Participant has an acute or chronic condition that, in the investigator's opinion, would limit the participants' ability to complete or participate in this clinical study.
1.11	Participant has a known or suspected mechanical bowel obstruction or pseudo-obstruction.
1.12	Participant has a known allergy or sensitivity to the study intervention or its components or other medications in the same drug class.
1.13	This criterion has been removed.
1.14	Participant has had surgery that meets any of the following criteria: a. Bariatric surgery for treatment of obesity, or surgery to remove a segment of the GI tract at any time before the Screening Visit b. Surgery of the abdomen, pelvis, or retroperitoneal structures during the 6 months before the Screening Visit c. An appendectomy or cholecystectomy during the 60 days before the Screening Visit d. Other major surgery during the 30 days before the Screening Visit
2.	**Prior/Concomitant Therapy**
2.01	Participant used a protocol-specified prohibited medicine before the start of the Preintervention Period or failed to meet the stable-dose requirements of certain medications.
2.02	Participant used rescue medication on the calendar day before the Randomization Visit and on the day of the Randomization Visit until randomized.

3.	**Prior/Concurrent Clinical Study Experience**
3.01	Participant received a study intervention during the 30 days before the Screening Visit or is planning to receive a study intervention (other than that administered during this study).
3.02	Participant has been randomized into any clinical study in which linaclotide was a study intervention.
4.	**Other**
4.01	The participant has a condition or is in a situation which, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study.
4.02	Participants who have positive urine drug screen results for cocaine, barbiturates, opiates, or cannabinoids will be excluded from study participation
4.03	Female participants who are currently pregnant or nursing, or plan to become pregnant or nurse during the clinical study. Details regarding pregnancy and contraception are provided in Section 10.7 Appendix 7.
4.04	Participant's parent/guardian/LAR or caregiver has been directly or indirectly involved in the conduct and administration of this study as an investigator, study coordinator, or other study staff member. In addition, any participant, parent/guardian/LAR or caregiver who has a first-degree family member, significant other, or relative residing with him/her directly or indirectly who is involved in this study

Rationale for Inclusion and Exclusion Criteria

The inclusion and exclusion criteria are meant to identify a population of pediatric participants that is well characterized as having FC or IBS-C as defined by modified Rome III criteria.

5.3. Lifestyle Considerations

All participants will be advised to adopt the following nonpharmacologic habits and instructed to maintain them throughout the study. There should be at least a 2-week interval between discussing the lifestyle modifications during the Screening Period and the participant's entry into the Preintervention Period.

- **Adequate fluids**: The investigator will discuss the fluid intake necessary to maintain a hydrated state (intake requirements may vary amongst children - eg, child athletes, children in hot climates).
- **Increased physical activity**: A goal of aerobic activity for 60 or more minutes of physical activity each day. The investigator will provide a selection of suitable, age-appropriate activity (eg, daily walk, daily run, gymnastics, play on a jungle gym, climb trees).

Participants with FC will also be advised to adopt the following habits and maintain them throughout the study:

- **Adequate time for bowel movements**: Encourage the child to sit on the toilet for 5 to 10 minutes twice daily within 30 minutes after a meal (breakfast and dinner). Follow the routine every day, even during holidays and vacations.
- **A high-fiber diet**: Adequate intake values for fiber range from 19 to 25 g/day for children 1 to 8 years of age, 26 to 38 g/day for children and adolescents 9 to 18 years of age. High-fiber foods include beans, whole grains, fruits, and vegetables. Start slowly, adding just several grams of fiber a day over the Screening Period to reduce the amount of gas and bloating that can occur in someone who is not used to consuming high-fiber foods.

Participants with IBS-C will also be advised to adopt the following habits and maintain them throughout the study:

- **Keep a food diary:** List what you eat and what the reaction is. The investigator will discuss the findings with you. Avoid foods that have provoked symptoms more than once.
- **Adequate sleep:** The investigator will discuss the importance of keeping good sleep hygiene. This includes: having a period of time of relaxation before going to bed, not staying in bed for more than 20 minutes without sleeping (get up and do something relaxing until feeling sleepy again), using the bed only for sleep and not for reading, watching TV, or eating, and avoiding food or drinks with caffeine for at least 4 hours before bedtime.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. 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 SAE.

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened. A participant who has not yet received any e-Diary training at Visit 2 (Preintervention) may be rescreened under special circumstances (eg, failure to meet prohibited medication washout requirements). All requests for rescreening must be sent to the sponsor and approved by the study physician. Any participant approved for rescreening by the study physician will be assigned a new participant identification (PID) and repeat the study screening procedures.

6. Study Intervention

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

FC participants meeting the eligibility criteria during the Randomization Visit will be randomized in a double-blind fashion to linaclotide or placebo.

Randomization will be stratified by age group (6 to 11 years of age versus 12 to 17 years of age) with a minimum of 40% of FC participants within each age group. All FC participants will be randomized to a linaclotide 72 µg dose or placebo with a 1:1 allocation ratio.

IBS-C participants meeting the eligibility criteria during the Randomization Visit will be randomized in a double-blind fashion to 145 µg or 290 µg linaclotide with a 1:1 allocation ratio.

Randomization will be stratified by age group (7 to 11 years of age versus 12 to 17 years of age) with a minimum of 40% of IBS-C participants within each age group.

The study intervention in this study does not have marketing authorization for the pediatric indication. A rationale for selection of the doses used is provided in Section 4.3 (Justification for Dose).

6.1. Study Intervention Administered

Linaclotide in the form of capsules will be packaged in bottles and provided by the sponsor. Study intervention will be administered at the study site during the Randomization Visit after confirming the participant has fasted for at least 2 hours. Participants may eat 30 minutes after dosing; the requirement is for study intervention to be administered 30 minutes before any meal at approximately the same time each day, with the exception of the first dose at Day 1 (Randomization Visit) when participants will receive linaclotide (FC and IBS-C participants) or placebo (FC participants) in the clinic. Confirmation will be recorded in the source documents that the dosing regimen and dosing instructions were discussed with the participant and caregiver.

Throughout the study, it is recommended that participants take linaclotide at approximately the same time each day.

	FC Participants	IBS-C Participants
Study Intervention Name	**Linaclotide or Placebo**	**Linaclotide**
Dosage Formulation	Capsules	Capsules
Unit Dose Strength	72 µg	145 µg or 290 µg
Route of Administration	Oral; capsule may be taken whole or contents sprinkled into 30 mL of bottled water or applesauce for participants who do not wish to take a capsule. Instructions for sprinkled dose are provided in Appendix 8.	
Dosing Instructions	Single dose, once daily at approximately the same time each day, 30 minutes before any meal	
Packaging and Labeling	All bottles will be labeled with the protocol number, storage information, and warning language (“Caution: New Drug—Limited by Federal Law to Investigational Use, Keep out of Reach of Children”)	
Manufacturer	Forest Laboratories Ireland, Limited	

Immediately before dispensing the study intervention, the investigator (or appropriately trained designee) will write the participant's initials, the participant number, and the date on the label.

6.1.1. Selection and Timing of Dose for Each Participant

Participants who continue to meet all eligibility criteria on the Randomization Visit will be dispensed the corresponding double-blind study intervention and receive their first dose of study intervention at the study site. Participants will receive 1 or more bottles containing study intervention. Participants will be instructed to take their assigned dose orally as a single daily dose 30 minutes prior to any meal at approximately the same time each day.

Participants will be instructed to return the bottle(s) at the next study visit whether there is any remaining study intervention or if the bottle is empty. Study intervention will be dispensed as per the schedule shown in Section 1.3.

The investigator may allow a participant to stop taking study intervention for up to 3 days because of an intolerable AE. If the investigator believes that the participant is unable to resume dosing after 3 days or requires a suspension of dosing on more than 1 occasion, the investigator is required to contact the study physician to discuss the participant's continued participation in the study.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the study reference manual or other specified location.
5. Study interventions in bottles containing capsules must be stored at the study site in an appropriate secure area (eg, a locked cabinet in a locked room) at 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F - 86°F). Keep the product in the original container. Do not subdivide or repackage. Protect from moisture. Do not remove desiccant from the container. Keep bottles tightly closed in a dry place.

6. The investigator or designee is responsible for recording the receipt and use of all study interventions supplied and for ensuring the supervision of the storage and allocation of these supplies. All unused study interventions and protocol-permitted rescue medication must be returned; and, whenever study interventions are returned, unit counts must be performed. All study interventions must be accounted for. At the end of the study, all unused or empty study intervention containers should be returned to the sponsor or the local distributor at the address provided in the Study Reference Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Given that this study will evaluate two pediatric populations (FC and IBS-C), and that the randomization has already occurred for FC participants, randomization for IBS-C participants will be carried out separately by applying a separate randomization code list.

After a participant and parent/LAR/caregiver sign the assent/permission/consent at the Screening Visit, study personnel will register the participant in the interactive web response system (IWRS), and the system will assign the participant a sequential PID number. The first participant entered in the system at each study site will be assigned the first number in the sequence by the system.

- Component 1: Study number (3 digits) = 364
- Component 2: Site number (5 digits) = 10001-19999
- Component 3: Participant number (3 digits) = 001-999

The randomization number encodes the participant's assignment to 1 of the study intervention groups of the study, according to the randomization schedule generated prior to the study by the statistics department at the sponsor. Each participant will be dispensed blinded study intervention, labeled with his/her unique PID number, throughout the study.

This PID number will be used to identify the participant throughout the study (ie, at all study phases). A detailed description of IWRS procedures is contained in the IWRS Manual in the Study Reference Manual.

6.3.1. Blinding and Unblinding

6.3.1.1. Blinding

A list of participant randomization codes will be generated by statistical programming and implemented by the IWRS vendor (an electronic version will be stored on a secure server). This list will identify each participant by randomization number and include the participant's corresponding intervention assignment.

6.3.1.2. Unblinding

This study will have two parallel parts: one in FC participants and one in IBS-C participants. Each part will have its own corresponding database lock and unblinding procedures. For more details see Section 9.

Any unblinding at the study site level should be done only in an emergency that requires for the study intervention to be identified for the medical management of the participant. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator is encouraged to contact the sponsor prior to unblinding a participant's study intervention assignment unless this could delay emergency treatment of the participant (see Section 10.3). If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable. Intervention codes may be broken by Global Patient Safety and Epidemiology for regulatory reporting purposes. In such cases, the study staff will be kept blinded and the participant will not need to be disqualified from the study. The unblinding of the bioanalytical representatives is to be carried out in a secure manner following the sponsor's standard operating procedures. Extreme care will be taken to ensure no other individuals outside the bioanalytical team will be unblinded.

For IWRS Unblinding

In an emergency, the investigator can obtain the intervention assignment of any participant at his or her study site through the IWRS. In an emergency, the investigator will access the IWRS to break the blind and record the unblinding.

6.4. Study Intervention Compliance

For home dosing, study intervention compliance will be closely monitored by counting the number of capsules dispensed and returned. Before dispensing new study intervention at visits designated in the SoA, study site personnel will make every effort to collect all unused study intervention and empty/partially used bottles.

The study site will keep an accurate drug disposition record that specifies the amount of study intervention administered to each participant and the date of administration.

Intervention compliance will be assessed through participant/caregiver and study site staff discussion at study visits and recorded on the eCRF. Every effort will be made to collect all unused study intervention at the final visit.

6.5. Prior and Concomitant Therapy

Prior medicine is defined as any medicine taken before the date of the first dose of study intervention. Concomitant medication is defined as any medication taken on or after the date of the first dose of study intervention. Any medication started after last dose date of study intervention will not be included in the summary of concomitant medications but will be included in the listing.

The use of both prior and concomitant medications will be summarized as the number and proportion of participants who took a particular medicine within each therapeutic class. Multiple medicine use by a participant in the same category (based on Anatomical Therapeutic Chemical classification) will only be counted once.

Medication history during the previous 3 months will be recorded at Screening (Visit 1) in the eCRF. Any changes in concomitant medicines or new medicines added will be recorded in the eCRF at visits throughout the study.

6.5.1. Prohibited Interventions and Washout Before the Study

Prohibited Medications

All medicines listed in the sections below (1-day washout and 14-day washout) will be excluded during the Preintervention, Study Intervention, and Postintervention Periods. A 1-day washout means that the particular medicine is not allowed during the calendar day before the Preintervention Visit; a 14-day washout means that the particular medicine is not allowed during the 14 calendar days before the Preintervention Visit.

1-Day Washout

1. Any over-the-counter or prescription laxative, suppository, or enema (eg, polyethylene glycol, lactulose, Fleet enema) and any herbal or natural agent that might be taken for constipation. (Note: The use of fiber, bulk laxatives, stool softeners [surfactants such as docusate], and probiotics is acceptable, provided that the participant has been on a stable dose for 30 days before the Screening Visit (Visit 1) and plans to continue stable dosing for the duration of the study)
2. Any medicine used to treat diarrhea (eg, bismuth subsalicylate, kaolin)
3. Nonsteroidal anti-inflammatory drugs and/or acetaminophen if taken for abdominal pain or discomfort

14-Day Washout

1. Drugs with known pharmacologic activity at 5-HT4, 5-HT2b or 5-HT3 receptors (eg, cisapride, tegaserod, prucalopride, ondansetron, tropisetron, granisetron, dolasetron, mirtazapine)
2. Any of the following treatments either alone or in combination: plecanatide, lubiprostone, colchicine, linaclotide, and misoprostol
3. Prokinetic agents (eg, metoclopramide, itopride, domperidone)
4. Anticholinergic agents (eg, dicyclomine, flavoxate, scopolamine, hyoscyamine, propantheline, oxybutynin, tolterodine, solifenacin, darifenacin, trospium). (Note: inhaled ipratropium and tiotropium are permitted)
5. Bile acid sequestrants (eg, cholestyramine, colestipol)
6. Cholinomimetic agents (eg, bethanechol, pyridostigmine, tacrine, physostigmine). (Note: intraocular cholinomimetic agents such as pilocarpine are permitted)

7. Antipsychotic agents (eg, risperidone, haloperidol, droperidol, chlorpromazine, perphenazine, all phenothiazines, quetiapine, olanzapine, clozapine), unless the participant has been on a stable dose for 30 days before the Screening Visit (Visit 1) and plans to continue stable dosing for the duration of the study. (Note: paliperidone is permitted without restriction)

8. Antidepressants, unless the participant has been on a stable dose for 30 days before the Screening Visit (Visit 1) and plans to continue stable dosing for the duration of the trial. Specifically included are the following:

    a. Tricyclic antidepressants (eg, amitriptyline, imipramine, nortriptyline)
    b. Monoamine oxidase inhibitors (eg, furazolidone, isocarboxazid, pargyline phenelzine, selegiline, tranylcypromine)
    c. Selective serotonin reuptake inhibitors (eg, fluoxetine, sertraline, paroxetine, escitalopram, citalopram, vilazodone)
    d. Serotonin-norepinephrine-reuptake inhibitors (eg, levomilnacipran, duloxetine, venlafaxine, desvenlafaxine succinate)
    e. Other antidepressants (eg, trazodone, bupropion)

9. Calcium-channel blocker verapamil, unless the participant has been on a stable dose for 30 days before the Screening Visit (Visit 1) and plans to continue stable dosing for the duration of the study. (Note: all other calcium-channel blockers [eg, nifedipine, diltiazem, amlodipine, felodipine, nicardipine, nimodipine, nisoldipine] are permitted and may be used without restriction)

10. Oral and parenteral antibiotics; however, 1 standard regimen (up to 10 days) of oral antibiotics is permitted during the Study Intervention and Postintervention Periods

11. Any study intervention or imported drugs that have not been approved for human use

12. All narcotics (eg, tramadol, codeine, morphine, propoxyphene, loperamide, diphenoxylate, paregoric), either alone or in combination. Note: narcotics used as anesthesia for a colonoscopy require a 5-calendar day wash-out prior to the participant entering into the Preintervention Period. Dextromethorphan, the cough suppressant in many over-the-counter cold and cough medicines, is allowed

13. Any medicine taken for the purpose of losing weight (eg, orlistat, phentermine, phendimetrazine, diethylpropion, benzphetamine, sibutramine)

14. Any medication to treat attention-deficit/hyperactivity disorder, unless the participant has been on a stable dose for ≥ 30 days before the Screening Visit (Visit 1) and plans to continue stable dosing for the duration of the study

15. Any medicine that is known to cause diarrhea (eg, acarbose)
16. Proton pump inhibitors (eg, omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole), unless the participant has been on a stable dose for 30 days before the Screening Visit (Visit 1) and plans to continue stable dosing for the duration of the study
17. Other drugs such as barbiturates (eg, butalbital, phenobarbital) and chronic oral or parenteral glucocorticoids, which must be discontinued at least 3 months before screening; however, one 10-day course of oral or 1 injection of parenteral glucocorticoids is permitted during the Study Intervention and Postintervention Periods. Pregabalin is acceptable, provided the participant has been on a stable dose during the 30 days before the Screening Visit and plans to continue stable dosing throughout the study.

6.5.2. Rescue Medication

Rescue medication is not allowed on the day prior to Visit 3 (Randomization Visit), on the day of Visit 3, and the day following Visit 3.

In the United States and Canada, protocol-permitted rescue medication will be a choice of senna (oral) or bisacodyl (oral or rectal) that will be dispensed according to the SOA (Section 1.3).

Outside of the United States and Canada, protocol-permitted rescue medication will be a choice of senna (oral), bisacodyl (oral or rectal) or sodium picosulphate (oral) that will be dispensed according to the SOA (Section 1.3). Participants outside of the United States and Canada will have a choice of at least one of these medications. When there is more than one option available, the participants will choose rescue medication(s) at the Preintervention Visit (Visit 2) and study site staff will register the rescue medication in IWRS, where applicable. The study site must contact the IWRS (if applicable) at all subsequent study visits to obtain the protocol-permitted rescue medication to be dispensed to the participant at each visit as needed.

Rescue medication may be taken when at least 72 hours have passed since the participant's previous BM or when their symptoms become intolerable.

Where available, the participant may continue using their original selection received from the study site throughout the duration of the study or may switch to another protocol-permitted rescue medication in coordination with the site staff.

