Title Page

Protocol Title: A Long-term Safety Study of Oral Linaclotide Administered to Pediatric Participants with Functional Constipation (FC) or Irritable Bowel Syndrome with Constipation (IBS-C)

Protocol Number: LIN-MD-66

Amendment Number: 2

Product: Linaclotide

Brief Protocol Title: Long-term Safety of Linaclotide in Pediatric Participants with FC or IBS-C

Development Phase: Extension study

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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 2	*Apr 2021*
Amendment 1	*Jun 2020*
Original Protocol	*Jul 2019*

Amendment 2 (April 2021)

The purpose of Global Protocol Amendment 2 is to provide LIN-MD-64 completers with IBS-C the option to continue on the same blinded dose they received in the LIN-MD-64 lead-in study, and to provide additional clarification and updates to the LIN-MD-66 protocol (Amendment 1 dated 10 June 2020).

The following is a summary of changes made in Global Protocol Amendment 2. Strikethrough text denotes text removed and bolded text denotes added text. Additional administrative edits were also made, but not specifically noted (e.g., 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 remove the words 'phase 3 open-label' • Revised the Development Phase as follows: ~~3~~ **Extension study** • Updated the sponsor signatory	• To account for the blinded treatment arm that was added to the study and for clarity • For clarification • Updated to reflect the 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. • The words 'open-label' and 'Phase 3' were removed from the study description throughout the protocol as needed.	• To align with the body of the protocol • To account for the blinded treatment arm that was added to the study and for clarification
Section 1.3 Study Schema for IBS-C Participants	• The label for the 52-week study intervention period was changed as follows: '~~Open label~~ Intervention Period' was changed to '**Study** Intervention Period'	• To include the blinded treatment arm that was added to the study
Section 1.4 Schedule of Activities (SoA) for FC Participants	• '**FC**' was added to the titles for Table 1-1 and Table 1-2	• For clarification
Section 1.5 Schedule of Activities (SoA) for IBS-C Participants	• '**IBS-C**' was added to the titles for Table 1-3 and Table 1-4 • For Table 1-4, the footnote for Study Day 365 was changed from 'd' to 'b' as follows: 365 (+3)[**d b**]	• For clarification • Updated to reflect the correct footnote
Section 2 Introduction	• The following text was revised: 'Linaclotide is approved for the treatment of irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) in the United States, Canada, Japan, Australia, **New Zealand, Kingdom of Saudi Arabia**, and Mexico'	• Updated to reflect the current information
Section 4.1 Overall Design	• The following text was added: **'For FC participants enrolling from studies LIN-MD-62 and LIN-MD-64, and IBS-C participants enrolling from study LIN-MD-63, linaclotide treatment will be open-label. For IBS-C participants enrolling from study LIN-MD-64, linaclotide treatment will be either blinded or open-label. Linaclotide treatment will be blinded if participants choose to**	• To include the blinded treatment arm that was added to the study

Protocol Section(s)	Description of Changes	Rationale for Changes
	remain on the same blinded linaclotide dose they were receiving in the lead-in LIN-MD-64 study and it will be open-label if participants choose to receive open-label linaclotide therapy.'	
	• Text was revised as follows: 'The present study will include a screening period and ~~an open-label~~**a 24-week (FC participants) or 52-week (IBS-C participants)** study intervention period (Section 1.2 **and Section 1.3, respectively**).'	• For clarification
	• The following text was added: 'Participants who turn 18 years of age during study LIN-MD-63 or LIN-MD-64, or after completing the lead-in study, may be eligible if they enroll within 28 days (inclusive) of the last day of study intervention in the lead-in study (Study LIN-MD-64 [Visit 7] or Study LIN-MD-63 [Visit 5]). **Such participants will be dosed as 17-year-old participants; refer to the Intervention Groups and Study Duration section below for dosing.'**	• To clarify the dosing for participants who turn 18 years of age
	• The intervention groups were updated to indicate that LIN-MD-64 completers with IBS-C will have the option to either remain on the same blinded linaclotide dose they were receiving in the lead-in Phase 3 study LIN-MD-64 or to receive open-label linaclotide therapy.	• To allow IBS-C participants who responded favorably to their dose in the LIN-MD-64 lead-in study to remain on the same dose in LIN-MD-66
	• Text describing the dose modifications permitted for participants has been deleted from this section and the following reference was added: '**Dose modifications permitted for FC and IBS-C participants are described in Section 6.6**.'	• To streamline this section for clarity
Section 4.3 Justification for Doses	• Text was added referring to the dosing options for LIN-MD-64 IBS-C completers.	• To include the blinded treatment arm that was added to the study
	• Text referring to dose adjustments permitted for a participant who experiences an intolerable AE was deleted from this section and the following reference was added: '**Dose modifications permitted for FC and IBS-C participants are described in Section 6.6**.'	• To streamline this section for clarity
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	• The following sentence was deleted: '~~Blinding is not applicable given this is an open-label study~~'.	• To include the blinded treatment arm that was added to the study

Protocol Section(s)	Description of Changes	Rationale for Changes
Section 6.3.1 Blinding and Unblinding	• Text was added to include blinding of study intervention for the blinded treatment arm and to describe the unblinding process if needed	• To include the blinded treatment arm that was added to the study
Section 6.6 Dose Modification	• Text describing the dose adjustments permitted for FC and IBS-C participants was streamlined and Table 6-1 Dose Reductions was added which summarizes the dose adjustments permitted for all participants.	• For clarity and to add the dose reductions permitted for IBS-C participants on blinded linaclotide treatment
Section 9.5 Interim Analyses	• The following text was deleted: '~~No interim analysis is planned~~.' The following text was added: '**An interim analysis to assess long-term safety of linaclotide may be performed after at least 120 participants have completed the study. Data will be locked after performing data cleaning. Results from the interim analysis will be described in an interim clinical study report.**'	• To evaluate the long-term safety of linaclotide once at least 120 participants have completed the study.
Section 10.6 Appendix 6: Study Tabular Summary	• The following text was revised: o Trial Phase Classification: ~~Phase 3 Trial~~ **Extension Study** • The following text was added: o 'Intervention Model: Open-label **and blinded**' o 'Planned Number of Arms: **2 arms for FC participants: open-label 72 and 145 µg** **4 arms for IBS-C participants: 2 arms for open-label (145 and 290 µg) and 2 arms for blinded (145 and 290 µg)**' o 'Trial Blinding Schema: Open-label **and blinded**'	• For clarification • To include the blinded treatment arm that was added to the study

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Long-term Safety Study of Oral Linaclotide Administered to Pediatric Participants with Functional Constipation (FC) or Irritable Bowel Syndrome with Constipation (IBS-C)

Protocol Number: LIN-MD-66

Amendment Number: 2

Brief Title: Long-term Safety of Linaclotide in Pediatric Participants with FC or IBS-C

Study Phase: Extension study

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 disimpaction (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, 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).

The primary objective of LIN-MD-66 is to assess the long-term safety of linaclotide administered to participants with FC (total exposure with linaclotide for 24 weeks) or IBS-C (total exposure with linaclotide for 52 weeks) who have completed study intervention in Study LIN-MD-62, LIN-MD-63, or LIN-MD-64.

Objectives and Assessments:

Objectives	Assessments
Primary	
The objective of this study is to assess the long-term safety of linaclotide in pediatric participants with FC (total exposure with linaclotide for 24 weeks) or IBS-C (total exposure with linaclotide for 52 weeks) who have completed study intervention in Study LIN-MD-62, LIN-MD-63, or LIN-MD-64.	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-66 is a long-term safety study with 24 weeks (FC participants) or 52 weeks (IBS-C participants) of linaclotide exposure that will enroll pediatric participants (6-17 years of age) with FC or IBS-C who completed study intervention in Phase 2 study LIN-MD-62 or LIN-MD-63, or Phase 3 study LIN-MD-64, based on the individual study criteria. For FC participants enrolling from studies LIN-MD-62 and LIN-MD-64, and IBS-C participants enrolling from study LIN-MD-63, linaclotide treatment will be open-label. For IBS-C

participants enrolling from study LIN-MD-64, linaclotide treatment will be either blinded or open-label. Linaclotide treatment will be blinded if participants choose to remain on the same blinded linaclotide dose they were receiving in the lead-in LIN-MD-64 study and it will be open-label if participants choose to receive open-label linaclotide therapy.

- Phase 2 completers are defined as pediatric participants who completed 4-week double-blind study intervention and EOT Visit (Visit 5) in the Phase 2 studies AND
  - Completed the EOS (Visit 6) in Study LIN-MD-62 **or**
  - Completed the EOS (Visit 6) in Study LIN-MD-63. However, this EOS Visit in LIN-MD-63 is not required for participants who enroll into LIN-MD-66 prior to that visit.
- Phase 3 completers are pediatric participants who completed 12-week double-blind study intervention in Study LIN-MD-64. Participants must have completed 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 LIN-MD-66 prior to that visit.

The present study will include a screening period and a 24-week (FC participants) or 52-week (IBS-C participants) study intervention period (Section 1.2 and Section 1.3, respectively). For participants who enroll in LIN-MD-66 on the same day as their EOT Visit or EOS Visit in LIN-MD-64, the EOT Visit or EOS Visit, respectively, may be combined with the Screening (Visit 1) and Day 1 Visit (Visit 2) in LIN-MD-66. For participants who enroll within ≤ 28 days (inclusive) from last study intervention in Study LIN-MD-64 (Visit 7), the LIN-MD-66 Screening Visit (Visit 1) and Day 1 Visit (Visit 2) procedures may be combined, with the exception of participants who are positive for fecal impaction assessment at the Screening Visit (Visit 1).

All participants are required to have a fecal impaction assessment prior to dosing. For those participants who do not combine Visit 1 and Visit 2, a fecal impaction assessment will be performed at the Screening Visit (Visit 1) and at the Day 1 Visit (Visit 2) prior to dosing. Please refer to Section 8.2.1 for further details.

Participants who turn 18 years of age during study LIN-MD-63 or LIN-MD-64, or after completing the lead-in study, may be eligible if they enroll within 28 days (inclusive) of the last day of study intervention in the lead-in study (Study LIN-MD-64 [Visit 7] or Study LIN-MD-63 [Visit 5]). Such participants will be dosed as 17-year-old participants; refer to the Intervention Groups and Study Duration section below for dosing.