6.6. Dose Modification

For both FC and IBS-C participants, the investigator may allow a participant to stop taking study intervention for up to 3 days because of an intolerable AE. If the investigator believes that the participant is unable to resume dosing after 3 days or requires a suspension of dosing on more than 1 occasion, the investigator is required to contact the study physician to discuss the participant's continued participation in the study.

For IBS-C participants experiencing an intolerable AE that may be related to the use of linaclotide,

- those randomized to the 145 µg dose can be dose reduced in a double-blinded fashion to 72 µg linaclotide, and
- those randomized to the 290 µg dose can be dose reduced in a double-blinded fashion to 145 µg linaclotide during the course of the study at the investigator's discretion.

6.7. Intervention after the End of the Study

Participants that complete LIN-MD-64 have the option to enroll into the open-label, long-term safety study, LIN-MD-66, if they meet the eligibility criteria. Participants will be considered to have completed LIN-MD-64 if he/she has completed 12 weeks of double-blind study intervention, the EOT visit (Visit 7), and the EOS visit (Visit 8). However, this EOS visit in LIN-MD-64 is not required for participants who enroll into the open-label, long-term safety study LIN-MD-66 prior to that visit.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

A premature discontinuation will occur when a participant who gave voluntary assent, and whose parent/guardian/LAR gave consent, ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

Definitions of the standard terms that may lead to discontinuations are provided in Appendix 5 (Section 10.5).

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Reasons for discontinuation from the study intervention and/or the study may include the following commonly used or other acceptable terms:

Commonly Used Terms	Other Acceptable Terms
Adverse event	Death
Completed	Disease relapse
Lack of efficacy	Progressive disease
Lost to follow-up	Recovery
Other	Technical problems
Physician decision	Withdrawal by parent/guardian
Pregnancy	
Screen failure	
Site terminated by sponsor	
Study terminated by sponsor	
Withdrawal by subject	

7.1.1. Removal of Individual Participants from Therapy or Assessment

Participants **must** be prematurely discontinued from the study for reasons of safety including those who experience:

- An SAE considered by the investigator or the sponsor to be possibly related or related to study intervention,
- An AESI (evidence of significant volume depletion and/or significant electrolyte and/or ECG abnormalities that are considered by the investigator or sponsor to be related to diarrhea) related to the study intervention (ie, intervention-related AESIs) see Section 8.3.4,
- Pregnancy,
- The presence of intentional overdose or intentional misuse per investigator discretion,
- The occurrence of any other AE that in the opinion of the investigator or the sponsor is possibly related or related to the study intervention that represents a clinically significant safety risk to the participant

Participants **may** also be prematurely discontinued from the study for reasons of safety including those who experience:

- A vital sign, ECG, 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 study intervention,
- An intolerable AE (defined as an AE that subjectively would cause a patient to consider study withdrawal), see Section 8.3

Additionally, discontinuation of study intervention for abnormal liver function should be considered by the investigator when a participant meets the criteria for Hy's law or the appearance of abnormal laboratory test results suggesting severe drug-induced liver injury (DILI), or if the investigator believes that it is in best interest of the participant (refer to Appendix 9).

All enrolled participants who prematurely discontinue from the study, regardless of cause, should be seen for the assessments to be completed at the EOT Visit. The EOT assessments are defined as completion of evaluations scheduled for all participants.

Participants who discontinue from the study and do not return to the study site for EOT Visit must be requested in writing to return to the study site for procedures required at the EOT Visit as defined in the SoA and return any unused study intervention. A copy of the letter, together with the source documentation, will be kept in the investigator's files. The reason for premature discontinuation from the study will be recorded on the Study Termination Page of the eCRF. Study site staff will be contacted by the sponsor after each premature discontinuation to ensure proper characterization of the reason for discontinuation is captured.

See the SoA for data to be collected at the time of study intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.2. Criteria for Consideration of Study Discontinuation

Monitoring of participant safety data will be performed by the DSMB. Study conduct may be interrupted or terminated by the sponsor based on DSMB recommendation or if, following a thorough review of all clinical, laboratory, and other available safety data, safety data becomes available which appears to represent an undue risk to the study participants' health or well-being.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own or their parent/guardian/LAR request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- 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.
- If a participant withdraws from the study, he/she or their parent/guardian/LAR may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- 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.

Participants in this study who prematurely discontinue intervention will not be replaced.

7.3. 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.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's study record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

A detailed listing of study assessments by day is presented in Appendix 10.

- 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 intervention.
- 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 informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

- The maximum amount of blood collected from each participant over the duration of the study will not exceed 15 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Additional details regarding study conduct during the novel coronavirus pandemic are provided in Appendix 11.

8.1. Efficacy Assessments

The clinical outcomes assessment (COA) instrument assessing the signs and symptoms of FC and IBS-C in a pediatric population was developed by Allergan Sales, LLC and Ironwood Pharmaceuticals based on extensive qualitative research with children with FC and IBS-C and their caregivers, as well as feedback from pediatric gastroenterologists, measurement experts, and health authorities. This COA instrument, the pediatric FC/IBS-C symptom diary, measures a comprehensive set of 7 core signs and symptoms reported to be important to patients. Data will be collected on an eDiary device and will be used for all primary, secondary, and other efficacy endpoints.

All efficacy assessments will be determined by responses entered in the eDiary (morning eDiary, evening eDiary, clinic eDiary, or weekly eDiary). Participants and parent/guardian/LAR or caregiver must be able to read and understand the eDiary as a condition for study participation (Inclusion Criterion 4.02). If the participant is 6 to 11 years of age (FC participants) or 7 to 11 years of age (IBS-C participants) and has difficulty reading and understanding the eDiary without help, the interviewer-administered version of the eDiary must be used and the parent/guardian/LAR or caregiver who will be administering the interviewer-administered version of the eDiary must undergo training. Participants and caregivers will receive full training in the use and completion of the eDiary and will be given the eDiary device at the Preintervention Visit (Visit 2). If the parent/guardian/LAR or caregiver supervising the participant in the completion of the eDiary or administering the interviewer-administered version changes, the study team should be notified and should document the date when it changed and who the new caregiver is.

8.1.1. Efficacy Assessments in FC Participants

8.1.1.1. Primary Efficacy Assessment

The primary efficacy assessments, which will be used to determine the primary efficacy endpoint of SBM frequency, are the items assessing BM frequency and rescue medication use. Participants will report their BM frequency (the number of BMs) and use of rescue medication by responding to the following:

Bowel Movement Frequency

- Morning eDiary

  From bedtime last night until now, how many times did you poop (and poop came out)?

  - Enter number of times

- Evening eDiary

  From when you got up this morning until now, how many times did you poop (and poop came out)?

  - Enter number of times

  If response is > 0 BMs, then the participant answers the following question for each BM reported:

  When did you poop today?

  - In the morning (from when you woke up until lunch)
  - In the afternoon (from lunch until dinner)
  - In the evening (from dinner until bedtime)

Rescue Medication Use

- Morning eDiary

  From bedtime last night until now, did you take any medicine to help you poop, other than the study medicine?

  - Yes
  - No

- Evening eDiary

  From when you got up this morning until now, did you take any medicine to help you poop, other than the study medicine?

  - Yes
  - No

  If the response is 'yes", then the participant answers the following question:

  When did you take the medicine (NOT your study medicine) to help you poop?

  - In the morning (from when you woke up until lunch)
  - In the afternoon (from lunch until dinner)
  - In the evening (from dinner until bedtime)

8.1.1.2. Secondary Efficacy Assessment

In addition to the assessments supporting the primary efficacy endpoint, an additional assessment will be used to determine the secondary efficacy endpoint of stool consistency for each BM.

Stool Consistency (Pediatric Bristol Stool Form Scale)

Stool consistency of each BM will be based on the p-BSFS. The BSFS is a well-accepted and widely used measurement of stool consistency (Lewis 1997). The p-BSFS was developed by the sponsors based on the original BSFS and was refined based on qualitative research with pediatric participants with FC and IBS-C. Participants will use the p-BSFS 7-point ordinal scale to rate their stool consistency for each BM in the morning and evening eDiaries:

"Choose the poop that is most like the poop you had."

Type 1 = looks like small hard lumps or balls, like pebbles

Type 2 = looks like fat sausage shape but lumpy and hard

Type 3 = looks like a sausage but with cracks on it

Type 4 = looks like a sausage or snake, smooth and soft

Type 5 = looks like chicken nuggets, soft smooth blobs

Type 6 = looks like oatmeal, fluffy mushy pieces

Type 7 = looks like a milkshake, watery

99 - I don't know

8.1.1.3. Additional Efficacy Assessments

Additional daily assessments will measure complete evacuation, straining with BMs, abdominal pain, abdominal bloating, and fecal incontinence. In addition, participant self-report (for all participants) and caregiver report (for participants 6 to 11 years of age) of global assessments of change in symptoms and symptom severity will be administered weekly in the eDiary device. Modified Rome III criteria will be assessed at the Screening visit (Visit 1) and at the end of the study intervention period at the EOT Visit (Visit 7).

Additional efficacy assessments include:

Complete Spontaneous Bowel Movement (CSBM)/Incomplete Evacuation

A CSBM is an SBM that is associated with a sense of complete evacuation. Participants will record their assessment of the sensation of incomplete evacuation for each BM by responding to the following in the morning and evening eDiaries:

- When you pooped, did it feel like there was more poop left inside that didn't come out?
  - Yes
  - No

Straining With BM

For every BM, participants will assess the degree of straining by responding to the following in the morning and evening eDiaries:

- When you pooped, how hard did you push?

  0 = not hard at all

  1 = I pushed a tiny bit hard

  2 = I pushed a little hard

  3 = I pushed hard

  4 = I pushed very hard

Abdominal Pain - Daytime

For this parameter, participants will rate their abdominal pain during the daytime by responding to the following in the evening eDiary:

- From when you got up this morning until now, did your tummy hurt at all?
    - Yes
    - No

  If "yes", then participant answers the following question:

- How much did your tummy hurt?

  1 = a tiny bit

  2 = a little

  3 = some

  4 = a lot

Abdominal Pain - Nighttime

For this parameter, participants will rate their abdominal pain during the nighttime by responding to the following in the morning eDiary:

- From bedtime last night until now, did your tummy hurt at all?
    - Yes
    - No

  If "yes", then the participant answers the following question:

- How much did your tummy hurt?

  1 = a tiny bit

  2 = a little

  3 = some

  4 = a lot

Abdominal Pain - Combination (Total 24-hour Period)

This parameter will be determined based on combined daytime symptoms of abdominal pain in evening eDiary assessments and nighttime symptoms of abdominal pain in morning eDiary assessments.

Abdominal Bloating - Daytime

For this parameter, participants will record their assessment of abdominal bloating during the day by responding to the following in the evening eDiary:

- From when you got up this morning until now, did your tummy FEEL big and full?
    - Yes
    - No

  If "yes" then participant answers the following question:

- How big and full did your tummy FEEL?

  1 = a tiny bit

  2 = a little

  3 = medium

  4 = very

Abdominal Bloating - Nighttime

For this parameter, participants will record their assessment of nighttime abdominal bloating by responding to the following in the morning eDiary:

- From bedtime last night until now, did your tummy FEEL big and full?
    - Yes
    - No

  If "yes", then the participant answers the following question:

- How big and full did your tummy FEEL?

  1 = a tiny bit

  2 = a little

  3 = medium

  4 = very

Abdominal Bloating - Combination (Total 24-hour Period)

This parameter will be determined based on combined daytime symptoms of abdominal bloating in evening assessments and nighttime symptoms of abdominal bloating in morning assessments.

Fecal Incontinence - Daytime

Participants will record their episodes of fecal incontinence by responding to the following assessment in their evening eDiary.

- From when you got up this morning until now, did you have a pooping accident (even a little)?
    - Yes
    - No

Modified Rome III Criteria

Modified Rome III criteria will be assessed by the investigator at the Screening Visit (Visit 1) and at the end of the study intervention period at the EOT Visit (Visit 7). A participant will be considered as fulfilling modified Rome III criteria if a "yes" response is recorded to the overall question of whether the participant meets modified Rome III criteria for functional constipation. For the EOT assessment, the criteria will be assessed over the last 4 weeks of the double-blind study intervention period. In the event a participant discontinues the study prematurely, these criteria will be assessed over the last 4 weeks of double-blind study intervention, or over the duration of double-blind study intervention if less than 4 weeks.

Participant-completed Global Items:

Participant-completed global change and global severity items were developed by the sponsors. The participant-completed global items consist of 4 items, 2 assessing global change in the participant's symptoms and 2 assessing the global severity of the participant's symptoms. All 4 participant-completed global items have a 7-day recall period and will be completed weekly on the eDiary device. The global severity items will be completed beginning at the Preintervention Visit (Visit 2) through the EOS Visit (Visit 8) and the global change items will be completed beginning at the Randomization Visit (Visit 3) through the EOS Visit (Visit 8).

Participant-completed Global Change Items

The 2 participant-completed global change items assess self-reported change in the participant's bowel symptoms ("pooping problems") and abdominal symptoms ("tummy problems") and are as follows:

- Compared to 7 days ago, my pooping problems today are:

  0 = a lot better

  1 = a little better

  2 = the same

  3 = a little worse

  4 = a lot worse

- Compared to 7 days ago, my tummy problems today are:

  0 = a lot better

  1 = a little better

  2 = the same

  3 = a little worse

  4 = a lot worse

Global Severity Items

The 2 participant-completed global severity items assess self-reported severity of the participant's constipation using the same child-friendly terminology as detailed for the global change items above and are as follows:

- How bad have your pooping problems been over the past 7 days:

  0 = I have not had pooping problems

  1 = a little bad

  2 = bad

  3 = very bad

- How bad have your tummy problems been over the past 7 days:

  0 = I have not had tummy problems

  1 = a little bad

  2 = bad

  3 = very bad

Observer-completed Global Items:

The observer-completed (parents/caregivers) global items consist of 2 items, 1 assessing global change in their child's symptoms and 1 assessing the global severity of their child's symptoms. Both observer-completed global items will be completed weekly on the eDiary device. The global severity item will be completed beginning at the Preintervention Visit (Visit 2) through the EOS Visit (Visit 8) and the global change item will be completed beginning at the Randomization Visit (Visit 3) through the EOS Visit (Visit 8).

Only parents/caregivers of participants 6 to 11 years of age will complete these items.

Observer-completed Global Change Item

The observer-completed global change item assesses the change in the child's constipation symptoms (1 item) as follows:

- Compared to 7 days ago, how would you rate your child's constipation symptoms today:
  - completely relieved
  - considerably relieved
  - somewhat relieved
  - unchanged
  - somewhat worse
  - considerably worse
  - as bad as I can imagine

Observer-completed Global Severity Item

The observer-completed global severity item assesses the severity of the child's constipation symptoms (1 item) as follows:

- How would you rate the severity of your child's constipation over the past 7 days?
  - none
  - mild
  - moderate
  - severe
  - very severe

8.1.2. Efficacy Assessments in IBS-C Participants

8.1.2.1. Primary Efficacy Assessment

The primary efficacy assessments, which will be used to determine the primary efficacy endpoint of 6/12 weeks APS (abdominal pain [combined daytime and nighttime symptoms] and SBM) + 2 responder, are the items assessing abdominal pain (combined daytime and nighttime symptoms) and BMs that meet the criteria for SBMs, based on the eDiary information.

Participants will report their abdominal pain (daytime, nighttime, and combined symptoms) as described in Section 8.1.1.3 for FC participants. Number of SBMs will be determined based on the items assessing BM frequency and rescue medication use as described in Section 8.1.1.1 for FC participants.

8.1.2.2. Secondary Efficacy Assessment

The efficacy assessments supporting the primary efficacy endpoint, along with the assessment measuring stool consistency, will be used to determine the secondary efficacy endpoints of:

- Change from baseline in 12-week SBM frequency rate (SBMs/week) during the study intervention period
- Change from baseline in 12-week abdominal pain (combined daytime and nighttime symptoms) during the study intervention period
- Change from baseline in 12-week stool consistency during the study intervention period
- 6/12 weeks SBM + 2 responder
- 6/12 weeks abdominal pain (combined daytime and nighttime symptoms) responder

Efficacy assessments which will be used to determine the secondary efficacy endpoints are as described for FC participants in Section 8.1.1.3 (abdominal pain), Section 8.1.1.1 (number of SBMs), and Section 8.1.1.2 (stool consistency).

8.1.2.3. Additional Efficacy Assessments

Along with assessments of abdominal pain and SBMs, additional daily efficacy assessments will measure straining with BMs, abdominal bloating, and complete evacuation. In addition, participant self-report (for all participants) and caregiver report (for participants 7 to 11 years of age) of global assessments of change in symptoms and symptom severity will be administered weekly in the eDiary device. Rome III criteria will be assessed at the Screening Visit (Visit 1) and at the end of the study intervention period at the EOT Visit (Visit 7).

Additional daily efficacy assessments measuring straining with BMs, abdominal bloating, and complete evacuation are performed as described in Section 8.1.1.3 for FC participants. Rome III criteria and participant- and caregiver-reported change in symptoms and symptom severity are assessed for IBS-C participants as described below.

Rome III Criteria

Rome III criteria will be assessed by the investigator at the Screening Visit (Visit 1) and at the end of the study intervention period at the EOT Visit (Visit 7). A participant will be considered as fulfilling Rome III criteria if a "yes" response is recorded to the overall question of whether the participant meets Rome III criteria for IBS-C. For the EOT assessment, the criteria will be assessed over the last 4 weeks of the double-blind study intervention period. In the event a participant discontinues the study prematurely, these criteria will be assessed over the last 4 weeks of double-blind study intervention, or over the duration of double-blind study intervention if less than 4 weeks.

Participant-completed Global Items:

Participant-completed global change and global severity items were developed by the sponsors. The participant-completed global items consist of 6 items, 3 assessing global change in the participant's symptoms and 3 assessing the global severity of the participant's symptoms. All

6 participant-completed global items have a 7-day recall period and will be completed weekly on the eDiary device. The global severity items will be completed beginning at the Preintervention Visit (Visit 2) through the EOS Visit (Visit 8) and the global change items will be completed beginning at the Randomization Visit (Visit 3) through the EOS Visit (Visit 8).

Participant-completed Global Change Items

The 3 participant-completed global change items assess self-reported change in the participant's bowel symptoms ("pooping problems") and abdominal symptoms ("tummy problems" and "tummy pain") and are as follows:

- Compared to 7 days ago, my pooping problems today are:

  0 = a lot better

  1 = a little better

  2 = the same

  3 = a little worse

  4 = a lot worse

- Compared to 7 days ago, my tummy problems today are:

  0 = a lot better

  1 = a little better

  2 = the same

  3 = a little worse

  4 = a lot worse

- Compared to 7 days ago, my tummy pain today is:

  0 = a lot better

  1 = a little better

  2 = the same

  3 = a little worse

  4 = a lot worse

Global Severity Items

The 3 participant-completed global severity items assess self-reported severity of the participant's constipation using the same child-friendly terminology as detailed for the global change items above and are as follows:

- How bad have your pooping problems been over the past 7 days:

  0 = I have not had pooping problems

  1 = a little bad

  2 = bad

  3 = very bad

- How bad have your tummy problems been over the past 7 days:

  0 = I have not had tummy problems

  1 = a little bad

  2 = bad

  3 = very bad

- How bad has your tummy pain been over the past 7 days:

  0 = I have not had tummy pain in the past 7 days

  1 = a little bad

  2 = bad

  3 = very bad

Observer-completed Global Items:

The observer-completed (parents/caregivers) global items consist of 2 items, 1 assessing global change in their child's symptoms and 1 assessing the global severity of their child's symptoms. Both observer-completed global items will be completed weekly on the eDiary device. The global severity item will be completed beginning at the Preintervention Visit (Visit 2) through the EOS Visit (Visit 8) and the global change item will be completed beginning at the Randomization Visit (Visit 3) through the EOS Visit (Visit 8).

Only parents/caregivers of participants 7 to 11 years of age will complete these items.

Observer-completed Global Change Item

The observer-completed global change item assesses the change in the child's IBS-C symptoms (1 item) as follows:

- Compared to 7 days ago, how would you rate your child's IBS with constipation symptoms today:
  - completely relieved
  - considerably relieved
  - somewhat relieved
  - unchanged
  - somewhat worse
  - considerably worse
  - as bad as I can imagine

Observer-completed Global Severity Item

The observer-completed global severity item assesses the severity of the child's constipation symptoms (1 item) as follows:

- How would you rate the severity of your child's IBS with constipation over the past 7 days?
  - none
  - mild
  - moderate
  - severe
  - very severe

8.2. Safety Assessments

Participants must be evaluated by a physician or an appropriately trained health care professional at every visit and the evaluation must be documented. The procedures discussed below will be completed at the designated visits. Safety assessments should not be administered to the participant unless the participant is accompanied by his or her consented caregiver.

Safety assessments will include monitoring of AEs, clinical laboratory assessments (clinical chemistry, CBC, urinalysis), vital sign measurements (including postural vital signs), ECGs, physical examinations, height, and weight.

Evidence of severe diarrhea, especially when accompanied by dehydration, volume depletion and/or significant electrolyte or ECG abnormalities will be actively monitored throughout.

All AEs will be monitored until symptom resolution or until the condition stabilizes. A DSMB will oversee AEs and safety of the overall study.

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

8.2.1. Physical Examinations

A complete physical examination will be done at screening and at the EOT Visit. Physical examinations may be repeated at the investigator's discretion. If fecal impaction is documented during an optional repeat physical examination, the study physician must be notified.

Any new physical examination abnormalities for the post-baseline physical examination or worsening of the change from the Screening Visit will be reported as an AE.

- A complete physical examination will include, at a minimum, assessments of general appearance, skin, HEENT (head, ears, eyes, nose, and throat), neck, thorax/lungs, cardiovascular, abdomen, musculoskeletal, lymph nodes, neurologic (including mental status), and visual inspection of the lumbosacral and perianal region.
- Breast and genitourinary examinations are optional at the discretion of the investigator
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

In addition to the physical examination, a fecal impaction assessment will be performed for all participants at both Screening (Visit 1) and Randomization (Visit 3) after eDiary eligibility is confirmed and prior to randomization. Fecal impaction is defined as a hard mass in the lower abdomen identified on physical examination or a dilated rectum filled with a large amount of stool on rectal examination. If a rectal examination is performed, the medically qualified site personnel should assess for and document the presence of anal wink and normal anal tone.

- If fecal impaction is identified at Screening (Visit 1), participants will receive a dis-impaction regimen with either oral or rectal medication. The choice of treatment will be determined by the investigator after discussing the options with the participant and the caregiver. Options will include any over-the-counter or prescription laxative, suppository, or enema (eg, polyethylene glycol, lactulose, Fleet enema). After the participant has received treatment for the impaction, the investigator must re-evaluate the participant for the presence of fecal impaction at the Preintervention Visit (Visit 2). If there is no fecal impaction at the Preintervention Visit, the participant may enter the Preintervention Period after adhering to any washout requirements (Appendix 3). If fecal impaction is present upon re-examination, the participant will not be eligible for the study (ie, they have failed their out-patient clean-out regimen).
- If fecal impaction is present upon examination at Randomization (Visit 3), the participant will not be eligible for the study.

8.2.2. Vital Signs

Vital signs and postural vital signs will be obtained and documented at all scheduled study visits (see Section 1.3). Vital signs will be assessed as follows:

- Vital signs include weight; temperature and respiratory rate; postural vital signs (supine and standing) include pulse rate and systolic and diastolic blood pressure. Temperature may be recorded as oral, rectal or tympanic (ear). If possible, temperature should be obtained using the same method throughout the course of the study.
- At all visits, postural vital signs must be obtained after participants have been in a supine position for at least 2 to 3 minutes, followed by a standing position for at least 1 minute.

8.2.3. Electrocardiograms

A standard 12-lead ECG will be performed at screening and at the EOT Visit. ECGs will be performed and electronically transmitted to a central ECG laboratory for analysis according to the instructions provided by the central ECG laboratory. Measurements (in msec) will be recorded for the following parameters: heart rate, RR interval, PR interval, QRS duration, and uncorrected QT interval. QTcB (Bazett-corrected QT interval) and QTcF (Fridericia-corrected QT interval) will be calculated.

Participants with clinically significant ECG abnormalities considered to be secondary to diarrhea (ie, an AESI) must be reported to the sponsor within 24 hours, on an SAE form if considered to be serious. Non-serious events do not require submission on an SAE form; rather, these events only need to be entered into the eCRF (Section 10.3). If the AE is assessed as causally related to the use of study intervention, the participant should be discontinued from the study; however, the study physician and investigator may discuss individual participants and AEs to make this determination (Section 10.3).

The overall interpretation and determination of the clinical relevance of ECG findings using the central ECG interpretation report will be recorded in the participant's eCRF.

Sites shall transmit all study-required ECGs obtained to the ECG vendor. All ECGs performed during a given visit should be recorded on the repeating eCRF in the respective visit. Unscheduled ECGs are recorded for unscheduled visits only. All readable ECGs received by the vendor shall be sent for cardiologist over-read. The sponsor will receive all ECG data, including cardiologist assessments and ECGs that could not be evaluated.

8.2.4. Clinical Safety Laboratory Assessments

See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

- At Screening (Visit 1), the investigator will assess the clinical significance of any values outside the reference ranges provided by the laboratory, and participants with abnormalities judged to be clinically significant will be excluded from the study.
- The investigator must review the laboratory reports, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. 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 significant during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical safety physician.
    - 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 Section 10.2, must be conducted in accordance with the SoA and the laboratory manual.
    - 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.
- Participants with clinically significant electrolyte abnormalities that are considered to be secondary to diarrhea (ie, an AESI) must be reported to the sponsor within 24 hours on an SAE form if considered to be serious. Non-serious events do not require submission on an SAE form; rather, these events only need to be entered into the eCRF (Section 10.3). If the AE is assessed as causally related to the use of study intervention, the participant should be discontinued from the study; however, the study physician and investigator may discuss individual participants and AEs to make this determination (Section 10.3).
- Positive results on the pregnancy test at Screening (Visit 1) and Randomization (Visit 3) will exclude participants from participating in the study. Positive pregnancy test results during the study intervention will result in participant termination from the study. Investigators must inquire at every study visit about the use of acceptable methods of contraception in participants of childbearing potential who are, or become, sexually active (see Inclusion Criterion 3.02), and perform a serum or urine pregnancy test if there is any question of noncompliance with contraception. Repeat pregnancy tests may be performed at the investigator's discretion at other times during the study.

- A central laboratory will be used to evaluate all urine (except urine pregnancy tests) and blood samples, which will be collected, processed, and stored according to the instructions provided by the laboratory. The urine pregnancy test will be completed on site at the study site.

8.3. Adverse Events and Serious Adverse Events

An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH-E2A). The definitions of an AE or SAE can be found in Section 10.3.

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

The investigator and any qualified 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 intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

Particular attention must be given to the AE of diarrhea, which was the most frequently reported AE in the adult linaclotide program. Please refer to Section 10.3 for details about AE reporting.

Examples of AEs are as follows:

- Changes in the general condition of the participant
- Subjective symptoms offered by or elicited from the participant
- Objective signs observed by the investigator or other study site personnel
- All diseases that occur after signing the informed consent, including any change in severity or frequency of preexisting disease
- All clinically relevant abnormalities in laboratory values or clinically relevant physical findings that occur during the study schedule

Please note medical procedures scheduled prior to consenting, but occurring during the study, should not be captured as AEs, but should be listed in the medical history if related to a pre-existing condition.

8.3.1. Adverse Events of Special Interest (AESIs)

AESIs are defined as significant volume depletion and/or significant electrolyte abnormalities and/or ECG abnormalities that are considered by the investigator or sponsor to be related to diarrhea. The investigator should contact the sponsor if there is any question whether the criterion for an AESIs has been met. All AESIs must be reported to the sponsor as described in Section 10.3.

8.3.2. Time Period and Frequency for Collecting Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest Information

- At each visit, participants are to be queried regarding any AEs or SAEs that have occurred since the previous visit. Participants will be asked to volunteer information with a nonleading question such as, "How do you feel since your last visit?" Study site personnel will record all pertinent information in the participant's eCRF. All SAEs from the signing of the ICF until 30 days after the last dose of study intervention will be collected at the timepoints specified in the SoA (Section 1.3), and as observed or reported spontaneously by study participants.
- All AEs from the signing of the ICF until 30 days after the last dose of study intervention will be collected at the timepoints specified in the SoA (Section 1.3), and as observed or reported spontaneously by study participants.
- Medical occurrences that begin before the start of study intervention, but after obtaining informed consent, will be recorded in the AE section of the eCRF.

All SAEs and serious AESIs will be recorded and reported to the sponsor or designee within 24 hours on an SAE form, as indicated in Section 10.3. Non-serious AESIs do not require submission on an SAE form; rather, these events only need to be entered into the eCRF. 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 after conclusion of the study participation. 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 intervention 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 Section 10.3.

8.3.3. Method of Detecting Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

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.

8.3.4. Follow-up of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

After the initial AE/ SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE/ SAE and non-serious AESIs (as defined in Section 8.3.1) will be followed until resolution, stabilization, the event's etiology is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

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.

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

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

8.3.5. Regulatory Reporting Requirements for Serious Adverse Events

- 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 intervention 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 intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ IECs, and investigators.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

At each visit, participants are to be queried regarding any AEs or SAEs that have occurred since the previous visit. Participants will be asked to volunteer information with a nonleading question such as, "How do you feel since your last visit?" Study site personnel will record all pertinent information in the participant's eCRF. Any AEs reported in diaries will also be reported on the relevant eCRF page.

Additional information is provided in Section 10.3 for the recording and follow-up of AEs and SAEs.

8.3.6. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention from the time the ICF was signed until 30 days after the last dose of study intervention.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 7.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are considered SAEs.

8.3.7. Potential Hy's Law Cases

Criteria for possible Hy's law cases are as follows:

- ALT or AST ≥ 3 × ULN AND
- Total bilirubin ≥ 2 × ULN AND
- ALP < 2 × ULN

Study site personnel must report every participant who meets the criteria for potential Hy's law as SAEs (see Appendix 9 for a detailed description on handling potential Hy's law cases and liver toxicity). Typically, all 3 analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period. This requirement applies from the time the participant signs the ICF for the study until 30 days after the last known dose of study intervention.

Additional details regarding liver safety assessments and follow-up are provided in Appendix 9.

8.3.8. Medication Errors

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

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

Medication errors include occurrences of overdose and underdose of the study intervention.

Overdose: Unintentional administration of a quantity of the study intervention given per administration or per day that is above the maximum recommended dose according to the reference safety information or protocol for the study intervention or comparator as applicable. This also takes into account cumulative effects due to overdose.

Underdose: Unintentional administration of a quantity of the study intervention given per administration or per day that is under the minimum recommended dose according to the reference safety information or protocol.

8.4. Treatment of Overdose

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical safety physician (MSP) immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically.
3. Document the quantity of the excess dose as well as the duration of the overdose in the site's source documents for the participant.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the MSP based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

PK parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Not applicable

8.8. Biomarkers and Other Assessments

Biomarkers are not evaluated in this study.

8.9. Health Economics

Not applicable

9. Statistical Considerations

This study will have two parallel parts: one in FC participants and one in IBS-C participants. Efficacy and safety data for FC and IBS-C participants will be clearly documented and managed in the study database; and statistical analysis and reporting will be provided separately for each study part upon completion of the corresponding study part.

Each study part will have its own corresponding database processing and locking procedure. The study database related to FC participants will be locked separately and will be unblinded for the analyses for FC participants when all FC participants complete the study. When all IBS-C participants complete the study, the study database will be locked for IBS-C participants to perform the unblinded analyses for IBS-C participants. There will be no overlapping of FC and IBS-C participants.

The statistical analysis plans for the FC and IBS-C parts of the study will be developed separately. Based on the timing of completion of each study part (with FC and IBS-C), the decision will be made accordingly whether to develop separate clinical study reports (CSRs) for each population or a single CSR incorporating both FC and IBS-C participants.

9.1. Statistical Considerations for FC Participants

9.1.1. Statistical Null Hypotheses – FC Participants

The primary endpoint is change from baseline in 12-week SBM frequency rate (SBMs/week) during the study intervention period. The statistical null hypothesis for the primary endpoint is as follows: linaclotide 72 µg is the same as placebo with respect to the primary efficacy analysis endpoint.

The secondary endpoint is change from baseline in 12-week stool consistency during the study intervention period. The statistical null hypothesis for the secondary endpoint is as follows: linaclotide 72 µg is the same as placebo with respect to the secondary efficacy analysis endpoint.

Each of the above null hypotheses will be tested against a 2-sided alternative (expected) hypothesis, with an overall alpha level of 0.05 (2-sided) adjusted for multiplicity.

9.1.2. Estimand Framework – FC Participants

9.1.2.1. Estimand Framework for Primary Endpoint – FC Participants

Population

The target population is participants with FC, ages 6-17 years old, satisfying the inclusion and exclusion criteria as specified in Section 5.1 and Section 5.2, respectively.

The analysis population includes all participants in the Randomized Population (as defined in Section 9.1.4) who receive at least 1 dose of double-blind study intervention and who had at least 1 postbaseline entry on BM characteristic assessments that determine occurrences of SBMs (ie, BM frequency and rescue medication use) during the study intervention period (ie, Modified Intent-to-Treat Population as defined in Section 9.1.4).

Variable

The variable is primary efficacy endpoint defined in Section 9.1.5.1.1, which is the change from baseline in the participant's 12-week SBM frequency rate (SBMs/week) during the study intervention period as derived from the twice daily eDiary (morning and evening).

Accounting for Intercurrent Events

Intercurrent events and their handling rules are as follows:

- The BMs for the participants who took a laxative, enema, or suppository on the calendar day of the BM or the calendar day before the BM will not be considered as SBMs for the analysis.
- Participants who discontinue from the double-blind study intervention period will have their eDiary data included up to the morning diary following the last dose date for primary endpoint.

Participants with missing diary data during the 12-week study intervention period will have their data included as observed. The SBM frequency rate (SBMs/week) will be calculated based on the available data (Section 9.1.5.1.1) and this SBM frequency rate will be considered to be equivalent to the rate over the 12-week study intervention period.

Participants with missing diary data during the 12-week study intervention period will have their data imputed in a sensitivity analysis assuming an underlying plausible missing data mechanism (Section 9.1.5.1.2) and details will be documented in the statistical analysis plan.

Population-level Summary

The population-level summary for the primary endpoint is the difference in primary variable means between the linaclotide dose arm and placebo.

9.1.2.2. Estimand Approach for the Secondary Endpoint – FC Participants

The secondary endpoint, change from baseline in 12-week stool consistency (as defined in Section 9.1.5.1.1) during the study intervention period, will be handled using the same estimand approach as defined for the primary endpoint.

If the participant has no SBM during baseline period, the stool consistency during baseline period will be missing and participant will be excluded from the change from baseline analysis for this secondary endpoint.

9.1.3. Sample Size Determination – FC Participants

The sample size of this study was determined based on the primary efficacy endpoint. A total of 326 participants are targeted to be randomized to this study in a 1:1 allocation ratio to receive either linaclotide 72 µg (163 participants) or placebo (163 participants) for 12-weeks of double-blind study intervention period. The assumptions and power estimate for this planned sample size are summarized in Table 9-1.