Number of Participants:

At least 120 participants are planned to be enrolled to receive 24 weeks (FC participants) or 52 weeks (IBS-C participants) of linaclotide study intervention. However, the actual number of participants in this study will depend on the number of participants who have completed study intervention in the lead-in study (LIN-MD-62, LIN-MD-64, or LIN-MD-63) and enroll into this long-term safety study after fulfilling the eligibility criteria.

Number of Sites:

Up to 120 sites from the United States, Canada, Europe, and the Middle East will have an option to participate in the study.

Intervention Groups and Study Duration:

FC participants (LIN-MD-62 and LIN-MD-64 completers) will receive open-label linaclotide 72 µg or 145 µg once daily for 24 weeks as follows based on their age at the time of enrollment into LIN-MD-66:

- 6 to 11 years of age: 72 µg linaclotide
- 12 to 17 years of age: will be randomly assigned at 1:1 ratio to 72 µg linaclotide or 145 µg linaclotide

IBS-C participants will receive linaclotide for 52 weeks as follows:

- LIN-MD-63 completers will receive open-label linaclotide 290 µg once daily except for the LIN-MD-63 completers who had received ≤ 145 µg linaclotide or placebo. These participants will have the option to receive open-label linaclotide 145 µg once daily.
- LIN-MD-64 completers will have the option to either remain on the same blinded linaclotide dose they were receiving in lead-in study LIN-MD-64 or to receive open-label 290 µg linaclotide. Study intervention in LIN-MD-66 is assigned via IWRS; treatment assignments for LIN-MD-64 completers who choose to remain on the same blinded linaclotide dose in long-term safety study LIN-MD-66 will remain blinded to participants, investigators, and all site personnel during the study.
    - LIN-MD-64 completers who choose to remain on the same blinded linaclotide dose received in the lead-in study LIN-MD-64 will continue to receive blinded linaclotide 145 or 290 µg once daily.
    - LIN-MD-64 completers who choose to receive open-label linaclotide therapy will receive linaclotide 290 µg once daily.

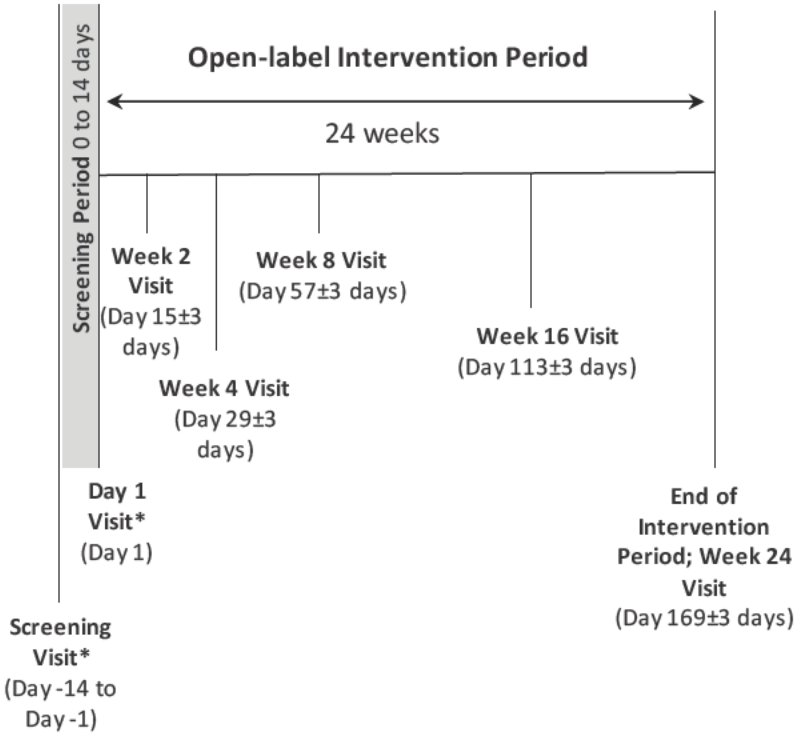
Participants will be instructed to take their assigned dose orally as a single daily dose at approximately the same time each day, 30 minutes prior to any meal, except for the Day 1 Visit, at which the linaclotide dose will be administered in the clinic.

Participants who took their last dose of lead-in study intervention on the day of the EOT Visit and enroll into LIN-MD-66 on that same day will take their first dose of LIN-MD-66 study intervention outside of the clinic the following day, at approximately the same time as the last dose in the lead-in study. Qualified site personnel will complete a follow-up phone call to participants within 48 hours following initial study intervention administration to assess safety.

Dose modifications permitted for FC and IBS-C participants are described in Section 6.6.

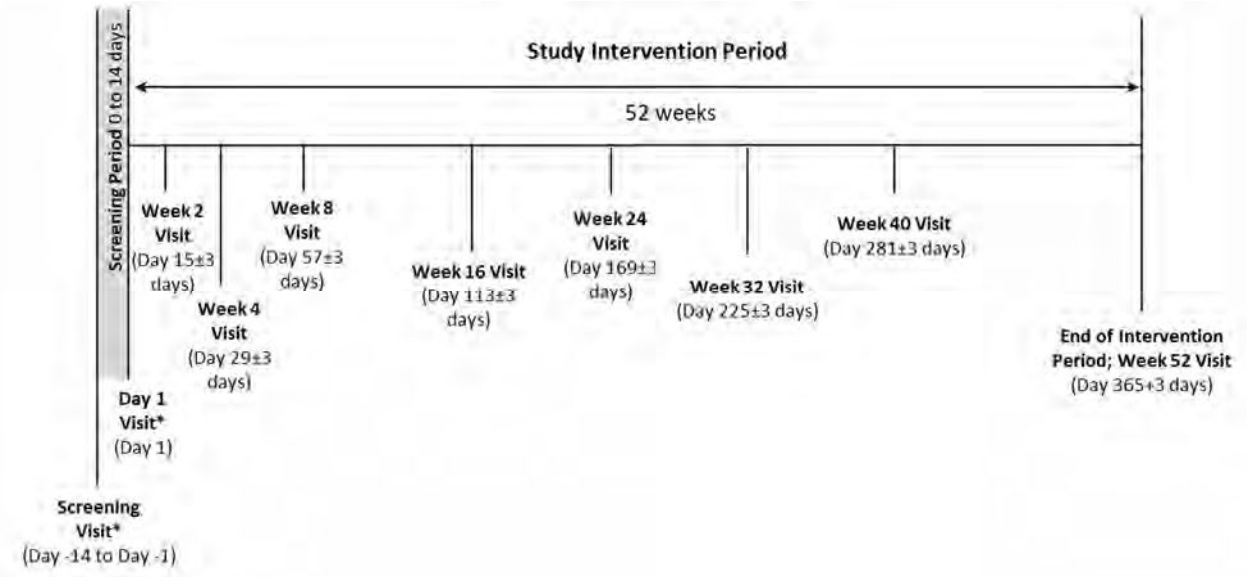
Data Monitoring Committee: Yes

1.2. Study Schema for FC Participants



* For participants who enroll in LIN-MD-66 on the same day as their EOT Visit or EOS Visit in LIN-MD-64, the EOT Visit or EOS Visit, respectively, may be combined with the Screening Visit (Visit 1). For participants who enroll within ≤ 28 days (inclusive) from last study intervention (Visit 7) in the LIN-MD-64 study, the Screening Visit (Visit 1) and Day 1 (Visit 2) procedures may be combined, with the exception of participants who are positive for fecal impaction assessment at Screening Visit.

1.3. Study Schema for IBS-C Participants



* For participants who enroll in LIN-MD-66 on the same day as their EOT Visit or EOS Visit in LIN-MD-63 or LIN-MD-64, the EOT Visit or EOS Visit, respectively, may be combined with the Screening Visit (Visit 1). For participants who enroll within ≤ 28 days (inclusive) from last study intervention in LIN-MD-63 (Visit 5) or LIN-MD-64 (Visit 7), the Screening Visit (Visit 1) and Day 1 (Visit 2) procedures may be combined, with the exception of participants who are positive for fecal impaction assessment at Screening Visit.

1.4. Schedule of Activities (SoA) for FC Participants

Table 1–1 Schedule of Activities - Phase 3 Study LIN-MD-64 FC Completers Who Enroll in Study LIN-MD-66 Within ≤ 28 Days From Last Study Intervention

Study Periods (Duration)	**Screening (Up to 14 days)**	**Study Intervention Period (24 weeks)**					
Study Visit[o]	**Screening**	**Day 1**	**Week 2**	**Week 4**	**Week 8**	**Week 16**	**Week 24 Visit/ EOT**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Study Day	**-14 to -1[a,b]**	**1[b]**	**15 (± 3)[c] (Phone Visit)**	**29 (± 3)**	**57 (± 3)**	**113 (± 3)**	**169 (+ 3)[d]**
Study Procedure							
Parent/caregiver consent/assent	X						
Inclusion and exclusion criteria	X	X					
Rome III assessment							X
IWRS	X	X		X	X	X	
Medical history	X						
Physical examination[e]							X
Fecal Impaction assessment[f]	X	X[g]					
Vital signs, and postural vital signs[h]		X		X	X	X	X
Height							X
Electrocardiogram							X
Prior and concomitant medication	X	X	X	X	X	X	X
Clinical laboratory tests[i]							X
Urine pregnancy test[j]	X	X		X	X	X	X
Study intervention administration in the clinic[l]		X[m]					
Adverse event evaluation[k]	X	X	X	X	X	X	X
Study intervention dispensed[n]		X		X	X	X	
Study intervention compliance and accountability				X	X	X	X

[a] Study procedures for screening may be combined with LIN-MD-64 EOT Visit.

[b] Provided there is no fecal impaction at Screening (Visit 1), study procedures for Screening (Visit 1) and Day 1 Visit (Visit 2) may be combined.

[c] Week 2 visit will be a phone visit for all participants.

[d] All enrolled participants who prematurely discontinue from the study, regardless of cause, are required to return for the EOT study assessments.

[e] Physical examinations will be performed by medically qualified site personnel at Visit 7 and may be done at the investigator's discretion at any time.

[f] 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 fecal impaction is documented during an optional repeat physical examination, the sponsor must be notified. 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.

[g] A fecal impaction assessment is performed at the study Day 1 Visit (Visit 2) prior to study intervention administration. If the participant is impacted at Visit 2, the participant would not be eligible for the study.