Table 9-1 Sample Size Assumptions for The Primary Efficacy Endpoint – FC Participants

Parameter	Assumption/Estimate
Primary efficacy analysis endpoint	Change from baseline in 12-week SBM frequency rate (SBMs/week) during the study intervention period.
Expected treatment difference	1 point (based on change from baseline in SBM frequency rate with a 72 µg dose: Phase 2 LIN-MD-62 data, including the 6-11 year age group weighing ≥ 35 kg and the 12-17 year age group, and recent adult study MCP-103-309 with FC)
Assumed standard deviation	3 (based on approximation from the Phase 2 LIN-MD-62 study with linaclotide 72 µg and placebo for change from baseline in SBM frequency rate)
Alpha	5%
Sides	2
Statistical test	2-sample t test
Sample size allocation ratio (Linaclotide: Placebo)	1:1
Power	85%

The secondary efficacy endpoint in this study is change from baseline in 12-week stool consistency during the study intervention period. Assuming a detectable difference of 1.0 point between linaclotide 72 µg and placebo and common standard deviation (SD) of 1.53 (based on LIN-MD-62), an 85% power test for this endpoint will require 88 participants in total (44 in each study intervention group). With 163 participants per group, there would be 99% power for the endpoint.

Depending on the enrollment status for FC participants in this study, an IA for futility may be considered. Assuming that this optional futility IA is performed at 50% of information based on using the primary efficacy endpoint for FC participants, a total sample size of 378 FC participants (189 participants in each study intervention group) will need to be randomized to ensure 85% power for the final analysis at a slightly reduced significance level of 4.9% (following a conservative approach, Section 9.1.5.1) to demonstrate that linaclotide is superior to placebo (based on the same assumptions as presented in Table 9-1). The optional IA for futility in FC participants is further discussed in Section 9.3.

9.1.4. Populations for Analyses – FC Participants

Four analysis populations will be defined for FC participants as follows:

- Screened Population: Defined as all participants who undergo the Screening Visit (Visit 1) and receive a PID number.
- Randomized Population: Defined as all participants in the Screened Population who are randomized to a study intervention group.

- Safety Population: Defined as all participants in the Randomized Population who receive at least 1 dose of double-blind study intervention. Participants will be summarized according to the study intervention they actually received for all safety analysis variables/endpoints.
- Modified Intent-to-Treat (mITT) Population: Defined as all participants in the Randomized Population who receive at least 1 dose of double-blind study intervention and who had at least 1 postbaseline entry on BM characteristic assessments that determine occurrences of SBMs (ie, BM frequency and rescue medication use). Participants will be summarized according to the randomized study intervention for all efficacy analysis variables/endpoints.

9.1.5. Statistical Analyses – FC Participants

The Statistical Analysis Plan (SAP) will be developed and finalized before database lock and unblinding and will describe the participant populations to be included in the analyses, and procedures for accounting for missing data. This section is a summary of the main features for the planned statistical analyses in FC participants in this study.

9.1.5.1. Efficacy Analyses

Efficacy analyses will be based on the mITT Population.

Baseline values for efficacy endpoints related to daily eDiary responses will be derived from the eDiary in the Preintervention Period, specifically the time period from 14 days before randomization up to the time of randomization.

The baseline weekly SBM or CSBM rate will be derived based on the total number of SBMs or CSBMs a participant had during this period. Baseline stool consistency and straining based on combined morning and evening assessments will be calculated as a mean of the participant's non-missing, SBM-associated p-BSFS scores and straining scores, respectively, during this period. A participant's baseline stool consistency and straining cannot be assessed if the participant does not have at least 1 SBM during the Preintervention Period. For participants who report no SBMs during a study period, the stool consistency and straining assessments will be considered missing for that study period in the analyses. Participants with missing baseline stool consistency and straining will be excluded from the respective stool consistency and straining analyses that involve change from baseline.

Baseline values for the participant symptom severity parameters (eg, abdominal bloating, abdominal pain) based on the combined morning and evening assessments will be calculated as the mean of non-missing specific abdominal symptom scores during this period. Baseline abdominal pain or bloating daytime symptoms, based on evening (or nighttime symptoms, based on morning) assessment, will be calculated as the average of the non-missing specific abdominal symptom scores reported in the evening (or in the morning).

Baseline value for the participant-completed global change and severity items, and observer completed global change and severity items, will be based on the last non-missing assessment on or before the date of first dose of study intervention.

An observed-cases approach to missing postbaseline data will be applied. All statistical tests will be 2-sided at 5% level of significance. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise. Multiplicity adjustment for the overall Type 1 error rate will be based on primary and secondary endpoints.

The overall Type 1 family-wise error rate for testing the primary and secondary efficacy endpoints will be controlled at the 5% level of significance (2-sided) using a sequential testing procedure as stated in Table 9-2.

Table 9-2 Sequential Testing Procedure

Step 1 Primary Endpoint: Change from baseline in 12-week SBM frequency rate (SBMs/week) during study intervention period	Compare the linaclotide 72 µg dose versus placebo for the primary efficacy endpoint. • If superiority is demonstrated over placebo at alpha=0.05 (2-sided), proceed to Step 2. • Otherwise stop.
Step 2 Secondary Endpoint: Change from baseline in 12-week stool consistency during study intervention period	Compare the linaclotide 72 µg dose versus placebo for the secondary efficacy endpoint. • Stop

Nominal p-values will be provided for the other efficacy endpoints.

A futility check in this IA (when performed) will be performed based on the pre-selected non-binding futility boundary. Following a conservative approach, the final analysis will be performed at a slightly reduced alpha level of 0.049 (2-sided) in case this futility IA is conducted. The optional futility IA at 50% information is not planned to stop the study for efficacy.

9.1.5.1.1. Efficacy Analysis Endpoints

The primary, secondary, and other efficacy endpoints for FC participants are provided below.

Primary efficacy endpoint:

The primary efficacy endpoint will be change from baseline in 12-week SBM frequency rate (SBMs/week) during the study intervention period.

An SBM is defined as a BM that occurs in the absence of laxative, enema, or suppository use on the calendar day of the BM or the calendar day before the BM. The defined study intervention period for eDiary starts from the evening diary on the day of randomization and ends at the morning diary on the day after last dose date of study intervention. Assessments of BM characteristics that determine occurrences of SBM (ie, BM frequency and rescue medication use) will be measured by using the eDiary completed twice daily (morning and evening) on the eDiary device.

The SBM frequency rate (SBMs/week) during the analysis period for each participant will be calculated as [(total number of SBMs in the analysis period/number of days in the analysis period)*7].

If the participant discontinued early during the study intervention period, the participant's SBM frequency rate (SBMs/week) based on the number of days in the study intervention period will be considered equivalent to the 12-week SBM frequency rate during the study intervention period.

For a sensitivity analysis to handle postbaseline missing data for the primary endpoint, if the participant has less than 4 completed diary days in an analysis week, participant's corresponding week response will be considered missing. Further details are included in Section 9.1.5.1.2 and will be provided in the SAP.

Secondary efficacy endpoint:

The secondary efficacy endpoint will be change from baseline in 12-week stool consistency during the study intervention period. Stool consistency will be measured twice daily, once in the morning and once in the evening eDiary, using the 7-point ordinal p-BSFS. A participant's p-BSFS score for the study intervention period will be the average of the non-missing p-BSFS scores from the SBMs reported by the participant during the 12-week study intervention period. If the participant has no SBM during the baseline period, the stool consistency (p-BSFS score) during the baseline period will be missing and the participant will be excluded from the change from baseline analysis for this secondary endpoint.

Other efficacy endpoints:

Other efficacy endpoints are listed below and will be further specified in the SAP as appropriate.

- Overall SBM responders during the study intervention period
- Weekly SBM + 2 responder during the study intervention period
- Change from baseline in 12-week CSBM frequency rate (CSBMs/week) during the study intervention period
- Change from baseline in 12-week abdominal pain (daytime, nighttime, and combined daytime and nighttime symptoms) during the study intervention period
- Proportion of days with daytime fecal incontinence during the study intervention period
- Change from baseline in 12-week straining during the study intervention period
- Change from baseline in 12-week abdominal bloating (daytime, nighttime, and combined daytime and nighttime symptoms) during the study intervention period
- Proportion of participants with an SBM within 24 hours after the first dose of study intervention
- Proportion of participants with an SBM within 48 hours after the first dose of study intervention
- Time to first report of SBM after the first dose of study intervention
- Proportion of participants with an increase in rescue medicine or any other laxative, suppository, or enema use during 12-week study intervention period

- Proportion of participants who report using rescue medicines or any other laxatives, suppositories, or enemas during 12-week study intervention period
- Proportion of participants who no longer fulfill modified Rome III criteria for functional constipation at the end of the study intervention period
- Proportion of participants with each individual item score for the participant-completed global change items (pooping problems and tummy problems) and global severity items (pooping problems and tummy problems) at each week during the study intervention period
- Proportion of participants with each individual item score for the observer-completed global change item and the global severity item at each week during the study intervention period (collected for age group of 6-11 years only)

Overall SBM Responders During the Study Intervention Period

Overall SBM responders are defined as participants who have a change from baseline of ≥ 2 SBMs/week in the 12-week SBM frequency rate over the study intervention period. The threshold of at least a 2 point change from baseline in the 12-week SBM frequency rate (SBMs/week) to define the overall SBM responder may be revisited before unblinding based on the findings of blinded psychometric analysis to determine within participant clinically meaningful change.

Determination of Response

To be considered a responder, a participant must have the following:

- At least 4 weeks of study intervention duration, and
- At least 48 completed diary days during the 12-week study intervention period, and
- At least 4 completed diary days per analysis week in the last 4 intervention weeks

Weekly SBM + 2 Responder During the Study Intervention Period

For any week in the study intervention period, a weekly SBM + 2 responder is a participant who has an SBM increase ≥ 2 in the SBM weekly rate from baseline for that week. For the analysis week, if a participant did not have at least 4 full days (with both completed morning and evening diaries) of diary entries, the participant will not be considered a weekly SBM + 2 responder for that corresponding week. The threshold of at least 2 to define the weekly SBM responder may be revisited before unblinding based on the findings of blinded psychometric analysis to determine within participant clinical meaningful change.

Change from Baseline in 12-Week CSBM Frequency Rate During the Study Intervention Period

A CSBM is an SBM that is associated with a sense of complete evacuation. Participants will record their assessment of the sensation of completeness of evacuation for each BM by responding to a question in the eDiary. This information will be collected twice daily in the eDiary device: in the morning when a participant wakes up and in the evening at bedtime.

A participant's 12-week CSBM frequency rate will be the CSBM rate (CSBMs/week) calculated over the 12-weeks of the study intervention period as ([total number of CSBMs in the analysis period/number of days in the analysis period]*7).

Definitions or derivations for the remaining other efficacy endpoints listed above will be included in the SAP.

9.1.5.1.2. Primary Analyses

The primary efficacy endpoint will be change from baseline in 12-week SBM frequency rate (SBMs/week) during the study intervention period.

For the primary efficacy parameter, comparison between linaclotide and placebo will be performed using an analysis of covariance (ANCOVA) model with study intervention group and age group (6 - 11 years of age and 12 - 17 years of age) as fixed factors and baseline value as a covariate. Least squares means (LSMs) for each study intervention group, difference in LSMs between linaclotide versus placebo, associated 2-sided 95% CI for these difference in LSMs, and the corresponding statistical test p-value will be reported. Study intervention-by-age group interaction will be investigated as an exploratory analysis to assess whether the effects of study intervention are consistent across age groups.

Cumulative distribution function plots will also be provided for the primary endpoint by study intervention group. A by-week summary of the primary endpoint will be provided by study intervention group.

A sensitivity analysis will be performed to assess the robustness of ANCOVA based on an observed case approach. In this sensitivity analysis, participants need to complete all daily questions in both morning and evening diaries to have a complete diary day. For each postbaseline analysis week, if participant has less than 4 completed diary days in that corresponding week, the postbaseline week value will be considered missing for that participant. In this sensitivity analysis, to handle missing data in the nature of missing at random (MAR), change from baseline in SBM frequency rate/week will be analyzed using a mixed effect model for repeated measures (MMRM) with study intervention (linaclotide and placebo), week, age group (6-11 years of age and 12-17 years of age), and study intervention-by-week interaction as fixed effects and baseline value as a covariate. All 12 weeks' data will be included in the MMRM model. The study intervention comparisons between linaclotide dose and placebo for change from baseline in 12-week SBM frequency rate (SBM/week) during the Intervention Period will be estimated from the MMRM model. An unstructured covariance matrix will be used to model the covariance of within-participant results. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom (Kenward and Roger 1997).

If the answer to the rescue medicine use question is missing for any assessment (morning or evening), it will be assumed that no rescue medicine was used during that diary period (morning or evening diary) in eDiary.

If the answer to the question related to BM frequency is missing in any assessment (morning or evening), BM frequency will be considered as zero for that diary period (morning or evening diary) in the eDiary.

Another sensitivity analysis will be conducted imputing the postbaseline missing daily data in the specific diary with the worst response for SBM (ie, assuming '0' frequency for missing BM response and assuming 'Yes' response for missing rescue medication use). Based on this imputed data, the primary efficacy endpoint will be analyzed using an ANCOVA model with study intervention and age group (6 - 11 years of age and 12 - 17 years of age) as fixed factors and baseline value as a covariate.

Other sensitivity analyses to handle missing data for the primary endpoint will be specified in detail in the SAP as necessary.

9.1.5.1.3. Secondary Analyses

The secondary efficacy endpoint is change from baseline in 12-week stool consistency during the study intervention period.

For the change from baseline secondary efficacy endpoint, the linaclotide group will be compared with the placebo group using an ANCOVA model with study intervention and age group (6-11 years of age and 12 - 17 years of age) as fixed effects and baseline value as a covariate. LSMs for each study intervention group, difference in LSMs between linaclotide group versus placebo, associated 2-sided 95% CI for this difference in LSMs, and the corresponding statistical test p-value will be reported. Cumulative distribution function plots will also be provided for the change from baseline secondary efficacy endpoint by study intervention group. Study intervention-by-age group interaction will be investigated as an exploratory analysis for secondary endpoint to assess the homogeneity of study intervention effects across age groups.

By-week summary of the secondary endpoint will be provided by study intervention group.

A sensitivity analysis for the secondary endpoint to handle missing data in the nature of missing at random (MAR) will be performed using a mixed effect model for repeated measures (MMRM) in a similar way as the primary efficacy parameter.

The other sensitivity analyses to handle missing data for the secondary efficacy endpoint will be specified in the SAP.

The analyses related to the other efficacy endpoints will be provided in the SAP.

9.1.5.2. Safety Analyses

The safety analysis will be performed using the safety population for FC participants. The safety parameters will include AEs, clinical laboratory parameters, vital sign measurements, height, weight, and ECG parameters. For each safety parameter, the last non-missing assessment made before the first dose of double-blind study intervention will be used as the baseline for all analyses of that safety parameter.

9.1.5.2.1. Adverse Events

An AE will be considered a TEAE if:

- The AE began on or after the date of the first dose of study intervention; or
- The AE was present before the date of the first dose of study intervention, but increased in severity or became serious on or after the date of the first dose of study intervention

An AE that occurs more than 1 day after the last dose of study intervention will not be counted as a TEAE

An AE will be considered a treatment-emergent SAE if it is a TEAE that additionally meets any SAE criteria.

The number and percentage of participants reporting TEAEs in each study intervention group will be tabulated by SOC and preferred term and by SOC, preferred term, and severity.

The number and percentage of participants reporting treatment-related TEAEs in each study intervention group will be tabulated by system organ class and preferred term.

If more than 1 AE is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the most severe and most related occurrence for the summarizations by severity and by causal relationship to study intervention.

Summary tables will be provided for participants with SAEs, AESIs, and participants with AEs leading to discontinuation if 5 or more participants reported such events. Listings of all AEs, SAEs, AESIs, and AEs leading to discontinuation by participant will be presented.

The definitions of an AE and SAE can be found in Section 10.3.

9.1.5.2.2. Clinical Laboratory Assessments

Descriptive statistics for clinical laboratory values (in SI units) at baseline (screening) and changes from baseline at each assessment time point will be presented by study intervention group.

The criteria for potentially clinically significant (PCS) laboratory values will be detailed in the SAP. The number and percentage of participants who have PCS postbaseline clinical laboratory values will be tabulated by study intervention during the double-blind study intervention period. The percentages will be calculated relative to the number of participants who have available non-PCS baseline values and at least 1 postbaseline assessment for the double-blind study intervention period. The numerator will be the total number of participants with available non-PCS baseline values and at least 1 PCS postbaseline value during the double-blind study intervention period. A supportive listing of participants with PCS postbaseline values will be provided for the Safety Population.

9.1.5.2.3. Vital Signs

Descriptive statistics for height and vital signs (supine systolic and diastolic BP, pulse rate, weight, respiration rate, and temperature) at baseline and changes from baseline at each assessment time point will be presented by study intervention group.

Vital sign values will be considered PCS if they meet both the observed-value criteria and the change-from-baseline-value criteria that will be detailed in the SAP. The number and percentage of participants who have PCS postbaseline vital sign values will be tabulated by study intervention within the double-blind intervention period and postintervention period separately. The percentages will be calculated relative to the number of participants who have available non-PCS baseline values and at least 1 postbaseline assessment in the specific period. The numerator will be the total number of participants with at least 1 PCS postbaseline value during the specific period. A supportive listing of participants with PCS postbaseline values will be provided for the safety population.

9.1.5.2.4. Electrocardiograms

Descriptive statistics for ECG parameters (ie, ventricular heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc) at baseline and changes from baseline values at each assessment time point will be presented by study intervention group. The QTc is calculated using both the Bazett and Fridericia corrections.

The number and percentage of participants with PCS postbaseline ECG values will be tabulated by study intervention group during the double-blind study intervention period. The criteria for PCS ECG values will be detailed in the SAP. The percentages will be calculated relative to the number of participants with available non-PCS baseline values and at least one postbaseline assessment for the double-blind study intervention period. The numerator will be the total number of participants with available non-PCS baseline values and at least one PCS postbaseline value during the double-blind study intervention period. A supportive listing of participants with PCS postbaseline values will be provided for the safety population.

9.1.5.2.5. Subgroup Analyses

Limited subgroup analyses may be performed on an exploratory basis for the CSR for FC and will be defined in the SAP.

9.2. Statistical Considerations for IBS-C Participants

9.2.1. Statistical Null Hypotheses – IBS-C Participants

There are no preconceived statistical hypotheses to be assessed in this study for the IBS-C population.

9.2.2. Estimand Framework – IBS-C Participants

Estimand Framework for Primary Endpoint – IBS-C Participants

Population

The target population is participants with IBS-C, ages 7-17 years old, satisfying the inclusion and exclusion criteria as specified in Section 5.1 and Section 5.2, respectively.

The analysis population includes all participants in the Randomized Population (as defined in Section 9.2.4) who receive at least 1 dose of double-blind study intervention and who had baseline and at least 1 postbaseline entry of the primary efficacy assessment (ie, an assessment of

abdominal pain [combined daytime and nighttime symptoms] or BM characteristic assessments that determine occurrences of SBMs [ie, BM frequency and rescue medication use]). This analysis population is known as mITT as defined in Section 9.2.4.

Variable

The variable is the primary efficacy endpoint defined in Section 9.2.5.1.1, which is 6/12 weeks APS (abdominal pain and SBM) + 2 responder. A 6/12 weeks APS + 2 responder is a participant who meets the weekly APS + 2 responder criteria for at least 6 out of the 12 weeks of the intervention period. A weekly APS +2 responder is a participant who has an increase of at least 2 in the SBM weekly rate from baseline, AND a decrease of at least 30% in the mean abdominal pain score from baseline, during that study intervention week.

SBM is derived based on responses for BM and rescue medication in the eDiary twice daily (morning and evening). Abdominal pain score is also derived based on responses in the eDiary twice daily for abdominal pain.

Accounting for Intercurrent Events

Intercurrent events and their handling rules are as follows:

- The BMs for the participants who took a laxative, enema, or suppository on the calendar day of the BM or the calendar day before the BM will not be considered as SBMs for the analysis.
- Participants who discontinue from the double-blind study intervention period will have their eDiary data included up to the morning diary following the last dose date. The early discontinued participants will be considered non-responders for the following weeks for primary endpoint.
- eDiary responses following the onset of dose de-escalation will not be included. The participants with dose de-escalation will be considered non-responders for the subsequent study intervention weeks (after the onset of dose de-escalation) for the primary endpoint based on the randomized study intervention group.
- A participant has to have at least 4 completed diary days per analysis week to be considered a responder for that week. The participant needs to fill out both morning and evening eDiary on the same day to have a completed diary day.

Population-level Summary

The population-level summary for the primary endpoint is the proportion of participants satisfying the APS+2 responder criteria for at least 6 out of 12 weeks during the study intervention period for each linaclotide dose.

In addition, a Bayesian analysis will be performed for the primary efficacy endpoint using adult IBS-C data (studies MCP-103-202, MCP-103-303, and LIN-MD-31) to inform the prior distribution of response in pediatric IBS-C patients. The 2.5 percentile of posterior distribution for the APS+2 responder rate for linaclotide 290 µg will be compared separately with the pooled placebo APS + 2 responder rate and with the upper limit of 95% CI of the pooled placebo

responder rate from contributing adult studies (Section 9.2.5.1.1). The details of the Bayesian analysis will be provided in a separate analysis plan.

9.2.3. Sample Size Determination – IBS-C Participants

Based on the sponsor's view that the IBS-C disease and patient response to linaclotide treatment will be similar between the adult and pediatric subjects, the sample size of at least 50 randomized participants per arm (at least 100 randomized participants in total) for IBS-C participants in this study was planned to inform the prescriber regarding the safe and efficacious use of linaclotide doses in this patient population. The planned sample size is not driven by any statistical consideration.

Extrapolation from IBS-C adult studies (MCP-103-202 [Phase 2b], LIN-MD-31 [Phase 3], and MCP-103-302 [Phase 3]) will be performed using Bayesian methodology with the primary efficacy endpoint of 6/12 week APS+2 responder endpoint (as defined in Section 9.2.5.1.1). APS + 2 responder rates for treated individuals from the adult IBS-C population in Phase 2b study MCP-103-202 and Phase 3 pivotal studies LIN-MD-31 and MCP-103-302 were used to form a prior probability distribution for the pediatric APS + 2 response rate. This prior was down-weighted. Responder data from LIN-MD-64 were simulated using the down-weighted prior and the lower 2.5 percentile of posterior samples compared separately against the pooled placebo rate and the upper limit of 95% CI of pooled placebo rate from the adult contributing studies. The probabilities (Bayesian powers) that the lower 2.5 percentile of the linaclotide responder rate were greater than the pooled placebo rate from contributing adult studies are provided in Table 9-3 by different sample size and effective sample size (and associated down-weight value). The probabilities (Bayesian powers) that the lower 2.5 percentile of the linaclotide responder rate were greater than the upper limit of the 95% confidence interval of the placebo responder rate from contributing adult studies are also provided in Table 9-4 by different sample size and effective sample size (and associated down-weight value).

It was felt that a modest weight of 0.017 on the prior, equivalent to 15 new subjects from adult data, would be appropriate with the planned trial size of 50 IBS-C participants per arm, and would sufficiently describe the efficacy in pediatrics when contextualized using the pooled placebo rate from adult contributing studies.

Table 9-3 Bayesian Power Estimates by Sample Size and ESS (vs. the Responder Rate of the Adult Placebo Response, 0.16*)

	N/Arm=30	N/Arm=40	N/Arm=50
ESS=12 (w = 0.0135)	0.763	0.808	0.836
ESS=15 (w = 0.017)	0.865	0.873	0.854
ESS=18 (w = 0.020)	0.865	0.904	0.904
ESS=24 (w = 0.027)	0.943	0.954	0.964

ESS (Effective Sample Size) is calculated as the number of subjects used to derive the prior distribution multiplied by the down-weight (w).
*Based on Phase 2b study MCP-103-202 and Phase 3 pivotal studies LIN-MD-31 and MCP-103-302.

Table 9-4 Bayesian Power Estimates by Sample Size and ESS (vs. the Upper Limit of the 95% CI of the Adult Placebo Response, 0.18*)

	N/Arm=30	N/Arm=40	N/Arm=50
ESS=12 (w = 0.0135)	0.674	0.762	0.741
ESS=15 (w = 0.017)	0.809	0.769	0.809
ESS=18 (w = 0.020)	0.800	0.855	0.828
ESS=24 (w = 0.027)	0.895	0.925	0.895

ESS (Effective Sample Size) is calculated as the number of subjects used to derive the prior distribution multiplied by the down-weight (w).
*Based on Phase 2b study MCP-103-202 and Phase 3 pivotal studies LIN-MD-31 and MCP-103-302.

9.2.4. Populations for Analyses – IBS-C Participants

Four analysis populations will be defined for IBS-C participants as follows:

- Screened Population: Defined as all participants who undergo the Screening Visit (Visit 1) and receive a PID number.
- Randomized Population: Defined as all participants in the Screened Population who are randomized to a study intervention group.
- Safety Population: Defined as all participants in the Randomized Population who receive at least 1 dose of double-blind study intervention. Participants will be summarized according to the study intervention they actually received for all safety analysis variables/endpoints.
- Modified Intent-to-Treat (mITT) Population: Defined as all participants in the Randomized Population who receive at least 1 dose of double-blind study intervention and who had baseline and at least 1 postbaseline entry of the primary efficacy assessment (ie, an assessment of abdominal pain [combined daytime and nighttime symptoms] or BM characteristic assessments that determine occurrences of SBMs [ie, BM frequency and rescue medication use]). Participants will be summarized according to the randomized study intervention for all efficacy analysis variables/endpoints.

9.2.5. Statistical Analyses – IBS-C Participants

The SAP will be developed and finalized before database lock and unblinding for IBS-C participants. The SAP will describe the participant populations to be included in the analyses, and procedures for accounting for missing data. This section is a summary of the main features for the planned statistical analyses in IBS-C participants in this study.

9.2.5.1. Efficacy Analyses

Efficacy analyses will be based on the mITT Population in IBS-C participants.

Baseline values for efficacy endpoints related to IBS-C participants will be defined similarly as discussed in Section 9.1.5.1 for FC participants.

An observed-cases approach to missing postbaseline data will be applied. The descriptive statistics for efficacy endpoints by study intervention group will be provided to evaluate the main objective of this study in IBS-C participants. Descriptive statistics for continuous endpoints in terms of mean, median, standard deviation, standard error of mean, minimum, and maximum will be provided by study intervention group. For any categorical endpoints, counts and percentages will be provided by study intervention group.

Efficacy responses following onset of dose de-escalation will not be included for primary analyses. No statistical testing will be performed to compare linaclotide doses. No multiplicity adjustment will be applied in this study for IBS-C participants.

9.2.5.1.1. Key Efficacy Endpoints

The primary, secondary, and other efficacy endpoints for IBS-C participants are provided below.

Primary efficacy endpoint:

The primary efficacy endpoint will be 6/12 weeks APS (abdominal pain and SBM) + 2 responder.

A 6/12 weeks APS + 2 responder is a participant that meets the weekly APS + 2 responder criteria for at least 6 out of the 12 weeks of the intervention period. A weekly APS +2 responder is a participant who has an increase of at least 2 in the SBM weekly rate from baseline, AND a decrease of at least 30% in the mean abdominal pain score from baseline, during that study intervention week.

A participant has to have at least 4 completed diary days per analysis week to be considered a responder for that week. The participant needs to fill out both morning and evening eDiary on the same day to have a completed diary day.

The primary efficacy endpoint will be summarized by counts and percentages by study intervention group.

Bayesian analyses will be conducted utilizing the adult IBS-C information on the primary endpoint to inform the prior distribution of response in the pediatric IBS-C population (Carlin and Louis 2009). Pooled information for the APS + 2 responder rate for linaclotide 290 µg from studies MCP-103-202, MCP-103-302, and LIN-MD-31 will be utilized as a down-weighted prior, for the pediatric responder rate for APS + 2. The responder data generated from this trial and its' down-weighted Beta prior distribution will be used to form a posterior distribution of response. The analysis will utilize the value of the weight 0.017 (equivalent ESS of 15). The lower 2.5 percentile of posterior distribution of APS + 2 response will be compared to the pooled placebo APS + 2 responder rate of 0.16 from contributing adult IBS-C studies (as listed above) as well as compared to the upper limit of 95% CI of the pooled placebo APS + 2 responder rate of 0.18 from contributing adult studies.

The details of the Bayesian extrapolation framework are provided in a separate analysis plan.

Any other supplemental and sensitivity analyses will be discussed in the SAP as necessary.

Secondary efficacy endpoints:

The secondary efficacy endpoints include:

- Change from baseline in 12-week SBM frequency rate (SBMs/week) during the study intervention period
- Change from baseline in 12-week abdominal pain during the study intervention period
- Change from baseline in 12-week stool consistency during the study intervention period
- 6/12 weeks SBM + 2 responder
- 6/12 weeks abdominal pain responder

The definitions for the secondary efficacy endpoints are provided below.

Change from Baseline in 12-Week Spontaneous Bowel Movement (SBM) Frequency Rate During the Study Intervention Period

This secondary endpoint in IBS-C participants will be derived similarly as discussed in Section 9.1.5.1 for the primary endpoint in FC participants.

Change From Baseline in 12-Week Abdominal Pain During the Study Intervention Period

Abdominal pain will be measured twice daily, once in the morning and once in the evening eDiary, using a 5-point scale. A participant's 12-week abdominal pain score is the average of the non-missing assessments of abdominal pain reported in the morning (ie, nighttime symptoms) and evening (ie, daytime symptoms) assessments in the eDiary during the 12-week study intervention period.

Change From Baseline in 12-Week Stool Consistency During the Study Intervention Period

This secondary endpoint in IBS-C participants will be derived similarly as discussed in Section 9.1.5.1 for the secondary endpoint in FC participants.

6/12 Weeks SBM + 2 Responder

A 6/12 weeks SBM + 2 responder is a participant who meets the weekly SBM + 2 responder criteria for at least 6 out of the 12 weeks of the study intervention period. A weekly SBM + 2 responder is a participant who had an increase of at least 2 in the SBM weekly rate from baseline during that study intervention week.

6/12 Weeks Abdominal Pain Responder

A 6/12 weeks abdominal pain responder is a participant who meets the weekly abdominal pain responder criteria for at least 6 out of the 12 weeks of the study intervention period. A weekly

abdominal pain responder is a participant who had a decrease of at least 30% in the mean abdominal pain score from baseline during that study intervention week.

For each secondary efficacy responder endpoint, a participant has to have at least 4 completed diary days per analysis week to be considered a responder for that week. The participant needs to fill out both morning and evening eDiary on the same day to have a completed diary day.

9.2.5.1.2. Other efficacy endpoints:

Other efficacy endpoints are listed below and will be further specified in the SAP as appropriate.

- 6/12 weeks APS + 1 responder
- 9/12 weeks SBM + 2 responder
- 9/12 weeks abdominal pain (combined daytime and nighttime symptoms) responder
- 9/12 weeks APS + 2 responder
- Proportion of participants with SBMs within 24 hours of first dose of study intervention
- Change from baseline in 12-week straining during the study intervention period
- Change from baseline in 12-week abdominal pain (daytime symptoms and nighttime symptoms separately) during the study intervention period
- Change from baseline in 12-week percent of abdominal pain (combined daytime and nighttime symptoms)-free days during the study intervention period
- Change from baseline in 12-week bloating (daytime, nighttime, and combined symptoms) during the study intervention period
- Change from baseline in 12-week CSBM frequency rate (CSBMs/week) during the study intervention period
- Proportion of participants who no longer fulfill Rome III criteria for IBS-C at the end of the study intervention period
- Proportion of participants with each individual item score for the participant-completed global change items (pooping problems, tummy problems, and tummy pain) and global severity items (pooping problems, tummy problems, and tummy pain) at each week during the study intervention period
- Proportion of participants with each individual item score for the observer-completed global change item and the global severity item at each week during the study intervention period (collected for age group of 7-11 years only)

9.2.5.2. Safety Analyses

The safety analysis will be performed separately using the safety population for IBS-C participants. The safety parameters will include AEs, clinical laboratory parameters, vital sign measurements, height, weight, and ECG parameters. For each safety parameter, the last non-missing assessment made before the first dose of double-blind study intervention will be used as

the baseline for all analyses of that safety parameter. The safety analyses in IBS-C participants will be conducted similarly as discussed in Section 9.1.5.2 for FC participants with the exception that the summary will be provided for each of the two linaclotide dose groups.

9.2.5.2.1. Subgroup Analyses

Limited subgroup analyses may be performed on an exploratory basis for the CSR for IBS-C and will be defined in the SAP.

9.3. Interim Analyses

9.3.1. FC Participants

An IA to assess futility of linaclotide using the primary endpoint at 50% information may be considered based on the enrollment of FC participants in this study (ie, if the rate of enrollment is below expectations). The IA for FC participants will provide unblinded analysis of the primary efficacy endpoint for FC to assess futility of linaclotide for FC with approximately 50% of FC participants who completed the 12-week double-blind intervention period or have discontinued prematurely from the 12-week double-blind intervention period (Table 9-5). In the event this interim futility analysis occurs, the DSMB (responsible for safety monitoring) will review the unblinded IA results and make recommendations regarding the continuation of the study. To maintain the scientific reliability of the final results and prevent potential bias into the conduct of the study and analysis, individuals involved in the IA will not be involved in any operational aspects of the study. The unblinded IA using the primary endpoint to assess futility will be performed by an independent statistician (not involved with study team).

Since there will be no plan to stop the trial for efficacy in this futility IA with nonbinding futility boundary, no alpha will be spent for the interim look. However, following a conservative approach, the final analysis for FC will still be conducted at an alpha level of 0.049 (2-sided) in case this futility IA is conducted.

Table 9-5 Summary of Interim Analysis Strategy for FC Participants

Key Endpoint for Interim Analysis	Timing of Interim Analysis	Purpose of Interim Analysis
Primary: Change from baseline in 12-week SBM frequency rate (SBMs/week) during the study intervention period	The IA will be performed when the first 189 FC participants randomized in this study complete the 12 weeks of study intervention or discontinue prior to the completion of the double-blind study intervention period. This represents approximately 50% of the total information available in the study in the corresponding treatment arm.	Stop for futility for FC

Note: Assumed standard deviation and treatment difference as in Table 9-1.

Conditional power (CP) will be utilized for futility assessment in FC according to the following guidelines:

For the comparison of linaclotide vs. placebo in FC, if the CP of rejecting the null hypothesis of no difference between linaclotide and placebo in the primary endpoint for FC participants at the final analysis (ie, final look) given the observed difference at the interim look is < 20%, the study in FC participants may be reconsidered to have met the futility boundary. In this case, the DSMB may recommend to stop further investigation in FC participants in this study.

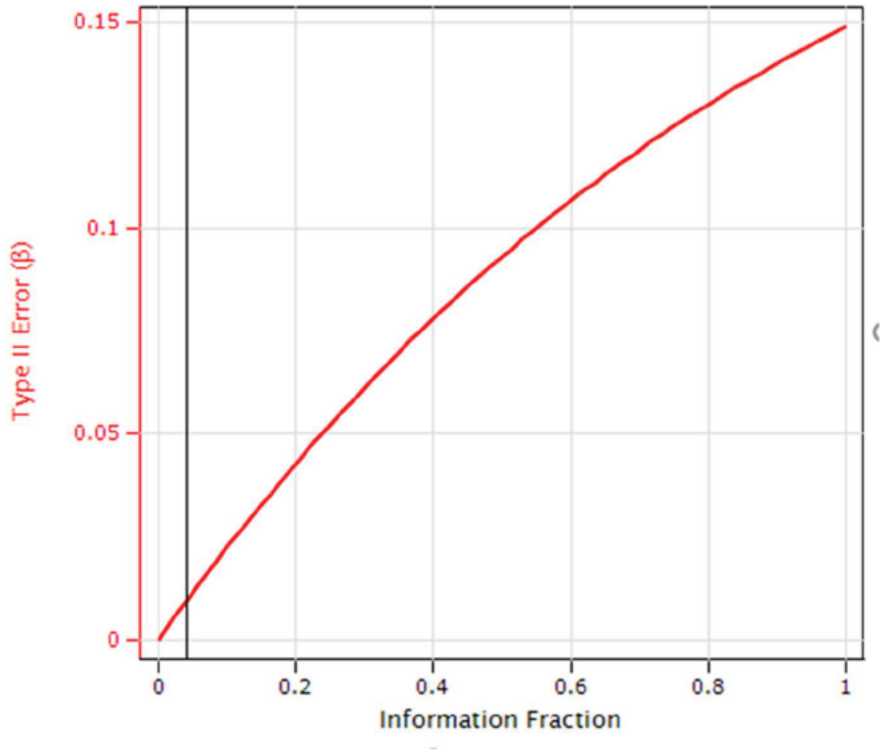
Conditional power will be calculated based on the formula of Chen et al (Chen 2004) which is given by:

$\Phi\left(\frac{z}{\sqrt{t(1-t)}}-\frac{z_{\alpha/2}}{\sqrt{1-t}}\right)$, where Φ is the cumulative distribution function of standard normal distribution; t is the information fraction at the IA; z is the assumed normalized test statistic at the interim look and α=0.05.