[h] Vital signs include weight, temperature (oral, rectal, or tympanic), and respiratory rate. 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.

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

[j] Urine pregnancy test will be performed in female participants of childbearing potential at Visit 1 and Visit 2 prior to dosing and at Visits 4 to 7 during study intervention. To continue in this study, a negative urine tests must be documented at Day 1 Visit (Visit 2) to start study intervention and at Visits 4 to 6 to continue study intervention. LIN-MD-64 completers who enroll in this study on the same day do not need to repeat the urine pregnancy test (Section 10.7).

[k] The ongoing AEs from LIN-MD-64 study will be transferred to LIN-MD-66 in the auto-rollover function in EDC.

[l] Study intervention will be administered in the clinic at the Day 1 Visit (Visit 2). On the day of this visit, all participants must fast for at least 2 hours before arriving at the clinic for their visit, where they will receive their initial dose of study intervention. Participants may eat 30 minutes after dosing (the requirement for linaclotide to be administered 30 minutes prior to any meal at the same time each day will not apply for the first dose). On all other days, it is recommended that participants take linaclotide at approximately the same time each day, 30 minutes before any meal.

[m] Participants who took their last dose of study intervention in LIN-MD-64 on the day of the EOT Visit and enroll into LIN-MD-66 on that same day will take their first dose of LIN-MD-66 study intervention outside of the clinic at a designated time the following day. Qualified site personnel will complete a follow-up phone call to participants within 48 hours following initial study intervention administration to assess safety.

[n] The number of bottles of study intervention that should be dispensed at each visit is as follows: V2 (1 bottle), V4 (1 bottle), V5 (2 bottles), and V6 (2 bottles) The bottles will be assigned via IWRS.

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

Table 1–2 Schedule of Activities - Phase 2 LIN-MD-62 and Phase 3 LIN-MD-64 FC Completers Who Enroll in LIN-MD-66 After > 28 Days From Last Study Intervention

Study Periods (Duration)	**Screening (Up to 14 days**	**Study Intervention Period (24 weeks)**					
Study Visit[m]	**Screening**	**Day 1**	**Week 2**	**Week 4**	**Week 8**	**Week 16**	**Week 24 Visit/ EOT**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Study Day	**-14 to -1**	**1**	**Day 15 (± 3)[a] (Phone Visit)**	**Day 29 (± 3)**	**Day 57 (± 3)**	**Day 113 (± 3)**	**Day (169+ 3)[b]**
Study Procedure							
Parent/caregiver consent/assent	X						
Inclusion and exclusion criteria	X	X					
Rome III assessment	X[n]						X
IWRS	X	X		X	X	X	
Medical history	X						
Lifestyle modifications review	X						
Physical examination[c]	X						X
Fecal impaction assessment[d]	X	X[e]					
Vital signs, and postural vital signs[f]	X	X		X	X	X	X
Height	X						X
ECG	X						X
Prior and concomitant medication	X	X	X	X	X	X	X
Clinical laboratory tests[g]	X						X
Urine drug screen[h]	X						
Serum pregnancy test[i]	X						
Urine pregnancy test[i]		X		X	X	X	X
Study intervention administration in the clinic[j]		X					
AE evaluation[k]	X	X	X	X	X	X	X
Study intervention dispensed[l]		X		X	X	X	
Study intervention compliance and accountability				X	X	X	X

[a] Week 2 visit (Visit 3) will be a phone visit for all participants.

[b] All enrolled participants who prematurely discontinue from the study, regardless of cause, are required to return for the EOT study assessments.

[c] Physical examinations performed by medically qualified site personnel at Visits 1 and 7 may be repeated at the investigator's discretion at any time.

[d] 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 fecal impaction is documented during an optional repeat physical examination, the sponsor must be notified. 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.

[e] A fecal impaction assessment is performed at the study Day 1 Visit (Visit 2) prior to study intervention administration. If the participant is impacted at Visit 2, the participant would not be eligible for the study.

[f] Vital signs include weight, temperature (oral, rectal, or tympanic), and respiratory rate. 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.

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

[h] The 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.

[i] A pregnancy test will be obtained for female participants of childbearing potential. Serum β-hCG will be performed at Screening (Visit 1), while urine pregnancy test will be performed at Visits 2 and 4 to 7 during study intervention. To continue in this study, a negative serum test must be documented at the Screening Visit (Visit 1) and negative urine tests must be documented at Day 1 Visit (Visit 2) to start study intervention and at Visits 4 to 6 to continue study intervention.

[j] Study intervention will be administered in the clinic at the Day 1 Visit (Visit 2). On the day of this visit, all participants must fast for at least 2 hours before arriving at the clinic for their visit, where they will receive their initial dose of study intervention. Participants may eat 30 minutes after dosing (the requirement for study intervention to be administered 30 minutes prior to any meal at the same time each day will not apply for the first dose). On all other days, it is recommended that participants take linaclotide at approximately the same time each day, 30 minutes before any meal.

[k] The ongoing AEs from LIN-MD-62 will be entered in the eCRF. The ongoing AEs from LIN-MD-64 will be transferred to LIN-MD-66 in the auto-rollover function in EDC.

[l] The number of bottles of study intervention that should be dispensed at each visit is as follows: V2 (1 bottle), V4 (1 bottle), V5 (2 bottles), and V6 (2 bottles).

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

[n] Rome III assessment at Screening will be assessed over the 2 month period immediately prior to the LIN-MD-66 Screening Visit (Visit 1), or over the 1 month period immediately prior to the LIN-MD-66 Screening Visit if 2 months have not elapsed.

1.5. Schedule of Activities (SoA) for IBS-C Participants

Table 1–3 Schedule of Activities - Phase 2 Study LIN-MD-63 and Phase 3 Study LIN-MD-64 IBS-C Completers Who Enroll in Study LIN-MD-66 Within ≤ 28 Days From the Last Study Intervention

Study Periods (Duration)	**Screening (Up to 14 days)**	**Study Intervention Period (52 weeks)**								
Study Visit[o]	**Screening**	**Day 1**	**Week 2**	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 32**	**Week 40**	**Week 52 Visit/ EOT**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Study Day	**-14 to -1[a,b]**	**1[b]**	**15 (± 3)[c] (Phone Visit)**	**29 (± 3)**	**57 (± 3)**	**113 (± 3)**	**169 (±3)**	**225 (±3)**	**281 (±3)**	**365 (+3)[d]**
Study Procedure										
Parent/caregiver consent/assent	X									
Inclusion and exclusion criteria	X	X								
Rome III assessment										X
IWRS	X	X		X	X	X	X	X	X	
Medical history	X									
Physical examination[e]										X
Fecal Impaction assessment[f]	X	X[g]								
Vital signs, and postural vital signs[h]		X		X	X	X	X	X	X	X
Height										X
Electrocardiogram										X
Prior and concomitant medication	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests[i]										X
Urine pregnancy test[j]	X	X		X	X	X	X	X	X	X
Study intervention administration in the clinic[l]		X[m]								

Study Periods (Duration)	Screening (Up to 14 days)	Study Intervention Period (52 weeks)								
Study Visit[o]	**Screening**	**Day 1**	**Week 2**	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 32**	**Week 40**	**Week 52 Visit/ EOT**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Study Day	**-14 to -1[a,b]**	**1[b]**	**15 (± 3)[c] (Phone Visit)**	**29 (± 3)**	**57 (± 3)**	**113 (± 3)**	**169 (±3)**	**225 (±3)**	**281 (±3)**	**365 (+3)[d]**
Adverse event evaluation[k]	X	X	X	X	X	X	X	X	X	X
Study intervention dispensed[n]		X		X	X	X	X	X	X	
Study intervention compliance and accountability				X	X	X	X	X	X	X

[a] Study procedures for screening may be combined with EOT Visit in study LIN-MD-63 or LIN-MD-64.

[b] Provided there is no fecal impaction at Screening (Visit 1), study procedures for Screening (Visit 1) and Day 1 Visit (Visit 2) may be combined.

[c] Week 2 visit will be a phone visit for all participants.

[d] All enrolled participants who prematurely discontinue from the study, regardless of cause, are required to return for the EOT study assessments.

[e] Physical examinations will be performed by medically qualified site personnel at Visit 10 and may be done at the investigator's discretion at any time.

[f] 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 fecal impaction is documented during an optional repeat physical examination, the sponsor must be notified. 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.

[g] A fecal impaction assessment is performed at the study Day 1 Visit (Visit 2) prior to study intervention administration. If the participant is impacted at Visit 2, the participant would not be eligible for the study.

[h] Vital signs include weight, temperature (oral, rectal, or tympanic), and respiratory rate. 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.

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

[j] Urine pregnancy test will be performed in female participants of childbearing potential at Visit 1 and Visit 2 prior to dosing and at Visits 4 to 10 during study intervention. To continue in this study, a negative urine tests must be documented at Day 1 Visit (Visit 2) to start study intervention and at Visits 4 to 9 to continue study intervention. LIN-MD-63 and LIN-MD-64 completers who enroll in this study on the same day do not need to repeat the urine pregnancy test (Section 10.7).

[k] The ongoing AEs from LIN-MD-63 will be entered in the eCRF. The ongoing AEs from LIN-MD-64 study will be transferred to LIN-MD-66 in the auto-rollover function in EDC.

[l] Study intervention will be administered in the clinic at the Day 1 Visit (Visit 2). On the day of this visit, all participants must fast for at least 2 hours before arriving at the clinic for their visit, where they will receive their initial dose of study intervention. Participants may eat 30 minutes after dosing (the requirement for linaclotide to be administered 30 minutes prior to any meal at the same time each day will not apply for the first dose). On all other days, it is recommended that participants take linaclotide at approximately the same time each day, 30 minutes before any meal.

[m] Participants who took their last dose of lead-in study intervention in LIN-MD-63 or LIN-MD-64 on the day of the EOT Visit and enroll into LIN-MD-66 on that same day will take their first dose of LIN-MD-66 study intervention outside of the clinic at a designated time the following day. Qualified site personnel will complete a follow-up phone call to participants within 48 hours following initial study intervention administration to assess safety.

[n] The number of bottles of study intervention that should be dispensed at each visit is as follows: V2 (1 bottle), V4 (1 bottle), V5 (2 bottles), V6 (2 bottles), V7 (2 bottles), V8 (2 bottles), and V9 (3 bottles). The bottles will be assigned via IWRS.