A gamma spending function (Hwang 1990) will be used for the futility check with a gamma parameter of 1.02.

Figure 9-1 plots the cumulative amounts of Type II error spent for different proportions of planned sample size.

Figure 9-1 Plot of Type II Error Spending Function[a]



[a] Plot was generated using East Version 6.4.

The stopping boundary for this study in FC participants is non-binding. β spent at the interim look for futility as described above is approximately 9.4%.

Scenarios of the IA at different information fractions with the corresponding conditional powers at current trend, treatment differences, amount of β spent, and the overall powers at total planned sample size of 378 are provided in Table 9-6 below.

Table 9-6 Different Interim Analysis Scenarios[a]

Percent of Randomized Participants at the IA	Conditional Power Under Current Trend (%)	Treatment Difference at Current Trend	β Spent	Overall Power (%)
30	2.5	0.1	0.055	86.7
40	9.6	0.295	0.074	85.8
50	20	0.424	0.094	85
60	31.5	0.513	0.111	84.5
70	43.4	0.579	0.127	84.1

Note: Assumed standard deviation and treatment difference as in Table 9-1.
East Version 6.4 was used.

[a] Based on a total sample size of 378.

An IA plan will document further details (if required) regarding the IA and be prepared separately when a decision to perform the above specified futility IA is made.

9.3.2. IBS-C Participants

No interim analysis is planned

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. 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/ISO Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, 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)

10.1.2. Financial Disclosure

Investigators and sub-investigators 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.

10.1.3. Informed Consent Process

Procedures will comply with 21 CFR, Parts 50 and 312. Signed informed consent will be obtained for the participant from the parent/guardian/LAR. This consent must include the following items:

- A statement that the study involves research and an explanation of the purposes of the research; a description of the procedures to be followed and the identification of any procedures that are experimental; and the expected duration of the participant's participation
- A description of any reasonably foreseeable risks or discomforts to the participant
- A description of any benefits to the participant or to others that may reasonably be expected from the research. If the participant is to be paid for participating in the study, the consent form must state the amount that he/she will receive and the schedule of payment (to ensure neither coercion nor undue influence)
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant
- A statement describing the extent, if any, to which confidentiality of records identifying the participant will be maintained and noting the possibility that the health authority, the sponsor, the IRB; or an authorized contract research organization may inspect the records
- For research involving more than minimal risk, an explanation of whether any medical treatment is available if injury occurs and, if so, what it consists of or where further information may be obtained
- An explanation of whom to contact, including the relevant telephone number, for answers to pertinent questions about the research and the research participant's rights and whom to contact in the event of a research-related injury to the participant. (Note: In some cases, it may be necessary to identify a person other than the investigator as the contact. The guidance of the IRB/IEC may be required)
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and that the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled
- A statement that the particular treatment or procedures may involve risks to the participant (or to the embryo or fetus if the participant is, or may become, pregnant) that are at present unforeseeable
- The expected circumstances for which the participant's participation may be terminated by the investigator without regard to the participant's consent
- Any additional costs to the participant that may result from participation in the research
- The consequences of a participant's decision to withdraw from the research and procedures for an orderly termination of participation

- A statement that significant new findings developed during the course of the research that may relate to the participant's willingness to continue participation will be provided to the participant
- The approximate number of participants involved in the study
- A statement of consent (eg, "I agree to allow (my child) to participate . . .")
- A place for the participant's parent/guardian/LAR signature and date of signing
- A statement indicating that information about this study has been, or will be, entered into a databank that is publicly accessible at www.ClinicalTrials.gov.

A copy of the signed consent form must be given to the participant's parent/guardian/LAR.

Signed informed consent will be obtained from caregiver of a participant and will include a statement agreeing to participate in the study.

In addition, the participant will be asked to provide assent that will include a statement agreeing to participate in the study.

10.1.4. Data Protection

- Participants will be assigned a unique identifier. 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.

10.1.5. Posting Clinical Study Data

All data generated in this study are the property of the sponsor. An integrated clinical and statistical report will be prepared at the completion of the study.

10.1.6. 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 at least 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.

10.1.6.1. Data Monitoring

Before any participant enters the study, a representative of the sponsor will meet with the investigator and the study site staff to review the procedures to be followed during the study. Electronic data capture (EDC) functionality training is provided via computer-based training to train investigators and authorized designees on recording the data in the eCRFs using the EDC system. After the first participant is enrolled, the sponsor's representative, a Regional Site Manager or designee, will periodically monitor the progress of the study by conducting on-site visits. This Regional Site Manager or designee will review query statuses remotely, possibly warranting more frequent communication and/or site visits with the investigator and the study site staff. The investigator will make available to the Regional Site Manager or designee source documents (written notes and electronic medical records, if used), signed consent forms, and all other study-related documents. The investigator and the study site staff will be responsible for data entry of participant data into the eCRFs via the EDC system, resolving data queries generated via the EDC system and providing missing or corrected data. The investigator or designee will be responsible for approving all changes performed on the data and endorsing the participant data within the EDC system. This approval method will include applying an electronic signature linked to a uniquely assigned username and password that together will represent a traditional handwritten signature used in the past.

The study site staff will be fully trained by a representative of the eDiary vendor on the use of the eDiary device and how to train participants and caregivers in the use of the eDiary device (ie, how to complete their daily and weekly assessments and download their data). The study site staff will then be responsible for ensuring that all participants and caregivers enrolled in the study are given full training and support materials in relation to the completion of the eDiary.

10.1.6.2. Data Recording and Documentation

Data collection will involve the use of the sponsor's EDC system, to which only authorized personnel will have access. Participant's data are to be entered into the EDC system by the investigator or designee using their assigned EDC user account. After data entry into the EDC system by the investigator or designee, a combination of manual and programmatic edit checks will be used to review the data for completeness, logic, and adherence to study protocol. As a result of these edits checks, data monitoring and reviews; queries may be electronically issued to the site and should be answered electronically via the EDC system.

Each query will carry identifying information (assigned username, date and time) to assist the sponsor and the investigator on the origin of the data clarification request and the response provided by the investigator. All data changes made to the participant's data via a data query will be approved by the investigator prior to final database lock.

After all data have been reviewed and all issues have been resolved, the database will be locked.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to guarantee participant confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (eg, copies of eCRFs, laboratory reports, participant diaries, regulatory documents) will be retained at the site, along with adequate source documentation, according to FDA and ICH requirements. All study records must be available for inspection by the sponsor, its authorized representatives, and health authorities.

10.1.6.3. Data and Safety Monitoring Board (DSMB)

An independent DSMB will review interim safety data at defined intervals throughout the study or ad hoc if needed. The DSMB will communicate their recommendations to the sponsor after each meeting but will serve in an advisory capacity only; the Board will not be empowered to stop the study or require changes in the protocol. Further details of the DSMB (composition, policy, and procedures) are specified in a separate DSMB Charter.

10.1.7. 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 source records must be available.

10.1.8. Study and Site Closure

The sponsor 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. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a 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 a 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 intervention development

10.1.9. Publication Policy

- Allergan as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.
- 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.

10.1.10. Compliance with Protocol

The investigator is responsible for compliance with the protocol at the investigational site. A representative of the sponsor will make frequent contact with the investigator and his/her research staff and will conduct regular monitoring visits at the site to review participant and study intervention accountability records for compliance with the protocol. Protocol deviations will be discussed with the investigator upon identification. The use of the data collected for the participant will be discussed to determine if the data are to be included in the analysis. The investigator will enter data that may be excluded from analysis as defined by the protocol deviation specifications. Significant protocol deviations will be reported to the IRB/IEC according to the IRB/IEC's reporting requirements.

Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the participants and must immediately be reported to the sponsor. Protocol deviations should be reported to the sponsor (either verbally or electronically) in a timely manner from the day of discovery.

Protocol deviations that may impact participant's rights (eg, failure to obtain informed consent prior to initiating study procedures), safety, or well-being (eg, deviations that resulted in an SAE, exposure during pregnancy), or the integrity and authenticity of the study data should be reported to the sponsor within 24 hours, if possible.

The IRB/IEC must be notified according to the criteria and time period dictated by the IRB/IEC associated with this study.

10.1.11. Study Documentation

The investigator must provide the following to the sponsor before the start of the study:

- For sites in the United States, a completed and signed Form FDA 1572. If, during the course of the study, any changes are made that are not reflected on Form FDA 1572, a new Form FDA 1572 must be completed and returned to the sponsor for submission to the FDA
- A fully executed contract

- For sites in the United States, the curricula vitae for the investigator and all sub-investigators listed on Form FDA 1572, including a copy of each physician's license
- A copy of the original IRB/IEC approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals. All subsequent modifications must be submitted and approved by the IRB/IEC, as stated in Section 10.1.1.
- A copy of the IRB/IEC- approved parent/LAR, caregiver ICFs, and participant's assent
- A copy of the HIPAA authorization form, or other local privacy applicable forms
- A list of the IRB/IEC members or the US Department of Health and Human Services general assurance number
- The Investigator's Statement page in this protocol signed and dated by the investigator
- For sites in the United States, financial disclosure agreement completed and signed by the investigator and all subinvestigators listed on Form FDA 1572. The investigator and all subinvestigators will provide an updated financial disclosure agreement to the sponsor 1 year after the completion of the study
- For sites in the EU and European Economic Area (EEA) the trial must be conducted in accordance with the national legislation that is set forth in the Directives 2001/20/EC, 2001/83/EC, and 2005/28/EC (and the Regulation (EU) No 536/2014 when in force).

10.2. Appendix 2: Clinical Laboratory Tests

Blood and urine samples for clinical laboratory tests will be collected as detailed in the SoA (Section 1.3). During the Screening Period, the investigator will assess the clinical significance of any values that are outside the reference ranges provided by the central laboratory. Participants with abnormalities judged to be clinically significant will be excluded from the study.

Participants with clinically significant electrolyte abnormalities that are considered to be secondary to diarrhea (ie, an AESI) must be reported to the sponsor within 24 hours on an SAE form if considered to be serious. Non-serious events do not require submission on an SAE form; rather, these events only need to be entered into the eCRF (Section 10.3). If the AE is assessed as causally related to the use of study intervention, the participant should be discontinued from the study; however, the sponsor and investigator may discuss individual participants and AEs to make this determination.

Clinical laboratory levels that will be measured are summarized in Table 10-1.

The clinical significance of a positive urine drug screen will be assessed by the investigator. Participants will be excluded from study participation if urine drug screening results are positive for cocaine, barbiturates, opiates, or cannabinoids.

Serum pregnancy test (for female participants of childbearing potential) will be obtained at Screening (Visit 1) and a urine pregnancy test will be performed at the Randomization Visit (Visit 3) prior to dosing as specified in the SoA (Section 1.3) and during treatment at Week 4 (Visit 5), Week 8 (Visit 6) and Week 12/EOT (Visit 7). Positive results on the pregnancy test at Screening (Visit 1) and Randomization (Visit 3) will exclude participants from participating in the study. Positive pregnancy test results during the study intervention will result in participant termination from the study. Investigators must inquire at every study visit about the use of acceptable methods of contraception in participants of childbearing potential who are, or become, sexually active (see Inclusion Criterion 3.02), and perform a serum or urine pregnancy test if there is any question of noncompliance with contraception. Repeat pregnancy tests may be performed at the investigator's discretion at other times during the study.

Other laboratory assessments may be repeated at any visit if there was an abnormal finding at the most recent previous evaluation or if additional information is clinically necessary to appropriately evaluate the participant's current condition, follow up, and/or manage an adverse experience.

A central laboratory will be used to evaluate all urine (except urine pregnancy tests) and blood samples, which will be collected, processed, and stored according to the instructions provided by the laboratory. The urine pregnancy test at Visits 3, 5 to 7 will be completed at the study site.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10-1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit	RBC indices: MCV MCH MCHC	White blood cell (WBC) count with differential (absolute): Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[a]	Blood urea nitrogen (BUN) Creatinine Glucose nonfasting	Potassium Sodium Bicarbonate Magnesium Phosphate Total protein Total bilirubin Calcium	AST ALT ALP	Total, direct and indirect bilirubin Total protein Total cholesterol chloride, albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Urine alcohol and drug screen (to include at minimum: benzoylecgonine (cocaine), barbiturates, amphetamines, benzodiazepines, cannabinoids, ethanol, opiates) • For female participants of child-bearing potential. Serum human chorionic gonadotropin (hCG) pregnancy test at screening and urine pregnancy test at Randomization prior to dosing[b]. • All study-required laboratory assessments will be performed by a central laboratory, with the exception of urine pregnancy test that will be performed locally at the site at Randomization (Visit 3), Week 4 (Visit 5), Week 8 (Visit 6) and Week 12/End of Treatment (Visit 7).			

a Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are provided in Appendix 9.

b Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- 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 intervention.

For the purpose of the site's data collection responsibilities, any untoward event that was reported from the time written consent was obtained until 30 days after the last known dose of study intervention is to be considered an AE. Particular attention must be given to the AE of diarrhea, which was the most frequently reported AE in the adult linaclotide program. Details about AE reporting are provided below.
Examples of AEs are as follows:

- Changes in the general condition of the participant
- Subjective symptoms offered by or elicited from the participant
- Objective signs observed by the investigator or other study site personnel
- All diseases that occur after signing the informed consent, including any change in severity or frequency of preexisting disease
- All clinically relevant abnormalities in laboratory values or clinically relevant physical findings that occur during the study schedule

Please note medical procedures scheduled prior to consenting, but occurring during the study, should not be captured as AEs, but should be listed in the medical history if related to a pre-existing condition.

AE of Special Interest (AESI)

An AESI (serious or nonserious) is one of scientific and medical concern specific to the sponsor's study drug 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 AESI(s) have been identified for the study intervention(s) in this protocol: significant volume depletion and/or significant electrolyte abnormalities and/or ECG abnormalities that are considered by the investigator or sponsor to be related to diarrhea. The investigator should contact the Study Physician if there is any question whether the criterion for an AESIs has been met.
All serious AESIs must be reported to the sponsor on an SAE form within 24 hours as noted below for SAEs.
Non-serious AESI do not require submission on an SAE form; rather, these events only need to be entered into the eCRF.

If the AESI is assessed as causally related to the use of study intervention, the participant should be discontinued from the study (Section 10.5).

Potential Hy's Law Cases

For potential Hy's Law cases, refer to Appendix 9.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, 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); for example:
  - The test result is associated with accompanying symptoms, and/or
  - The test result requires additional diagnostic testing or medical/surgical intervention, and/or
  - The test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
  - The test result is considered to be an AE by the investigator or sponsor.
- 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 intervention 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 intervention or a concomitant medication. Overdose per se will not be reported as an AE or 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. Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE. • 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. • The following disease-related events (DREs) are common in participants with FC and can be serious/life threatening: o Abdominal bloating o Straining o Sense of incomplete evacuation o Fecal incontinence If the investigator considers these manifestations to have a reasonable possibility of relationship to the study intervention(s), then they should be reported as AEs or SAEs. • 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

10.3.2. Definition of SAE

SAEs must meet both the AE criteria described above and the seriousness criteria listed below.

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 that 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 intervention 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 intervention 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 intervention 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.

All cancers that occur during a study are considered SAEs and will be documented and reported per Section 10.3.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording
• When an AE or 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 or SAE information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the eCRF. • 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 or SAE eCRF 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 one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Any AEs that are ongoing at the time of the final protocol-defined study visit will be followed until the condition returns to prestudy status, has resolved, or has stabilized. If a follow-up visit is deemed necessary for appropriate safety surveillance, it will take place within 30 days of the final protocol-defined study visit.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or 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 intervention administration will be considered and investigated.
- The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or 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.

10.3.4. Reporting of SAEs

SAE Reporting to Sponsor or Designee Within 24 Hours

- All SAEs will be recorded and reported to the sponsor within 24 hours on an SAE form.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.
- Email is the preferred method to transmit SAE information. The email address is IR-Clinical-SAE@allergan.com.
- Facsimile transmission of the SAE information is also acceptable. The fax number is +1-714-796-9504 (backup number is +1-714-246-5295).
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE form, 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 form within the designated reporting time frames.
- Contacts for SAE reporting can be found on the protocol title page.

10.4. Appendix 4: Abbreviations

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BM	bowel movement
BP	blood pressure
BSFS	Bristol Stool Form Scale
CBC	complete blood count
CFR	Code of Federal Regulations
CIC	chronic idiopathic constipation
CIOMS	Council for International Organizations of Medical Sciences
COA	clinical outcomes assessment
CONSORT	Consolidated Standards of Reporting Trials
CSBM	complete spontaneous bowel movement
CSR	clinical study report
DILI	drug-induced liver injury
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EEA	European Economic Area
EMA	European Medicines Agency
EOS	End-of-Study
EOT	End-of-Treatment
ESS	effective sample size
EU	European Union
FC	functional constipation
FDA	Food and Drug Administration
GC-C	guanylate cyclase subtype C
GCP	Good Clinical Practice
GI	gastrointestinal
hCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
IA	interim analysis
IB	investigator's brochure

IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome with constipation
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent to treat
IV	intravenous
IWRS	interactive web response system
LAR	legally authorized representative
LSM	least squares means
MAR	missing at random
mITT	modified intent to treat
MMRM	mixed effect model for repeated measures
mRNA	messenger ribonucleic acid
MSP	medical safety physician
p-BSFS	pediatric Bristol Stool Form Scale
PCS	potentially clinically significant
PID	participant identification
PRO	patient reported outcome
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBM	spontaneous bowel movement
SD	standard deviation
SoA	Schedule of Activities
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WOCBP	woman of childbearing potential

10.5. Appendix 5: 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, serious adverse experience. (CDISC glossary)
Completed	To possess every necessary or normal part or component or step; having come or been brought to a conclusion (NCI)
Death	The absence of life or state of being dead (NCI)
Disease relapse	The return of a disease after a period of remission
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
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)
Progressive disease	A disease process that is increasing in extent or severity (NCI)
Recovery	A healing process and/or an outcome implying relative health. The term is typically used in the context of direct and indirect effects of sickness or injury. (NCI)
Screen failure	The potential subject who does not meet one or more criteria required for participation in a trial
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)
Technical problems	A problem with some technical aspect of a clinical study, usually related to an instrument (NCI)
Withdrawal by parent/guardian	An indication that a study participant has been removed from the study by the parent or legal guardian
Withdrawal by subject	An indication that a study participant has removed itself from the study (NCI)

10.6. Appendix 6: Study Tabular Summary

Parameter Group	Parameter	Value
Trial information	Trial Title	A Phase 3, Multicenter, Randomized, Double-blind, Parallel-group, Safety and Efficacy Study of Linaclotide in Pediatric Participants, Ages 6 to 17 Years, With Irritable Bowel Syndrome with Constipation (IBS-C) and of Linaclotide versus Placebo in Pediatric Participants with Functional Constipation (FC)
	Clinical Study Sponsor	Allergan Sales LLC
	Trial Phase Classification	3
	Trial Indications	FC and IBS-C
	Trial Indication Type	Treatment
	Trial Type	Efficacy Safety
	Trial Length	17-20 weeks
	Planned Country of Investigational Sites	United States, Canada, Europe, and the Middle East
	Planned Number of Participants	326 FC participants 100 IBS-C participants
	FDA-Regulated Device Study	No
	FDA-Regulated Drug Study	Yes
	Pediatric Study	Yes
Subject information	Diagnosis Group	FC Participants: Children, Ages 6 to 17 Years, Who Fulfill Modified Rome III Criteria for Child/Adolescent FC IBS-C Participants: Children, Ages 7 to 17 Years, Who Fulfill Rome III Criteria for Child/Adolescent IBS and Fulfill Modified Rome III Criteria for Child/Adolescent FC
	Healthy Subject Indicator	No
	Planned Minimum Age of Subjects	6 for FC participants 7 for IBS-C participants
	Planned Maximum Age of Subjects	17 for both FC and IBS-C participants
	Sex of Participants	Both
	Stable Disease Minimum Duration	2 months

Parameter Group	Parameter	Value
Treatments	Study Intervention Therapy or Treatment	Linaclotide
	Intervention Type	drug
	Pharmacological Class of Invest. Therapy	
	Dose per Administration	72 µg for FC participants 145 µg or 290 µg for IBS-C participants
	Dose Units	µg
	Dosing Frequency	single dose, once daily at approximately the same time each day, 30 minutes prior to any meal
	Route of Administration	Oral
	Current Therapy or Treatment	None
	Added on to Existing Treatments	No
	Control Type	Placebo for FC participants
	Comparative Treatment Name	NA
Trial design	Study Type	Double-blind, placebo-controlled, confirmatory safety and efficacy study in FC participants Double-blind confirmatory safety and efficacy study in IBS-C participants
	Intervention Model	Parallel
	Planned Number of Groups	2 for FC participants 2 for IBS-C participants
	Trial is Randomized	Yes
	Randomization Quotient	1:1 for FC participants 1:1 for IBS-C participants
	Trial Blinding Schema	Double blind
	Stratification Factor	FC participants: Age group (6 to 11 years of age and 12 to 17 years of age) with a minimum of 40% of participants within each age group IBS-C participants: Age group (7 to 11 years of age and 12 to 17 years of age) with a minimum of 40% of participants within each age group
	Adaptive Design	No
	Study Stop Rules	Monitoring of participant safety data will be performed by the DSMB. Study conduct may be interrupted or terminated by the sponsor based on DSMB

Parameter Group	Parameter	Value
		recommendation or if, following a thorough review of all clinical, laboratory, and other available safety data, safety data becomes available which appears to represent an undue risk to the study participants' health or well-being.

10.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

10.7.1. Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

     Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

10.7.2. Contraception Guidance:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10-2.

Table 10-2 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of < 1% per year when used consistently and correctly*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[a]
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Etonogestrel implant (ie, Nexplanon®) Bilateral tubal occlusion Intrauterine copper contraceptive (ie, ParaGard®)
Vasectomized Partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period

10.7.3. Pregnancy Testing:

- WOCBP should have a negative serum pregnancy test at screening and a negative urine test on Randomization/Day 1.
- Additional pregnancy testing should be performed every 4 weeks during the treatment period and at the protocol-defined timeframe in Section 5.1 after the last dose of study intervention and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Pregnancy testing with a sensitivity of ≤ 25 mIU/mL will be performed.

10.7.4. Collection of Pregnancy Information:

Study site personnel must report every pregnancy. Within 24 hours of learning of the pregnancy, the study site personnel must report the event to Global Drug Safety on the Clinical Trial

Pregnancy Form, even if no AE has occurred. Email is the preferred method to transmit pregnancy information. The email address is IR Clinical-SAE@allergan.com. Facsimile transmission of the pregnancy information is also acceptable. The fax number is +1-714-796-9504 (backup number is +1-714-246-5295). In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the Clinical Trial Pregnancy Form, sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the investigator to complete and sign the Clinical Trial Pregnancy Form within the designated reporting time frames.

The pregnancy must be followed to term and the outcome reported by completing a follow-up a Clinical Trial Pregnancy Form. If the pregnancy is associated with an SAE (eg, if the mother is hospitalized for hemorrhage), a separate SAE Form for Clinical Trials must be filed as described in Section 10.3 with the appropriate serious criterion (eg, hospitalization) indicated in addition to the Pregnancy Form.

Female Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to [the sponsor]. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. A spontaneous or elective abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study

10.8. Appendix 8: Instructions for Sprinkled Dose

For participants who do not wish to take the dose as a capsule, a sprinkled dose may be prepared as follows:

Oral Administration in Applesauce:

1. Place one teaspoonful of room-temperature applesauce into a clean container.

2. Open the capsule.

3. Sprinkle the entire contents (beads) on applesauce.

4. Consume the entire contents immediately. Do not chew the beads. Do not store the bead-applesauce mixture for later use.

Oral Administration in Bottled Water:

1. Pour approximately 30 mL of room-temperature bottled water into a clean cup.

2. Open the capsule

3. Sprinkle the entire contents (beads) into the water

4. Gently swirl beads and water for at least 20 seconds.

5. Swallow the entire mixture of beads and water immediately.

6. Add another 30 mL of water to any beads remaining in cup, swirl for 20 seconds, and swallow immediately.

7. Do not store the bead-water mixture for later use.

Note that the drug is coated on the surface of the beads and will dissolve off the beads into the water. The beads will remain visible and will not dissolve. Therefore, it is not necessary to consume all the beads to deliver the complete dose.

10.9. Appendix 9: Liver Safety: Suggested Actions and Follow-up Assessments

Close monitoring should be initiated for the following participants:

- Participants with normal baseline serum aminotransferases (AT) who develop an increase of serum AT ≥ 3 × ULN
- Participants with elevated baseline AT who develop an increase of serum AT > 2 × the baseline value

The participant should return to the study site and be evaluated for potential drug-induced liver injury (DILI) as soon as possible, preferably within 48 to 72 hours from the time the investigator becomes aware of the abnormal results. Evaluation should typically include repeat testing of all 4 of the usual serum biochemical measures (ALT, AST, ALP, and TBL) to confirm the abnormalities and to determine if they are increasing or decreasing.

If it is difficult for the participant to return to the study site promptly, the participant should be retested locally, but normal laboratory ranges should be recorded, results should be made available to sponsor's study physician and the investigator immediately, and the data should be included in the eCRF. If repeat testing within this time frame is not possible, the study intervention should be discontinued.

It is critical to initiate close monitoring immediately upon detection and confirmation of signals of potential DILI as early as possible and not to wait until the next scheduled visit or monitoring interval. Close monitoring of the participant should be initiated in conjunction with the sponsor and consideration given to the following:

- Obtain a more detailed history of symptoms and prior or concurrent diseases.
- Obtain a history of concomitant drug use, including nonprescription medications, herbal products and dietary supplements, alcohol and recreational drug use, and special diets.
- Obtain a history of exposure to environmental chemical agents.
- Initiation of appropriate evaluations including applicable laboratory tests (eg, direct bilirubin, INR), physical assessments, and other assessments (eg, imaging)
    - Rule out other potential causes of biochemical abnormalities, eg, acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Consider gastroenterology or hepatology consultations.

If any of the following criteria are met, discontinuation of study intervention should be considered (if indicated, prior to receipt of confirming retest biochemistry laboratory test results) and the sponsor notified of the discontinuation:

- ALT or AST ≥ 3 × ULN and the participant is symptomatic with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> 5%)
- ALT or AST ≥ 3 × ULN and total bilirubin > 2 × ULN or INR > 1.5

- ALT or AST ≥ 5 × ULN for more than 2 weeks
- ALT or AST ≥ 8 × ULN

If the study intervention is discontinued, the participant may be re-challenged with study intervention only after consultation with the Allergan MSP. All participants showing potential DILI should be followed until all abnormalities return to normal or to the baseline state.

Reporting of Potential Hy's Law Cases

Potential Hy's law cases are defined by biochemical test results of hepatocellular injury and impaired hepatic function. They are considered Adverse Events of Special Interest (AESIs) and should be evaluated and followed further (ie, close monitoring initiated) to determine whether these laboratory abnormalities are indicative of DILI. As indicated above, discontinuation of study intervention should also be considered. Criteria that identify a potential Hy's law case are as follows:

- ALT or AST ≥ 3 × ULN AND
- Total bilirubin ≥ 2 × ULN AND
- Alkaline phosphatase < 2 × ULN

Sites must report every participant who meets the Hy's law criteria if this occurs within the time the participant signs the ICF until 30 days after the last dose of study intervention.

A laboratory alert for a potential DILI case will be sent immediately to the sponsor and investigators when the above criteria have been met, even if no clinical symptoms have been experienced. In addition, both an SAE and Adverse Event of Interest Abnormal Liver Function Reporting Form (GPSE-PVOPS-F-01-28) for all potential Hy's law DILI cases should be completed as soon as possible (within 24 hours of learning that a participant fulfills the potential Hy's law criteria) and submitted to the sponsor as noted in Appendix 3. The eCRF pages associated with the potential Hy's law cases must be completed within 7 calendar days.

10.10. Appendix 10: Study Schedule Supplement

The schedule of study procedures and assessments is tabulated by visit in the SoA in Section 1.3. The descriptions of the procedures to be performed at each visit are provided below.

10.10.1. Screening Period (Visit 1)

The Screening Period will occur up to 7 weeks before Randomization (Visit 3/Day 1) and last for 14 to 28 days during which time study procedures will be reviewed with the participant, parent/guardian/LAR, and caregiver; and informed assent (from participant), and parent/guardian/LAR and caregiver consent will be obtained and documented (Section 10.1.3). After informed consent is obtained, participants will be registered in IWRS and assigned a unique PID number (Section 6.3). A review of inclusion/exclusion criteria and other screening assessments will be conducted to determine the participant's eligibility for enrollment (Sections 5.1 and 5.2).

At Screening (Visit 1) the following procedures will also be performed:

- Review inclusion and exclusion criteria
- Complete Rome III assessment
- Register participant in IWRS
- Obtain medical history, medication history, and current medication status
- Perform a physical examination, including: general appearance, skin, HEENT (head, ears, eyes, nose, and throat), neck, thorax/lungs, cardiovascular, abdomen, musculoskeletal, lymph nodes, neurologic (including mental status), and visual inspection of the lumbosacral and perianal region. Breast and genitourinary examinations are optional at the discretion of the investigator. Investigators should pay special attention to clinical signs related to previous serious illnesses.
- A fecal impaction assessment will be performed. Fecal impaction is defined as a hard mass in the lower abdomen identified on physical examination or a dilated rectum filled with a large amount of stool on rectal examination. If a rectal examination is performed, the medically qualified site personnel should assess for and document the presence of anal wink and normal anal tone. If fecal impaction is identified, participants will receive a dis-impaction regimen with either oral or rectal medication. The choice of treatment will be determined by the investigator after discussing the options with the participant and the caregiver. Options will include any over-the-counter or prescription laxative, suppository, or enema (eg, polyethylene glycol, lactulose, Fleet enema). After the participant has received treatment for the impaction, the investigator must re-evaluate the participant for the presence of fecal impaction at the Preintervention Visit (Visit 2).
- Obtain height and weight; temperature (oral, rectal, or tympanic) and respiratory rate; and postural vital signs (supine and standing systolic and diastolic BP and pulse rate) (Section 8.2.2)
- Obtain standard 12-lead ECG (supine)

- Obtain clinical laboratory tests consisting of clinical chemistry, hematology, and urinalysis. All laboratory tests requiring blood draws should be collected at the same time
- Obtain serum β-hCG pregnancy test for female participants of childbearing potential.
- Obtain a urine drug screen at Screening (Visit 1) for all participants 12 to 17 years of age; a urine drug screen will be obtained for participants 6 to 11 years of age only if deemed necessary by the investigator. Urine drug screens may be repeated at the investigator's discretion at any time during the study
- Review any AEs occurring after assent/consent is obtained

Additionally, during the Screening Period, the participant and all caregivers will receive information about lifestyle modifications: for all participants increased water intake and increased physical activity, for FC participants high fiber diet and consistent toileting habits, for IBS-C participants keeping a food diary and adequate sleep. Participants will be advised to adopt these nonpharmacologic habits and instructed to maintain them throughout the study. There should be at least a 2-week interval between discussing the lifestyle modifications during the Screening Period and the participant's entry into the Preintervention Period.

10.10.2. Preintervention Period (Visit 2)

The Preintervention Period will occur up to 3 weeks before Randomization (Visit 3/Day 1) and last for 14 to 21 days. Participants will not receive study intervention during the Preintervention Period. If fecal impaction was documented during the Screening Visit, a fecal impaction assessment must be performed to determine continued eligibility for study participation. If there is no fecal impaction at the Preintervention Visit (Visit 2), the participant may enter the Preintervention Period after adhering to any washout requirements. If fecal impaction is present upon re-examination, the participant will not be eligible for the study (ie, they have failed their out-patient clean-out regimen).

Inclusion/exclusion criteria will be reviewed, patients and caregivers will receive full training on the use and completion of the daily eDiary. IWRS registration will include rescue medication assignment (ie, senna [oral] or bisacodyl [oral or rectal]), where applicable. Participants and caregivers will be instructed how to properly recognize signs of dehydration, how to administer oral rehydration therapy, and how to determine when the participant appears to be markedly ill or appears not to be responding to treatment for dehydration.

At the start of the Preintervention Period, the decision regarding whether participants, who are ages 6 to 11 years for FC or 7 to 11 for IBS-C, can complete the eDiary on their own or if they require assistance will be made at the discretion of the caregiver and carried through to study completion. Participants and caregivers will be trained in the use and completion of the eDiary including how to download eDiary responses and how to access the helpdesk if they encounter any problems using the eDiary. The eDiary will be completed by all participants or caregivers twice daily (morning and evening) throughout the Preintervention Period and compliance will be documented. Minimal compliance with the eDiary during the Preintervention Period for eligibility will be defined as completion of both morning and evening assessments for 10 out of the 14 days immediately preceding the Randomization Visit.

Participants and caregivers will be instructed to have the participant fast for at least 2 hours before receiving their first dose of study intervention at the study site during the Randomization Visit (Visit 3/Day 1). Water will be allowed.

Participants and caregivers will be instructed not to take rescue medication on the day before Visit 3 and on the day of Visit 3.

During the Preintervention Period (Visit 2), the following procedures will be performed:

- Review inclusion and exclusion criteria
- IWRS verification
- Perform a fecal impaction assessment if fecal impaction was documented during screening (Section 10.10.1)
- Obtain weight; temperature (oral, rectal, or tympanic) and respiratory rate; and postural vital signs (supine and standing systolic and diastolic BP and pulse rate) (Section 8.2.2).
- Review any AEs occurring since the last visit
- Review concomitant medications
- Contact the IWRS, where applicable, for rescue medication to be dispensed to the participant.
- Remind participant and caregiver to bring the bottle(s) of the rescue medication to the next visit.
- Instruct participants when to fast to ensure they have fasted for at least 2 hours before receiving the first dose of study intervention at the study site during the Randomization Visit; participants will be allowed to eat 30 minutes after dosing.
- Instruct participants and caregivers not to take rescue medication on the day before Visit 3 and on the day of Visit 3.
- Provide participants/caregivers with the eDiary along with instructions

10.10.3. Randomization (Visit 3, Day 1)

Participants' eligibility to enter the Study Intervention Period must be confirmed prior to randomization by review of inclusion and exclusion criteria, including a fecal impaction assessment, adherence to instructions regarding the use of rescue medication and prohibited medications, meeting eligibility criteria captured in the eDiary device, including full compliance with eDiary on at least 10 of the 14 days immediately preceding Visit 3. Participants will be required to complete the eDiary in the clinic for the time period up to immediately prior to randomization. The study coordinator will obtain the eDiary eligibility report to determine eDiary-related eligibility to be randomized. Once the participant's randomization eligibility is confirmed based on the eDiary eligibility report and other inclusion and exclusion criteria, the IWRS will randomize the participant. Study personnel will review the study procedures with participants and instruct them to resume eDiary entries later on the day of randomization.