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

Table 1–4 Schedule of Activities – Phase 2 Study LIN-MD-63 and Phase 3 Study LIN-MD-64 IBS-C Completers Who Enroll in LIN-MD-66 After > 28 Days From Last Study Intervention

Study Periods (Duration)	**Screening (Up to 14 days**	**Study Intervention Period (52 weeks)**								
Study Visit[m]	**Screening**	**Day 1**	**Week 2**	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 32**	**Week 40**	**Week 52 Visit/ EOT**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Study Day	**-14 to -1**	**1**	**Day 15 (± 3)[a] (Phone Visit)**	**Day 29 (± 3)**	**Day 57 (± 3)**	**Day 113 (± 3)**	**Day 169 (± 3)**	**225 (±3)**	**281 (±3)**	**365 (+3)[b]**
Study Procedure										
Parent/caregiver consent/assent	X									
Inclusion and exclusion criteria	X	X								
Rome III assessment	X[n]									X
IWRS	X	X		X	X	X	X	X	X	
Medical history	X									
Lifestyle modifications review	X									
Physical examination[c]	X									X
Fecal impaction assessment[d]	X	X[e]								
Vital signs, and postural vital signs[f]	X	X		X	X	X	X	X	X	X
Height	X									X
ECG	X									X
Prior and concomitant medication	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests[g]	X									X
Urine drug screen[h]	X									
Serum pregnancy test[i]	X									
Urine pregnancy test[i]		X		X	X	X	X	X	X	X

Study Periods (Duration)	Screening (Up to 14 days	Study Intervention Period (52 weeks)								
Study Visit[m]	**Screening**	**Day 1**	**Week 2**	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 32**	**Week 40**	**Week 52 Visit/ EOT**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Study Day	**-14 to -1**	**1**	**Day 15 (± 3)[a] (Phone Visit)**	**Day 29 (± 3)**	**Day 57 (± 3)**	**Day 113 (± 3)**	**Day 169 (± 3)**	**225 (±3)**	**281 (±3)**	**365 (+3)[b]**
Study Procedure										
Study intervention administration in the clinic[j]		X								
AE evaluation[k]	X	X	X	X	X	X	X	X	X	X
Study intervention dispensed[l]		X		X	X	X	X	X	X	
Study intervention compliance and accountability				X	X	X	X	X	X	X

[a] Week 2 visit (Visit 3) will be a phone visit for all participants.

[b] All enrolled participants who prematurely discontinue from the study, regardless of cause, are required to return for the EOT study assessments.

[c] Physical examinations performed by medically qualified site personnel at Visits 1 and 10 may be repeated at the investigator's discretion.

[d] 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 fecal impaction is documented during an optional repeat physical examination, the sponsor must be notified. 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.

[e] A fecal impaction assessment is performed at the study Day 1 Visit (Visit 2) prior to study intervention administration. If the participant is impacted at Visit 2, the participant would not be eligible for the study.

[f] Vital signs include weight, temperature (oral, rectal, or tympanic), and respiratory rate. 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.

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

[h] The 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 7 to 11 years of age.

[i] A pregnancy test will be obtained for female participants of childbearing potential. Serum β-hCG will be performed at Screening (Visit 1), while urine pregnancy test will be performed at Visits 2 and 4 to 10 during study intervention. To continue in this study, a negative serum test must be documented at the Screening Visit (Visit 1) and negative urine tests must be documented at Day 1 Visit (Visit 2) to start study intervention and at Visits 4 to 9 to continue study intervention.

[j] Study intervention will be administered in the clinic at the Day 1 Visit (Visit 2). On the day of this visit, all participants must fast for at least 2 hours before arriving at the clinic for their visit, where they will receive their initial dose of study intervention. Participants may eat 30 minutes after dosing (the requirement for study intervention to be administered 30 minutes prior to any meal at the same time each day will not apply for the first dose). On all other days, it is recommended that participants take linaclotide at approximately the same time each day, 30 minutes before any meal.

[k] The ongoing AEs from LIN-MD-63 will be entered in the eCRF. The ongoing AEs from LIN-MD-64 study will be transferred to LIN-MD-66 in the auto-rollover function in EDC.

[l] The number of bottles of study intervention that should be dispensed at each visit is as follows: V2 (1 bottle), V4 (1 bottle), V5 (2 bottles), V6 (2 bottles), V7 (2 bottles), V8 (2 bottles), and V9 (3 bottles). The bottles will be assigned via IWRS.

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

[n] Rome III assessment at Screening will be assessed over the 2 month period immediately prior to the LIN-MD-66 Screening Visit (Visit 1), or over the 1 month period immediately prior to the LIN-MD-66 Screening Visit if 2 months have not elapsed.

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 guanylate cyclase subtype C (GC-C) receptor. Linaclotide is approved for the treatment of irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) in the United States, Canada, Japan, Australia, New Zealand, Kingdom of Saudi Arabia, and Mexico; for the treatment of IBS-C in China, the European Union (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 intestinal fluid secretion and intestinal transit, and to 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 (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 (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.

This study will assess the long-term safety of linaclotide administered to pediatric participants with FC (total exposure with linaclotide for 24 weeks) or IBS-C (total exposure with linaclotide for 52 weeks) who have completed Study LIN-MD-62, LIN-MD-63, or LIN-MD-64:

- LIN-MD-62 (Phase 2): A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Safety and Efficacy Study of a Range of Linaclotide Doses Administered Orally to Children, Ages 6 to 17 Years, Who Fulfill Modified Rome III Criteria for Child/Adolescent FC
- LIN-MD-63 (Phase 2): A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Safety and Efficacy Study of a Linaclotide Dose Administered Orally to Children, Ages 7 to 17 Years, With Irritable Bowel Syndrome With Constipation (IBS-C) (ie, Fulfill Rome III Criteria for Child/Adolescent IBS and Fulfill Modified Rome III Criteria for Child/Adolescent Functional Constipation)
- LIN-MD-64 (Phase 3): 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)

2.1. 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 nonpharmacological interventions include education, behavioral modifications, and keeping a bowel diary. Despite these interventions, many children require pharmacological interventions. Treatment consists of disimpaction (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, 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).

The primary objective of this study (LIN-MD-66) is to assess the long-term safety of linaclotide administered to participants with FC (total exposure with linaclotide for 24 weeks) or IBS-C (total exposure with linaclotide for 52 weeks) who have completed Study LIN-MD-62, LIN-MD-63, or LIN-MD-64.

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 doses for the treatment of CIC and 290 µg dose 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.

- 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 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.

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 only in China. Results from these studies were consistent with those reported for the 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 Study LIN-MD-62 was to evaluate the dose response, safety, and efficacy of 4 weeks of study intervention with 1 of 3 linaclotide doses (Dose A, B, and C) or 145 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, who fulfilled modified Rome III criteria for child/adolescent FC with the goal of selecting an optimal dose of linaclotide to evaluate in a confirmatory study.

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

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

A total of 173 participants were randomized to receive 1 of 3 proposed linaclotide doses (Dose A, B, or C in 116 participants), the approved adult linaclotide dose (145 µg in 16 participants), or placebo (41 participants) for 4 weeks of study intervention followed by a 1-week Postintervention Period. For the primary and key secondary endpoints of the 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. 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.

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 Nonclinical Information

2.2.3.1. Non-clinical Toxicology

In nonclinical studies, oral administration of linaclotide at 10 µg/kg/day caused deaths in young neonatal mice (human age equivalent of approximately 0 to 28 days old). These deaths were due to rapid and severe dehydration produced by significant fluid shifts into the intestinal lumen resulting from GC-C agonism in neonatal mice. Supplemental subcutaneous fluid administration prevented death after linaclotide administration in neonatal mice. Tolerability to linaclotide increases with age in juvenile mice. In 2-week-old mice, linaclotide was well tolerated at a dose of 50 µg/kg/day, but deaths occurred after a single oral dose of 100 µg/kg. In 3-week-old mice, linaclotide was well tolerated at 100 µg/kg/day, but deaths occurred after a single oral dose of 600 µg/kg. Significantly higher doses (≥ 200 times the clinically relevant adult dose) were tolerated in 4-week-old juvenile mice, human age equivalent of approximately > 2 to 7 years of age without supplemental fluid administration. Based on these nonclinical results, the Linzess PI has a contraindication in pediatric patients less than 6 years of age and a boxed warning regarding its use in pediatric patients.

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, 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.

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. 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 (linaclotide IB).

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 at the same time for the 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 Assessments

Objectives	Assessments
Primary	
The objective of this study is to assess the long-term safety of linaclotide in pediatric participants with FC (total exposure with linaclotide for 24 weeks) or IBS-C (total exposure with linaclotide for 52 weeks) who have completed Study LIN-MD-62, LIN-MD-63, or LIN-MD-64.	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.

4. Study Design

4.1. Overall Design

LIN-MD-66 is a long-term safety study with 24 weeks (FC participants) or 52 weeks (IBS-C participants) of linaclotide exposure that will enroll pediatric participants (6-17 years of age) with FC or IBS-C who completed study intervention in Phase 2 study LIN-MD-62 or LIN-MD-63, or Phase 3 study LIN-MD-64, based on the individual study criteria. For FC participants enrolling from studies LIN-MD-62 and LIN-MD-64, and IBS-C participants enrolling from study LIN-MD-63, linaclotide treatment will be open-label. For IBS-C participants enrolling from study LIN-MD-64, linaclotide treatment will be either blinded or open-label. Linaclotide treatment will be blinded if participants choose to remain on the same blinded linaclotide dose they were receiving in the lead-in LIN-MD-64 study and it will be open-label if participants choose to receive open-label linaclotide therapy.

- Phase 2 completers are defined as pediatric participants who completed 4-week double-blind study intervention and EOT Visit (Visit 5) in the Phase 2 studies AND:
  - Completed the EOS (Visit 6) in Study LIN-MD-62 **or**
  - Completed the EOS (Visit 6) in Study LIN-MD-63. However, the EOS Visit is not required for participants who enroll prior to that visit.
- Phase 3 completers are pediatric participants who completed 12-week double-blind study intervention in Study LIN-MD-64. Participants must have completed the EOT Visit (Visit 7) and the EOS Visit (Visit 8). However, the EOS visit is not required for participants who enroll prior to that visit.

The present study will include a screening period and a 24-week (FC participants) or 52-week (IBS-C participants) study intervention period (Section 1.2 and Section 1.3, respectively). For participants who enroll in LIN-MD-66 on the same day as their EOT Visit or EOS Visit in LIN-MD-63 or LIN-MD-64, the EOT Visit or EOS Visit, respectively, may be combined with the Screening Visit (Visit 1) and Day 1 Visit (Visit 2) in LIN-MD-66. For participants who enroll within ≤ 28 days (inclusive) from last study intervention in Study LIN-MD-64 (Visit 7) or Study LIN-MD-63 (Visit 5), the LIN-MD-66 Screening Visit (Visit 1) and Day 1 Visit (Visit 2) procedures may be combined, with the exception of participants who are positive for fecal impaction assessment at the Screening Visit (Visit 1).

All participants are required to have a fecal impaction assessment prior to dosing. For those participants who do not combine Visit 1 and Visit 2, a fecal impaction assessment will be

performed at the Screening Visit (Visit 1) and at the Day 1 Visit (Visit 2) prior to dosing. Please refer to Section 8.2.1 for further details.

Participants who turn 18 years of age during study LIN-MD-63 or LIN-MD-64, or after completing the lead-in study, may be eligible if they enroll within 28 days (inclusive) of the last day of study intervention in the lead-in study (Study LIN-MD-64 [Visit 7] or Study LIN-MD-63 [Visit 5]). Such participants will be dosed as 17-year-old participants; refer to the Intervention Groups and Study Duration section below for dosing.

Number of Participants:

At least 120 participants are planned to be enrolled to receive 24 weeks (FC participants) or 52 weeks (IBS-C participants) of linaclotide study intervention. However, the actual number of participants in this study will depend on the number of participants who have completed study intervention in the lead-in study (LIN-MD-62, LIN-MD-64, and LIN-MD-63) and enroll into this long-term safety study after fulfilling the eligibility criteria.

Number of Sites:

Up to 120 sites from the United States, Canada, Europe, and the Middle East will have an option to participate in the study.

Intervention Groups and Study Duration:

FC participants (LIN-MD-62 and LIN-MD-64 completers) will receive open-label linaclotide 72 µg or 145 µg once daily for 24 weeks as follows based on their age at the time of enrollment into LIN-MD-66:

- 6 to 11 years of age: 72 µg linaclotide
- 12 to 17 years of age: will be randomly assigned at 1:1 ratio to 72 µg linaclotide or 145 µg linaclotide

IBS-C participants will receive linaclotide for 52 weeks as follows:

- LIN-MD-63 completers will receive open-label linaclotide 290 µg once daily except for the LIN-MD-63 completers who had received ≤ 145 µg linaclotide or placebo. These participants will have the option to receive open-label linaclotide 145 µg once daily.

- LIN-MD-64 completers will have the option to either remain on the same blinded linaclotide dose they were receiving in lead-in study LIN-MD-64 or to receive open-label 290 µg linaclotide. Study intervention in LIN-MD-66 is assigned via IWRS; treatment assignments for LIN-MD-64 completers who choose to remain on the same blinded linaclotide dose in long-term safety study LIN-MD-66 will remain blinded to participants, investigators, and all site personnel during the study.
    - LIN-MD-64 completers who choose to remain on the same blinded linaclotide dose received in the lead-in study LIN-MD-64 will continue to receive blinded linaclotide 145 or 290 µg once daily.
    - LIN-MD-64 completers who choose to receive open-label linaclotide therapy will receive linaclotide 290 µg once daily.

Participants will be instructed to take their assigned dose orally as a single daily dose at approximately the same time each day, 30 minutes prior to any meal, except for the Day 1 Visit, at which the linaclotide dose will be administered in the clinic.

Participants who took their last dose of lead-in study intervention on the day of the EOT Visit and enroll into LIN-MD-66 on that same day will take their first dose of LIN-MD-66 study intervention outside of the clinic the following day, at approximately the same time as the last dose in the lead-in study. Qualified site personnel will complete a follow-up phone call to participants within 48 hours following initial study intervention administration to assess safety.

Dose modifications permitted for FC and IBS-C participants are described in Section 6.6.

Detailed descriptions of each study visit can be found in the SoA (Section 1.4 for FC participants, Section 1.5 for IBS-C participants) and Section 10.10.

4.2. Scientific Rationale for Study Design

The Phase 2 studies LIN-MD-62, LIN-MD-63, and the Phase 3 study, LIN-MD-64 will provide placebo-controlled information on the safety and efficacy of linaclotide for the treatment of pediatric participants with FC and IBS-C. This study, LIN-MD-66, will provide additional information on the long-term safety of linaclotide in the 6 to 17-year-old pediatric population.

4.3. Justification for Doses

The linaclotide dosages chosen for FC participants in this long-term safety study (72 and 145 µg) were well tolerated among participants 6 to 17 years of age with FC in LIN-MD-62. The safety profile was consistent with prior adult linaclotide studies for CIC. FC participants 6 to 17 years of

age who complete either LIN-MD-62 or LIN-MD-64, will have the option to enroll into this study. FC participants, 6 to 11 years of age, will receive open-label 72 µg linaclotide. FC participants, 12 to 17 years of age, will be randomly assigned open-label linaclotide at a 1:1 ratio to 72 µg linaclotide or 145 µg linaclotide.

The linaclotide doses of 290 µg or 145 µg once daily chosen for IBS-C participants in this long-term safety study were well tolerated among participants 12 to 17 years of age (290 µg dose) and 6 to 17 years of age (145 µg dose) with IBS-C in LIN-MD-63. The safety profile was consistent with prior adult linaclotide studies for IBS-C. While the 290 µg linaclotide dose is the highest dose being evaluated in IBS-C participants 6 to 17 years of age in the lead-in Phase 3 study LIN-MD-64, LIN-MD-63 completers who received ≤ 145 µg linaclotide or placebo in LIN-MD-63 will have the option to receive open-label linaclotide 145 µg once daily for 52 weeks. LIN-MD-64 completers with IBS-C will have the option to either remain on the same blinded linaclotide dose they were receiving in lead-in study LIN-MD-64 (blinded linaclotide 290 µg or 145 µg once daily) or to receive open-label linaclotide 290 µg once daily.

Dose modifications permitted for FC and IBS-C participants are described in Section 6.6.

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 in the study including the last visit.

5. Study Population

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

Participants who have completed the lead-in Phase 2 (LIN-MD-62 or LIN-MD-63) or Phase 3 (LIN-MD-64) studies must meet all the inclusion and exclusion criteria as described in the following sections.

Where applicable for this pediatric population, the term “participant” refers to the participant, parent, guardian, legally authorized representative (LAR), and/or caregiver.

5.1. Inclusion Criteria

Specific inclusion and exclusion criteria are presented individually for the following participant populations who completed the following studies per the individual protocols.

5.1.1. General Inclusion Criteria (All Participants)

1.01 Participant weighs ≥ 18 kg at the time the parent/guardian/LAR and/or caregiver has provided signed consent.

1.02 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 Appendix 7.

1.03 Male or female participants must be 6 to 17 years of age (inclusive), at the time the parent/guardian/LAR and/or caregiver provides written informed consent and the participant must provide assent before the initiation of any study-specific procedures.

1.04 Participants must have completed study intervention in their lead-in study as defined in Section 4.1.

1.05 Female participants of childbearing potential must have a negative pregnancy test at both Screening (Visit 1) and at Study Day 1 (Visit 2) (Section 1.4 [SoA] and Section 10.7).

5.1.2. Inclusion Criteria for Phase 3 LIN-MD-64 Completers and Phase 2 LIN-MD-63 Completers Who Enroll in LIN-MD-66 Within ≤ 28 Days From Last Study Intervention

2.01 Participants who turn 18 years of age prior to enrollment must provide consent for the study.

5.1.3. Inclusion Criteria for Phase 2 LIN-MD-62 or Phase 2 LIN-MD-63 and Phase 3 LIN-MD-64 Completers Who Enroll in LIN-MD-66 After > 28 Days From Last Study Intervention

3.01 Female participants of childbearing potential must have a negative serum pregnancy test at the Screening Visit (Visit 1) and negative urine pregnancy test prior to the first dose on the Day 1 Visit (Visit 2).

3.02 This criterion has been removed.

3.03 This criterion has been removed.

5.2. Exclusion Criteria

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

5.2.1. General Exclusion Criteria (All Participants)

1.01 Participant has an unresolved AE or a clinically significant finding on a physical examination or vital sign assessment along with ECG or clinical laboratory tests (if results are available by the time of enrollment) that; in the opinion of the investigator, 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.

1.02 Participant has a known allergy or sensitivity to the study intervention or its components or other medications in the same drug class.

1.03 Participant is not willing or able to abide by the restrictions regarding concomitant medicine use defined in Section 6.5.

1.04 Participant received an investigational drug, other than linaclotide, during the 30 days before the Screening Visit (Visit 1) or is planning to receive an investigational drug (other than that administered during this study) or use an investigational device at any time during the study.

1.05 Female participants who are currently pregnant or nursing, or plan to become pregnant or nurse during the clinical study.

1.06 Participant has fecal impaction at the Day 1 Visit (Visit 2).

1.07 Participant has required manual disimpaction any time prior to study intervention.

1.08 Participant has any of the following conditions:

a) Down's syndrome or any other chromosomal disorder
b) Anatomic malformations (eg, imperforate anus, anal stenosis, anterior displaced anus)

c) Intestinal nerve or muscle disorders (eg, Hirschprung disease, visceral myopathies, visceral neuropathies)
d) Neuropathic conditions (eg, spinal cord abnormalities, neurofibromatosis, tethered cord, spinal cord trauma)
e) 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 by the participant

1.09 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.

1.10 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.

1.11 Participant has a known or suspected mechanical bowel obstruction or pseudo-obstruction.

1.12 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.