Randomization will occur on the first day of the Study Intervention Period. Based on randomization, participants will receive placebo (FC participants) or linaclotide (FC and IBS-C participants). Participants will complete at least 12 weeks of intervention during the double-blind Study Intervention Period (ie, Study Intervention Period).

During the Randomization Visit (Visit 3), the following procedures will be performed:

- Review inclusion and exclusion criteria, including review of eDiary-related criteria
- IWRS verification
- Perform a fecal impaction assessment after eDiary eligibility is confirmed and prior to randomization. If fecal impaction is present, the participant will not be eligible for the study.
- Obtain weight; temperature (oral, rectal, or tympanic) and respiratory rate; and postural vital signs (supine and standing systolic and diastolic BP and pulse rate).
- Obtain clinical laboratory tests consisting of clinical chemistry, hematology, and urinalysis. All laboratory tests requiring blood draws should be collected at the same time
- Obtain a urine pregnancy test for female participants of childbearing potential. A negative urine pregnancy test is required prior to receiving study intervention
- Review any AEs occurring since the last visit
- Review concomitant medications
- Review eDiary completion, including the Clinic eDiary
- Ensure participants have refrained from using rescue medicine on the prior calendar day and on the day of the Randomization (Visit 3) until the time of the clinic visit.
- Remind participants not to use rescue medicine for the remainder of the day and on the next calendar day after the Randomization Visit
- Run the eDiary Eligibility Report to confirm that the participant can be randomized.
- Review use of protocol-permitted rescue medication dispensed in IWRS where applicable. Participants may choose a different protocol-permitted rescue medication at any visit, where available. Additional protocol-permitted rescue medications may be dispensed as needed at any visit.
- Prior to dosing, the investigator or appropriate site staff member will assess Rome IV criteria for Child/Adolescent IBS and/or FC. Assessment result will be captured in the eCRF. Eligibility for the study is not based on this assessment
- Contact the IWRS to obtain the study intervention (bottle number) to be dispensed to the participant based on randomization
- Administer the first dose of study intervention after completion of all Visit 3 assessments and after confirming the participant has fasted for at least 2 hours. Participants may resume eating 30 minutes after receiving their first dose of study intervention at the study site

- Dispense assigned study intervention for this study after the first dose has been administered. Provide study intervention reconstitution instructions for sprinkles to participants and caregivers for participants who may not be able to swallow capsules (Section 10.8)
- Record the date and time the first dose was administered
- Remind participant and caregiver to bring the bottle(s) of the study intervention and rescue medication to the next visit

10.10.4. Week 2 (Visit 4)

During Week 2 (Visit 4), the following procedures will be performed:

- Obtain weight; temperature (oral, rectal, or tympanic) and respiratory rate; and postural vital signs (supine and standing systolic and diastolic BP and pulse rate)
- Review any AEs occurring since the last visit
- Review concomitant medications
- Review use of protocol-permitted rescue medication dispensed in IWRS where applicable. Participants may choose a different protocol-permitted rescue medication at any visit, where available. Additional protocol-permitted rescue medications may be dispensed as needed at any visit
- Review study intervention and rescue medication compliance and accountability
- Review eDiary completion
- Remind participant and caregiver to bring the bottle(s) of the study intervention and rescue medication to the next visit

10.10.5. Week 4 (Visit 5)

During Week 4 (Visit 5), the following procedures will be performed:

- IWRS verification
- Obtain weight; temperature (oral, rectal, or tympanic) and respiratory rate; and postural vital signs (supine and standing systolic and diastolic BP and pulse rate)
- Obtain urine pregnancy test for female participants of childbearing potential
- Review any AEs occurring since the last visit
- Review concomitant medications
- Review use of protocol-permitted rescue medication dispensed in IWRS where applicable. Participants may choose a different protocol-permitted rescue medication at any visit where available. Additional protocol-permitted rescue medications may be dispensed as needed at any visit
- Review study intervention and rescue medication compliance and accountability

- Review eDiary completion
- Dispense assigned study intervention for this study
- Remind participant and caregiver to bring the bottle(s) of the study intervention and rescue medication to the next visit

10.10.6. Week 8 (Visit 6)

During Week 8 (Visit 6), the following procedures will be performed:

- IWRS verification
- Obtain weight; temperature (oral, rectal, or tympanic) and respiratory rate; and postural vital signs (supine and standing systolic and diastolic BP and pulse rate)
- Obtain urine pregnancy test for female participants of childbearing potential
- Review any AEs occurring since the last visit
- Review concomitant medications
- Review use of protocol-permitted rescue medication dispensed in IWRS where applicable. Participants may choose a different protocol-permitted rescue medication at any visit where available. Additional protocol-permitted rescue medications may be dispensed as needed at any visit
- Review study intervention and rescue medication compliance and accountability
- Review eDiary completion
- Dispense assigned study intervention for this study
- Remind participant and caregiver to bring the bottle(s) of the study intervention and rescue medication to the next visit

10.10.7. Week 12/End-of-Treatment Visit (Visit 7)

The participant must complete at least 12 weeks of study intervention before arriving at the study site for the Week 12 Visit. All randomized participants who prematurely discontinue from study intervention, regardless of cause, should complete assessments at this visit.

During the End of Treatment Visit (Visit 7), the following procedures will be performed:

- IWRS verification
- Perform a physical examination, including: general appearance, skin, HEENT (head, ears, eyes, nose, and throat), neck, thorax/lungs, cardiovascular, abdomen, musculoskeletal, lymph nodes, neurologic (including mental status), and visual inspection of the lumbosacral and perianal region. Breast and genitourinary examinations are optional at the discretion of the investigator.
- Complete Rome III assessment.

- Obtain height, weight, temperature (oral, rectal, or tympanic) and respiratory rate; and postural vital signs (supine and standing systolic and diastolic BP and pulse rate)
- Obtain standard 12-lead ECG (supine)
- Obtain clinical laboratory tests consisting of clinical chemistry, hematology, and urinalysis. All laboratory tests requiring blood draws should be collected at the same time
- Obtain urine pregnancy test for female participants of childbearing potential
- Review any AEs occurring since the last visit
- Review eDiary completion
- Review concomitant medications
- Review use of protocol-permitted rescue medication dispensed in IWRS where applicable. Participants may choose a different protocol-permitted rescue medication at any visit where available. Additional protocol-permitted rescue medications may be dispensed as needed at any visit
- Review study intervention and protocol-permitted rescue medications use and accountability.
- Study intervention will be returned
- For participants who enroll into LIN-MD-66 before the EOS Visit:
  - rescue medication will be returned
  - eDiary device will be returned

10.10.8. End of Study Visit /Postintervention Follow-up (Visit 8)

Participants will not receive study intervention during the Postintervention Period.

Participants that complete LIN-MD-64 have the option to enroll into the open-label, long-term safety study, LIN-MD-66, if they meet the eligibility criteria. Participants will be considered to have completed LIN-MD-64 if he/she has completed 12 weeks of double-blind study intervention, the EOT visit (Visit 7), and the EOS visit (Visit 8). However, this EOS visit is not required for participants who enroll into the open-label, long-term safety study LIN-MD-66 prior to that visit.

During this EOS Visit (Visit 8), the following procedures will be performed:

- Obtain weight; temperature (oral, rectal, or tympanic) and respiratory rate; and postural vital signs (supine and standing systolic and diastolic BP and pulse rate)
- Review any AEs occurring since the last visit
- Review eDiary completion
- Review concomitant medications
- Review use of protocol-permitted rescue medication dispensed in IWRS where applicable.

- Review rescue medication compliance and accountability.
- Rescue medication will be returned
- eDiary device will be returned

10.11. Appendix 11: Study Conduct During the Novel Coronavirus Pandemic

Any participant who was designated as a screen failure or a preintervention failure during the screen hold due to the novel coronavirus pandemic may be rescreened.

Any participant that terminated study treatment early due to the novel coronavirus pandemic can enroll into long-term safety study LIN-MD-66, if they meet the eligibility criteria.

In the event of a prolonged persistence or re-emergence of the novel coronavirus pandemic, interim actions to mitigate the potential risks to participants and study staff while continuing study conduct will be communicated to sites via a Protocol Clarification Letter, which would be implemented in accordance with the appropriate local IRB/EC approval process.

10.12. Supporting Information from the Adult Linaclotide Program

Table 10-3 Summary of Studies in the Linaclotide Adult Program Conducted in North America

Study Number	Study Design/Study Population	Major Conclusions
MCP-103-312	**Phase 3b, randomized, double-blind, placebo-controlled, parallel-group trial of linaclotide 290 µg administered orally for 12 weeks followed by a 4-week randomized withdrawal period in patients with irritable bowel syndrome with constipation**	• Linaclotide showed a statistically significant improvement in Overall Change from Baseline in Abdominal Score Throughout the Treatment Period compared with placebo for the primary analysis of the primary endpoint ($p<0.0001$), as well as for the secondary time-course analysis of the primary endpoint ($p<0.0005$ at all weeks). • Linaclotide showed statistically significant improvements compared with placebo for the secondary endpoints of Change from Baseline in 12-week Abdominal Score (comparison of cumulative distribution function curves) and 6/12 Week Abdominal Score Responder (both $p<0.0001$). • Statistically significant improvement in abdominal score with linaclotide versus placebo was observed within the first week of dosing and was sustained over the 12-week Treatment Period. • Diarrhea was the most commonly reported TEAE during the trial. During the treatment period, 4.6% of linaclotide patients reported at least 1 episode of diarrhea, compared with 1.6% of placebo patients; this represented a lower diarrhea rate than previously observed in linaclotide trials.
LIN-MD-31	**Phase 3 study multicenter, randomized, double-blind, placebo-controlled, parallel-group study in adults with IBS-C comparing one dose (266 µg) of linaclotide with placebo. Included a 4-week double blind, randomized withdrawal period immediately following the 12-week treatment period to assess the potential for rebound worsening of bowel or abdominal symptoms**	• Linaclotide showed a statistically significant improvement versus placebo for all 4 primary efficacy parameters controlling for multiplicity: 9/12 Week APC 3+1 responder ($p = 0.0004$), 9/12 Week CSBM 3+1 responder ($p < 0.0001$), 9/12 Week abdominal pain responder ($p = 0.0262$), and 6/12 Week APC +1 responder ($p = < 0.0001$). • Linaclotide showed a statistically significant improvement versus placebo for each of the 10 secondary efficacy parameters (all p-values statistically significant controlling for multiplicity). The results were observed within the first week of dosing and were sustained over the 12-week treatment period. • There was no evidence of a rebound effect when linaclotide treatment was withdrawn. • Diarrhea was the most frequently reported TEAE during the trial. In the treatment period, 79 (19.5%) of 406 patients treated with linaclotide reported at least 1 episode of diarrhea compared to 14 (3.5%) of 396 patients treated with placebo.

Study Number	Study Design/Study Population	Major Conclusions
MCP-103-302	**Phase 3 randomized, double blind, placebo-controlled, parallel-group study of linaclotide administered orally for 26 weeks in adults with IBS-C**	• Safety and efficacy of linaclotide 290 µg administered as a solid oral capsule for 12 or 26 weeks: Results showed improvement in abdominal and bowel symptoms at 12 weeks that was maintained throughout 26 weeks of treatment. Diarrhea was the most frequently reported TEAE during the study. • Linaclotide showed a statistically significant difference from placebo for each of the 4 primary efficacy parameters ($p < 0.0001$ for all 4 parameters): 9/12 week APC 3+1 Responder, 9/12 week CSBM 3+1 Responder, 9/12 week Abdominal Pain Responder, and 6/12 week APC +1 Responder, all of which were statistically significant controlling for multiplicity. • Differences in linaclotide versus placebo were observed within the first week of dosing and were sustained over the 26-week Treatment Period. • Diarrhea was the most common TEAE reported during the trial. During the Treatment Period, 79 (19.7%) of 402 linaclotide patients reported at least 1 episode of diarrhea, compared to 10 (2.5%) of 403 placebo patients.

Study Number	Study Design/Study Population	Major Conclusions
LIN-MD-01	**Phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel-group, multiple-dose, 12-week trial comparing 2 doses of linaclotide with placebo in adults with CIC**	• Linaclotide showed a statistically significant improvement compared with placebo for the primary efficacy parameter, 12-week CSBM overall responder, at both the 266- and 133-µg/day doses ($p = 0.0012$ and $p < 0.0001$, respectively, statistically significant after controlling for multiplicity). • The odds of linaclotide patients being 12-week CSBM overall responders are approximately 3 to 4 times those of patients receiving placebo. • Linaclotide showed a statistically significant improvement compared with placebo for each of the secondary efficacy parameters at both the 266- and 133-µg/day doses (all p-values statistically significant after controlling for multiplicity). • For most parameters, improvements versus placebo were observed for both doses of linaclotide within the first week, often on the first day of dosing, and were sustained over the 12-week treatment period. • None of the patients tested had quantifiable serum levels of linaclotide or its primary metabolite (MM-419447), supporting previous clinical studies that demonstrated that linaclotide is minimally absorbed. • Diarrhea was the most frequently reported TEAE during the trial. In the treatment period, 72 (17.2%) of 418 linaclotide patients reported at least 1 episode of diarrhea compared with 6 (2.8%) of 215 placebo patients. Diarrhea incidence was not dose related; 42 (19.7%) and 30 (14.6%) patients in the 133- and 266-µg/day linaclotide groups, respectively, experienced TEAEs of diarrhea. • There were no clinically meaningful differences between placebo and linaclotide groups in the mean or change from baseline QT interval (corrected by either Bazett's or Fridericia's formula). Overall the data indicated that linaclotide does not adversely affect the ECG of linaclotide-treated adult participants.

Study Number	Study Design/Study Population	Major Conclusions
MCP-103-303	**Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Trial of Linaclotide Administered Orally for 12 Weeks Followed by a 4-Week Randomized Withdrawal Period in adults with CIC**	• Linaclotide showed a statistically significant improvement from placebo for the primary efficacy parameter, 12-week CSBM Overall Responder, at both the 133 and 266 µg doses. The odds of being a 12-week CSBM Overall Responder are approximately 7 times higher in patients on linaclotide than in patients on placebo. • Linaclotide showed a statistically significant improvement from placebo for each of the secondary efficacy parameters at both the 266 and 133 µg doses (all p-values statistically significant after controlling for multiplicity). • The results were robust and consistent across the primary and secondary efficacy parameters. • No patient had quantifiable plasma levels of linaclotide or its primary metabolite (MM-419447), supporting previous clinical studies that demonstrated that linaclotide is minimally absorbed. • Diarrhea was the most common TEAE reported during the study. In the Treatment Period, diarrhea was reported by 27 (12.4%) and 30 (13.8%) patients in the 133 and 266 µg linaclotide groups, respectively, compared to 14 (6.7%) placebo patients. • No rebound of constipation symptoms was observed and there was no evidence of withdrawal symptoms in the RW Period.
LIN-MD-02	**Multicenter, open-label study examining the long-term (78-week) safety of linaclotide in adult participants with CIC and IBS-C who completed 1 of the linaclotide Phase 2 or 3 studies or the Pretreatment Period of 1 of the Phase 3 double-blind studies, but failed to meet specific inclusion or exclusion criteria to be randomized**	• As observed in previous studies with linaclotide, diarrhea was the most frequently reported TEAE during the study, with 524 (33.7%) of 1554 patients reporting at least 1 episode of diarrhea. Most of the TEAEs were reported as mild or moderate and unrelated to linaclotide. • The incidence of SAEs was low for both the CC Safety and IBS-C Safety Populations (with 5.9% and 5.5% of patients, respectively) reporting 1 or more SAEs over the duration of the 18 month study)
MCP-103-305	**Multicenter, open-label, long-term safety study of oral linaclotide in adult participants with CIC and IBS-C who completed 1 of the linaclotide Phase 2 or 3 studies or the Pretreatment Period of 1 of the Phase 3 double-blind studies, but failed to meet specific inclusion or exclusion criteria to be randomized**	• As observed in previous studies with linaclotide, diarrhea was the most common TEAE. • Reduction in linaclotide dose from 290 µg to 145 µg seemed to enable patients to remain in the study when they might otherwise have withdrawn • The incidence of SAEs was low for both the CC Safety and IBS-C Safety Populations (with 6.8% and 5.0% of patients, respectively reporting one or more SAEs over the duration of the 18 month study). The nature of the SAEs did not raise any safety concerns regarding treatment with linaclotide.

Study Number	Study Design/Study Population	Major Conclusions
LIN-MD-04	**Randomized, double-blind, placebo controlled, parallel-group, study of linaclotide at doses of 145 µg/day and 290 µg /day, administered orally for 12 weeks to adult participants with CIC and prominent abdominal bloating at baseline (ie, bloating ≥ 5.0 on an 11-point numerical rating scale)**	• Patients treated with linaclotide 145 µg/day met the primary efficacy endpoint of 3 or more CSBMs per week and an increase of 1 or more CSBMs per week from baseline for at least 9 of 12 weeks compared with placebo-treated patients. • The odds of being a 9/12-week CSBM 3 + 1 responder were approximately 2.2 times higher for patients treated with linaclotide 145-µg/day than for patients who were treated with placebo. • Patients with prominent abdominal bloating at baseline experienced improvement in their bloating symptoms within the first week of treatment with linaclotide 145- and 290-µg/day relative to placebo treatment and the improvement was sustained for the duration of treatment. • Diarrhea was the most common TEAE reported among linaclotide-treated patients in this study; however, none of the observed TEAEs of diarrhea had serious sequelae.
MCP-103-309	**Phase 3 randomized, double-blind, placebo-controlled, parallel-group study of linaclotide at doses of 72 µg/day and 145 µg/day was administered orally for 12 weeks in adults with CIC at baseline.**	• Overall, once-daily linaclotide 72 µg showed statistically significant improvement in CIC symptoms compared with placebo during the Treatment Period, with treatment effects that were similar to the linaclotide 145 µg dose. • Consistent with the established linaclotide AE profile, diarrhea was the most common TEAE reported during the study and was experienced by 19.2% and 22.1% of patients in the linaclotide 72 µg and 145 µg groups, respectively, compared with 7.0% in the placebo group. Diarrhea was mostly mild to moderate in severity

11. References

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