1.13 Participant has an active anal fissure (Note: history of anal fissure is not an exclusion).

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 (Visit 1).
b) Surgery of the abdomen, pelvis, or retroperitoneal structures during the 6 months before the Screening Visit (Visit 1)
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 (Visit 1)

1.15 This criterion has been removed.

1.16 This criterion has been removed.

5.2.2. Exclusion Criteria for LIN-MD-62, LIN-MD-63 and LIN-MD-64 Completers Who Enroll in LIN-MD-66 > 28 Days From Last Study Intervention

2.01 Participant has a history of nonretentive fecal incontinence.

2.02 This criterion has been removed.

2.03 Participant has a history of drug or alcohol abuse.

2.04 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 1)
d) Lead toxicity, hypercalcemia
e) Inflammatory bowel disease
f) Childhood functional abdominal pain syndrome
g) Childhood functional abdominal pain
h) Poorly treated or poorly controlled psychiatric disorders that might influence his or her ability to participate in the study
i) Lactose intolerance that is associated with abdominal pain or discomfort and could confound the assessments in this study
j) 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.)
k) History of diabetic neuropathy

2.05 Participants who have positive urine drug screen results for cocaine, barbiturates, opiates, or cannabinoids.

Rationale for Inclusion and Exclusion Criteria

The inclusion and exclusion criteria are meant to identify a population of participants that is well characterized as having FC or IBS-C symptoms as defined by Rome III criteria. This population has been previously studied in studies LIN-MD-62, LIN-MD-63, or LIN-MD-64 during which the safety and efficacy of study intervention was assessed.

5.3. Lifestyle Considerations

Not applicable.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered into 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 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 under special circumstances (eg, failure to meet prohibited medication requirements). All requests for rescreening must be sent to the sponsor for approval.

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.

The study intervention in this study does not have marketing authorization in the EU for the pediatric indication.

6.1. Study Intervention Administered

Linaclotide in the form of capsules will be packaged in bottles and provided by the sponsor. Participants will be instructed to take their assigned dose orally as a single daily dose at approximately the same time each day, 30 minutes prior to any meal, except for the Day 1 Visit, at which the linaclotide dose will be administered 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.

Study Intervention Name	Linaclotide
Dosage Formulation	Capsules
Unit Dose Strength	72 µg, 145 µg, or 290 µg
Route of Administration	Oral; capsule may be taken whole, or sprinkled into 30 mL of bottled water or applesauce for participants who do not wish to take a capsule
Dosing Instructions	Single dose, once daily at the same time each day, 30 minutes before any meal, except for the Day 1 Visit, at which the linaclotide dose will be administered in the clinic. Instructions for sprinkled dose are provided in Appendix 8.
Packaging and Labeling	All bottles will be labeled with the protocol number, storage information, and warning language (viz, "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.

6.2. 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 intervention in bottles containing solid oral 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 to 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 intervention supplied and for ensuring the supervision of the storage and allocation of these supplies. All unused study intervention must be returned and, whenever study intervention is returned, unit counts must be performed. All study intervention must be accounted for. At the end of the study, all unused study intervention and empty study intervention bottles 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

Participants with FC, 12 to 17 years of age, will be randomly assigned at a 1:1 ratio to 72 µg linaclotide or 145 µg linaclotide.

6.3.1. Blinding and Unblinding

6.3.1.1. Blinding

Study intervention in LIN-MD-66 is assigned via IWRS. For LIN-MD-64 completers with IBS-C who choose to remain on the same blinded linaclotide dose they were receiving in the lead-in study LIN-MD-64, participants, investigators, and all site personnel will remain blinded to the individual treatment assignments until all subjects have completed the study and the database has been locked, except in the case of emergency unblinding described below.

6.3.1.2. Unblinding

Any unblinding at the study site level should be done only in an emergency that requires 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 discontinued from study drug.

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 each visit, study site personnel will make every effort to collect all unused study intervention and empty 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.

Study 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 in this study (LIN-MD-66). Concomitant medication is defined as any medication taken on or after the date of the first dose of study intervention in this study. Any medication started after last dose date 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 medication within each therapeutic class.

Multiple medication use by a participant in the same category (based on Anatomical Therapeutic Chemical classification) will only be counted once.

For all participants, any changes in concomitant medications or new medications added will be recorded in the eCRF at visits throughout the study.

The following medicines are excluded during the study, including screening and study intervention periods:

- Lubiprostone
- Plecanatide
- Prucalopride
- Narcotics either alone or in combination (eg, tramadol, codeine, morphine, propoxyphene, loperamide, diphenoxylate, paregoric) if they are being used chronically (ie, 5 days or longer) and are expected to be taken indefinitely in the future

Any investigational or imported drugs that have not been approved for human use.

6.6. Dose Modification

At the discretion of the investigator, any participant who experiences an AE intolerable enough to prompt a consideration of study withdrawal may receive a temporary suspension of dosing. The duration of a dosing suspension will be at the investigator's discretion; however, after a participant has been off study intervention for 3 days, or if the participant requires a suspension of dosing on more than 1 occasion, the investigator must contact the sponsor to discuss the participant's continued participation in the study.

Participants who experience an intolerable AE that may be related to the use of linaclotide can be dose reduced one dose level only during the course of the study at the investigator's discretion as shown in Table 6-1. Subsequent dose adjustments (between the initial dose and reduced dose) are also permitted at the investigator's discretion. Participants receiving blinded linaclotide treatment will be dose adjusted in a blinded fashion via IWRS.

Table 6-1 Dose Reductions

	IBS-C				FC	
	Open-label (µg)		Blinded (µg)		Open-label (µg)	
Initial dose	290	145	290	145	145	72
Reduced dose	145	72	145	72	72	N/A

The decision of whether to temporarily suspend dosing or dose reduce following the occurrence of an intolerable AE is per the investigator's discretion.

6.7. Intervention after the End of the Study

No intervention is planned after the end of the study.

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 and/or caregiver 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.

See the SoAs 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
AE	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 participant	

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, treatment-related AESIs)
- Pregnancy
- 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) (refer to Appendix 9), or if the investigator believes that it is in best interest of the participant.

All enrolled participants who prematurely discontinue from the study, regardless of cause, are required to return for the EOT study assessments. The EOT assessments are defined as completion of the 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 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 SoAs for data to be collected at the time of 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 the DSMB recommendation or if, following a thorough review of all clinical, laboratory, and other available safety data, safety data become available which appear 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 request, at the request of his/her parent/guardian/LAR and/or caregiver 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 his/her parent/guardian/LAR and/or caregiver 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 intervention discontinuation and follow-up and for any further evaluations that need to be completed.

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/or the parent/guardian/LAR and/or caregiver 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 source record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study 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 5 mL for Phase 2 LIN-MD-63 and Phase 3 LIN-MD-64 participants who enroll in LIN-MD-66 within ≤ 28 days of last study intervention in the lead-in studies and will not exceed 10 mL for LIN-MD-62, LIN-MD-63, or LIN-MD-64 completers who enroll in LIN-MD-66 > 28 days from last study intervention. 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

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 for FC participants and Visit 10 for IBS-C participants) as an additional efficacy assessment.

- For participants who enroll in LIN-MD-66 within ≤ 28 days since last study intervention in lead-in study LIN-MD-64, the Week 12 Visit/EOT Rome III assessment will be used as the Screening Visit assessment in LIN-MD-66.
- For participants who enroll in LIN-MD-66 after > 28 days from last study intervention in their lead-in study, Rome III assessment at Screening will be assessed over the 2 month period immediately prior to the LIN-MD-66 Screening Visit (Visit 1), or over the 1 month period immediately prior to the LIN-MD-66 Screening Visit if 2 months have not elapsed.

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 FC or IBS-C. For the EOT assessment, the criteria will be assessed over the last 4 weeks of the study intervention period. In the event a participant discontinues the study prematurely, these criteria will be assessed over the last 4 weeks of study intervention, or over the duration of study intervention if less than 4 weeks.

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.

The safety parameters will comprise physical examination, AEs, clinical laboratory parameters (clinical chemistry, CBC, urinalysis), vital signs, postural vital signs, height, weight, and ECG.

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

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 SoAs (Section 1.4 FC participants and Section 1.5 IBS-C participants).

8.2.1. Physical Examinations

A complete physical examination will be done

- At screening for participants who enroll > 28 days after completion of the lead-in studies
- At the EOT Visit for all FC participants (Week 24) and all IBS-C participants (Week 52).

Physical examinations may be repeated at the investigator's discretion. Any new significant physical examination abnormalities for the postbaseline physical examination or worsening of the change 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.

All participants are required to have a fecal impaction assessment prior to dosing. For those participants who do not combine Visit 1 and Visit 2, a fecal impaction assessment will be performed at the Screening Visit (Visit 1) and at the Day 1 Visit (Visit 2) prior to dosing. 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 the Screening Visit (Visit 1), Visit 1 and Visit 2 cannot be combined. Participants will receive a disimpaction 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). The fecal impaction assessment will be repeated for all participants at Visit 2 (if visits are not combined) prior to study intervention administration. If there is no fecal impaction, the participant may enter the study intervention period. If fecal impaction is present during the Visit 2 assessment, the participant will not be eligible for the study.

For those participants who plan to combine Visit 1 and Visit 2, a fecal impaction assessment will be performed prior to receiving study intervention. If there is no fecal impaction, the participant may enter the study intervention period. If fecal impaction is present during this assessment participants will receive a disimpaction 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). The participant will need to return for a Visit 2 where the fecal impaction assessment will be repeated. If fecal impaction is present during this repeat assessment, the participant will not be eligible for the study.

If fecal impaction is documented during an optional repeat physical examination, the sponsor must be notified.

8.2.2. Vital Signs

Refer to the appropriate SoAs for the timing and frequency of height and vital signs measurements (Section 1.4 FC participants and Section 1.5 IBS-C participants).

Vital signs will be assessed as follows:

- Vital signs include weight, temperature (oral, rectal, or tympanic), and respiratory rate. 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.
- 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.

8.2.3. Electrocardiograms

A standard 12-lead ECG will be performed at Screening (Visit 1) for participants who complete LIN-MD-62 and participants who enroll in LIN-MD-66 after > 28 days from last study intervention in LIN-MD-63 or LIN-MD-64. In addition, ECGs will be performed at the EOT Visit for all FC participants (Week 24) and all IBS-C participants (Week 52). 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 (Appendix 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 (Appendix 3).

The overall interpretation and determination of the clinical relevance of ECG findings using the central ECG interpretation report will be the responsibility of the investigator and 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. Only ECGs done at unscheduled visits will be recorded as unscheduled ECGs. All readable ECGs received by the vendor shall be sent for cardiologist over-read. The sponsor will receive all ECG data,

including cardiologist over-read interpretation, in the data transfer, including those 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 SoAs (Section 1.4 FC participants and Section 1.5 IBS-C participants) for the timing and frequency.

For all participants:

- At Screening (Visit 1), the investigator will assess the clinical significance of any laboratory values outside the reference ranges for clinical labs done at EOT in the lead-in study, if applicable, or done at Screening, 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 Appendix 2, must be conducted in accordance with the SoAs 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 (Appendix 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 (Appendix 3).

- A pregnancy test will be obtained for female participants of childbearing potential. Serum β-hCG will be performed at Screening (Visit 1) for participants who complete LIN-MD-62, LIN-MD-63, and LIN-MD-64 and enroll in LIN-MD-66 after > 28 days from last study intervention in the lead-in studies. Urine pregnancy test will be performed at Screening (Visit 1) for participants who complete LIN-MD-62, LIN-MD-63, and LIN-MD-64 and enroll in LIN-MD-66 after ≤ 28 days from last study intervention in the lead-in studies. LIN-MD-64 completers who enroll in this study on the same day as their EOT Visit in the lead-in study do not need to repeat the urine pregnancy test. Urine pregnancy test will be performed at Day 1 for all study participants prior to dosing and during study intervention period as specified in the SoAs (Section 1.4 and Section 1.5).
- Positive results on the pregnancy test at Screening (Visit 1) or Day 1 Visit (Visit 2) will exclude participants from enrolling in the study. Positive pregnancy test results during the study 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 5, Section 5.1.1). 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 Appendix 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 Appendix 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 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 AE of special interest has been met. All AESIs must be reported to the sponsor as described in Appendix 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 SAE 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 SoAs (Section 1.4 and Section 1.5), 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 SoAs (Section 1.4 and Section 1.5), 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 (including serious AESIs) will be recorded and reported to the sponsor or designee within 24 hours on an SAE form, as indicated in Appendix 3. Nonserious 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 Appendix 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 nonleading 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 Appendix 3) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). 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.

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 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.

Additional information is provided in Appendix 3 for the recording and follow-up of AEs and SAEs.

8.3.6. Pregnancy

- Details of all pregnancies that occur in female participants after the start of study intervention, from the time the ICF was signed until 30 days after the last dose of study intervention, will be collected.
- 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 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/device
- 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

Not applicable

8.6. Pharmacodynamics

Not applicable

8.7. Genetics

Not applicable

8.8. Biomarkers and Other Assessments

Not applicable

8.9. Health Economics

Not applicable

9. Statistical Considerations

9.1. Statistical Hypotheses

There are no preconceived statistical hypotheses to be assessed in this long-term safety study.

9.2. Sample Size Determination

At least 120 participants are planned to be enrolled in this long-term safety study, LIN-MD-66. However, the actual number of participants in this study will depend on the number of participants who complete the lead-in studies (LIN-MD-62, LIN-MD-63, and LIN-MD-64) and who are eligible to be enrolled into this long-term study after fulfilling the eligibility criteria. The sample size in this study is not driven by any statistical consideration.

9.3. Populations for Analyses

For this long-term safety study, only 1 analysis population, ie, Safety Population, is considered. The Safety Population is defined as all treated study participants who receive/take ≥ 1 administration of study intervention in this study. Participants will be summarized according to the study intervention they actually received.

9.4. Statistical Analyses

The Statistical Analysis Plan (SAP) will be developed and finalized before database lock.

The summary of the other efficacy endpoint of proportion of participants who no longer fulfill Rome III criteria at the end of the study intervention period will be discussed in the SAP.

This section is a summary of the planned statistical analyses for safety. Further details will be included in the SAP. All safety analyses or summaries will be performed using the Safety Population, for overall and for each age group (unless mentioned otherwise) by study intervention group separately for the FC and IBS-C pediatric populations.

The safety parameters will include AEs, clinical laboratory parameters, vital sign measurements, weight, height, and ECG parameters. For each safety parameter, the baseline value for all analyses of the corresponding safety parameter (laboratory, vital signs, body weight, height, and ECG) will be defined as below:

1) If participants enroll into LIN-MD-66 within 28 days of last dose date of the lead-in study, baseline of the lead-in study will be used as the baseline value in LIN-MD-66.
2) If participants enroll into LIN-MD-66 after 28 days of last dose date of the lead-in study, the last non-missing assessment made before the first dose of study intervention in this study will be used as the baseline value in LIN-MD-66.

Safety data analyses will be provided descriptively based on the observed safety data, without data imputation for missing safety parameter assessment(s).

9.4.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 23.0 or newer.

An AE will be considered a TEAE if:

- The AE began on or after the date of the first dose of study intervention in LIN-MD-66; or
- The AE was present before the date of the first dose of study intervention in LIN-MD-66 but increased in severity or became serious on or after the date of the first dose of study intervention in LIN-MD-66.

An AE that occurs more than 1 day after the last dose of study intervention in LIN-MD-66 will not be counted as a TEAE.

An AE will be considered a treatment-emergent SAE (TESAE) 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 SOC 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 relationship to study intervention.

Summary tables will be provided for participants with TESAEs, AESIs, and participants with TEAEs 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 Appendix 3.

9.4.2. Clinical Laboratory Assessments

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

The criteria for 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. The percentages will be calculated relative to the number of participants who have available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided for the Safety Population.

9.4.3. Vital Signs

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

Vital sign values will be considered to be PCS values if they meet both the observed-value criteria and the change-from-baseline-value criteria (as defined in the SAP). The number and percentage of participants who have PCS postbaseline vital sign values will be tabulated by study intervention group. The percentages will be calculated relative to the number of participants who have available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided for the Safety Population.

9.4.4. Electrocardiograms

Descriptive statistics for ECG parameters (ie, ventricular heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc) 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. 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 1 postbaseline assessment. The numerator will be the total number of participants with available non-PCS baseline values and at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided for the Safety Population.

9.5. Interim Analyses

An interim analysis to assess long-term safety of linaclotide may be performed after at least 120 participants have completed the study. Data will be locked after performing data cleaning. Results from the interim analysis will be described in an interim clinical study report.

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

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 and/or the caregiver of each participant participating in a clinical research study. 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/EC; 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/EC 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 the participant's 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 eCRFs 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 eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- 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 eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

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.

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

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. 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 documents 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 subinvestigators listed on Form FDA 1572, including a copy of each physician's license
- A copy of the original IRB/EC 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/EC, as stated in Section 10.1.1.
- A copy of the IRB/EC-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/EC 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 the study 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 SoAs (Section 1.4 and Section 1.5). 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 AE of special interest) must be reported to the sponsor within 24 hours on an SAE form if considered to be serious. Nonserious events do not require submission on an SAE form; rather, these events only need to be entered into the eCRF (Appendix 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 decision.

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.

For female participants of childbearing potential urine pregnancy test will be obtained at Screening (Visit 1) for participants who enroll ≤ 28 days from last study intervention and serum pregnancy test will be obtained at Screening (Visit 1) for participants who enroll > 28 days from last study intervention. Urine pregnancy test will be performed for all participants at the Day 1 Visit (Visit 2) prior to dosing as specified in the SoAs (Section 1.4 and Section 1.5) and Visits 4 to 7 during study intervention for FC participants and Visits 4 to 10 for IBS-C participants. Positive results on the pregnancy test at Screening (Visit 1) or Day 1 Visit (Visit 2) will exclude participants from participating in the study. Positive pregnancy test results during the study 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. 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 tests will be completed on site 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)	Potassium	Aspartate aminotransferase (AST)	Total, direct and indirect bilirubin
	Creatinine	Sodium Bicarbonate Magnesium Phosphate Total Protein Total Bilirubin	Alanine aminotransferase (ALT)	Total protein Total Cholesterol chloride, albumin
	Glucose nonfasting	Calcium	Alkaline phosphatase	
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 childbearing potential: Serum human chorionic gonadotropin (hCG) pregnancy test at screening for LIN-MD-62, LIN-MD-63, and LIN-MD-64 completers who enroll > 28 days from last study intervention; urine pregnancy test for participants who enroll ≤ 28 days from last study intervention[b]. LIN-MD-64 completers who enroll in this study on the same day as their EOT Visit in the lead-in study do not need to repeat the urine pregnancy test. • For all female participants of childbearing potential: Urine pregnancy test at Visit 2 prior to dosing and at Visits 4 to 7 for FC participants and Visits 4 to 10 for IBS-C participants during study intervention[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 all visits during study intervention.			

[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring events 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 patient 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 final protocol-defined study visit (or the last known dose of study intervention if the final visit does not occur) 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 pre-existing 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 intervention or program, which warrants ongoing monitoring and rapid

communication by the investigator to the sponsor. Such an event might warrant further investigation in order to characterize and understand it.

The following AESIs have been identified for the study intervention 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 sponsor 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 Appendix 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 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 fulfill 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, then they should be reported as AEs or SAEs as per Section 8.3. • 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.

10.3.3. Recording and Follow-Up of AEs or SAEs

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 an 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
• 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
AST	aspartate aminotransferase
AT	aminotransferase
BP	blood pressure
CBC	complete blood count
CFR	Code of Federal Regulations
CIC	chronic idiopathic constipation
CIOMS	Council for International Organizations of Medical Sciences
CRF	case report form
DILI	drug-induced liver injury
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EOS	End-of Study
EOT	End-of Treatment
EU	European Union
FC	functional constipation
FDA	Food and Drug Administration
GC-C	guanylate cyclase subtype C
GCP	Good Clinical Practice
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
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
mRNA	messenger ribonucleic acid
MSP	medical safety physician
NASH	non-alcoholic steatohepatitis
PCS	potentially clinically significant
PI	package insert
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBM	spontaneous bowel movement
SoA	Schedule of Activities
SOC	System Order Class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TESAE	treatment emergent serious adverse event
ULN	upper limit of normal
US	United States
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 participant 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

CDISC Submission Value	CDISC Definition
Site terminated by sponsor	An indication that a clinical study was stopped at a particular site by its sponsor (NCI)
Study terminated by sponsor	An indication that a clinical study was stopped by its sponsor (NCI)
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 Long-term Safety Study of Oral Linaclotide Administered to Pediatric Participants with Functional Constipation (FC) or Irritable Bowel Syndrome with Constipation (IBS-C)
	Clinical Study Sponsor	Allergan Sales LLC
	Trial Phase Classification	Extension Study
	Trial Indication	FC and IBS-C
	Trial Indication Type	Study intervention
	Trial Type	Safety
	Trial Length	24 weeks (FC participants) 52 weeks (IBS-C participants)
	Planned Country of Investigational Sites	United States of America (USA), Canada, Europe, and the Middle East
	Planned Number of Participants	At least 120
	FDA-Regulated Device Study	No
	FDA-Regulated Drug Study	Yes
	Pediatric Study	Yes
Participant information	Diagnosis Group	Pediatric participants with FC or IBS-C; specifically, participants who have completed study intervention in Phase 2 Studies LIN-MD-62, LIN-MD-63 or Phase 3 Study LIN-MD-64
	Healthy Participant Indicator	No
	Planned Minimum Age of Participants	6 years
	Planned Maximum Age of Participants	18 years
	Sex of Participants	Both
	Stable Disease Minimum Duration	Not applicable

Parameter Group	Parameter	Value
Treatments	Investigational Therapy or Treatment	Linaclotide
	Intervention Type	Drug
	Pharmacological Class of Invest. Therapy	Agonist of guanylate cyclase C
	Dose per Administration	Single
	Dose Units	72 µg, 145 µg, or 290 µg
	Dosing Frequency	Once daily
	Route of Administration	Oral
	Current Therapy or Treatment	None
	Added on to Existing Treatments	No
	Control Type	None
	Comparative Treatment Name	Not applicable
Trial design	Study Type	Interventional
	Intervention Model	Open-label and blinded
	Planned Number of Arms	2 arms for FC participants: open-label 72 and 145 µg 4 arms for IBS-C participants: 2 arms for open-label (145 and 290 µg) and 2 arms for blinded (145 and 290 µg)
	Trial is Randomized	Applicable to FC participants 12 to 17 years of age only: will be randomly assigned at 1:1 ratio to 72 µg linaclotide or 145 µg linaclotide
	Randomization Quotient	Not applicable
	Trial Blinding Schema	Open-label and blinded
	Stratification Factor	None
	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 recommendation or if, following a thorough review of all clinical, laboratory, and other available safety data; safety data become available which appear 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 study intervention period.

10.7.3. Pregnancy Testing:

- Phase 3 Study LIN-MD-64 completers and Phase 2 Study LIN-MD-63 completers who are WOCBP and who enroll in LIN-MD-66 within ≤ 28 days from last study intervention must have a negative urine test at Screening (Visit 1) and on Study Day 1 (Visit 2). LIN-MD-64 completers who enroll in this study on the same day as their EOT Visit in the lead-in study do not need to repeat the urine pregnancy test.
- Phase 2 LIN-MD-62, Phase 2 LIN-MD-63, and Phase 3 LIN-MD-64 completers who are WOCBP and who enroll in LIN-MD-66 after > 28 days from last study intervention should have a negative serum pregnancy test at Screening (Visit 1) and also a negative urine test on Study Day 1 (Visit 2).

- Additional urine pregnancy testing will be performed in female participants of childbearing potential at Visits 4 to 7 (FC participants) and at Visits 4 to 10 (IBS-C participants) during study intervention.
- 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.

Additional details regarding pregnancy testing are provided in Section 10.2.

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 Appendix 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 SoAs in Section 1.4 (FC participants) and Section 1.5 (IBS-C participants). The descriptions of the procedures to be performed at each visit are provided below.

10.10.1. Screening (Visit 1)

Study procedures for screening may be combined with EOT Visit or EOS Visit in the lead-in LIN-MD-64 or LIN-MD-63 studies. The screening period will occur 0 to 14 days before Study Day 1 (Visit 2) and last for up to 14 days during which time study procedures will be reviewed with the participant, parent/guardian/LAR, and/or caregiver; and informed assent (from participant), and parent/guardian/LAR and/or 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 (Section 5.1 and Section 5.2). Screening Visit may be combined with Study Day 1 Visit in participants who enroll within ≤ 28 days from last study intervention in the lead-in study provided no fecal impaction is found at Screening Visit.

For all participants, the following procedures will also be performed at Screening (Visit 1):

- Obtain informed consent from parent/guardian/LAR and caregiver
- Obtain informed assent from participant
- Review inclusion and exclusion criteria
- Register participant in IWRS
- Obtain medical history, medication history, and current medication status
- 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 disimpaction 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). Refer to Section 8.2.1 for additional details.

- Participants and caregivers will be instructed to have the participant fast for at least 2 hours before receiving their first dose of linaclotide at the study site during study Day 1. Water will be allowed.
- Review any AEs occurring after assent/consent is obtained. Ongoing AEs from the prior study should be entered into the eCRF.

Participants who enroll into LIN-MD-66 from LIN-MD-63 or LIN-MD-64 within ≤ 28 days of last study intervention may have the Screening (Visit 1) combined with Study Day 1 (Visit 2).

- Obtain informed consent for participants who turn 18 and enroll within ≤ 28 days of the last study intervention.
- Obtain urine pregnancy test in female participants of childbearing potential. Participants from LIN-MD-63 or LIN-MD-64 studies who enroll in this study on the same day as their EOT Visit in the lead-in study do not need to repeat the urine pregnancy test (Section 10.7).

In addition, for Phase 2 LIN-MD-62, LIN-MD-63, and Phase 3 LIN-MD-64 study intervention completers who enroll in LIN-MD-66 > 28 days from last study intervention, the following procedures will be performed at Screening (Visit 1):

- Complete Rome III assessment
- Instruct participants and caregivers about lifestyle modifications: increased water and fiber intake, increased physical activity, and consistent toileting habits.
- Perform a complete physical examination, including, at a minimum: 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
- Obtain height, vital signs (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 (see Table 10–1); 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.

10.10.2. Study Day 1 (Visit 2)

Screening Visit may be combined with Study Day 1 Visit in participants who enroll within ≤ 28 days from last study intervention in the lead-in study provided no fecal impaction is found at Screening Visit. A fecal impaction assessment will be performed for all participants to determine continued eligibility for study participation. If there is no fecal impaction at Study Day 1 (Visit 2) the participant may enter the study intervention period. If fecal impaction is present upon examination, the participant will not be eligible for the study. Participants will have to be in a fasted state for at least 2 hours before receiving their first dose of study intervention at the study site during Study Day 1 (Visit 2). Water will be allowed.

During the Study Day 1 (Visit 2), the following procedures will be performed for all participants:

- Review inclusion and exclusion criteria
- Perform a fecal impaction assessment prior to dosing (Section 8.2.1)
- Obtain vital signs (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 a urine pregnancy test for female participants of childbearing potential per guidance in Appendix 7: Pregnancy Testing.
- Review any AEs occurring since the last visit, if applicable
- Review prior and concomitant medications
- Contact IWRS to obtain study intervention
- Administer the first dose of linaclotide after completion of all Visit 2 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
    - Participants who took their last dose of lead-in study intervention on the day of the EOT Visit and enroll into this study on that same day will take their first dose of study intervention outside of the clinic at a designated time the following day. Qualified site personnel will complete a follow-up phone call to participants within 48 hours following initial study intervention administration to assess safety.
- Dispense 1 bottle of linaclotide for this study after the first dose has been administered.

- Record the date and time the first dose was administered
- Remind participant and caregiver to bring the bottle of linaclotide to the next on-site visit

10.10.3. Week 2 (Visit 3)

During Week 2 (Visit 3), the following will be performed via a phone visit with the participant:

- Review any AEs occurring since the last visit
- Review concomitant medications
- Remind participant and caregiver to bring the bottle(s) of linaclotide to the next visit

10.10.4. Week 4 (Visit 4)

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

- Obtain urine pregnancy test for female participants of childbearing potential
- Review any AEs occurring since the last visit
- Review concomitant medications
- Obtain vital signs (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 linaclotide compliance and accountability
- Remind participant and caregiver to bring the bottle of linaclotide to the next visit
- Contact IWRS to obtain study intervention
- Dispense 1 bottle of linaclotide for this study

10.10.5. Week 8 (Visit 5)

During Week 8 (Visit 5), the following procedures will be performed:

- Obtain vital signs (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 urine pregnancy test for female participants of childbearing potential
- Review any AEs occurring since the last visit
- Review concomitant medications
- Remind participant and caregiver to bring the bottles of linaclotide to the next visit

- Contact IWRS to obtain study intervention
- Dispense 2 bottles of linaclotide

10.10.6. Week 16 (Visit 6)

During Week 16 (Visit 6), the following procedures will be performed:

- Obtain vital signs (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 urine pregnancy test for female participants of childbearing potential
- Review any AEs occurring since the last visit
- Review concomitant medications
- Review linaclotide compliance and accountability
- Remind participant and caregiver to bring the bottles of linaclotide to the next visit
- Contact IWRS to obtain study intervention
- Dispense 2 bottles of linaclotide

10.10.7. Week 24/EOT Visit (Visit 7) for FC Participants

All enrolled participants who prematurely discontinue from the study, regardless of cause, are required to return for the EOT study assessments.

During Week 24/EOT (Visit 7), the following procedures will be performed:

- Perform a complete 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, vital signs (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 urine pregnancy test for female participants of childbearing potential
- Review any AEs occurring since the last visit
- Review concomitant medications
- Review linaclotide compliance and accountability
- Return study intervention

10.10.8. Week 24 (Visit 7) for IBS-C Participants

During Week 24 (Visit 7), the following procedures will be performed:

- Obtain vital signs (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 urine pregnancy test for female participants of childbearing potential
- Review any AEs occurring since the last visit
- Review concomitant medications
- Review linaclotide compliance and accountability
- Remind participant and caregiver to bring the bottles of linaclotide to the next visit
- Contact IWRS to obtain study intervention
- Dispense 2 bottles of linaclotide

10.10.9. Week 32 (Visit 8) for IBS-C Participants

During Week 32 (Visit 8), the following procedures will be performed:

- Obtain vital signs (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 urine pregnancy test for female participants of childbearing potential
- Review any AEs occurring since the last visit
- Review concomitant medications
- Review linaclotide compliance and accountability
- Remind participant and caregiver to bring the bottles of linaclotide to the next visit
- Contact IWRS to obtain study intervention
- Dispense 2 bottles of linaclotide

10.10.10. Week 40 (Visit 9) for IBS-C Participants

During Week 40 (Visit 9), the following procedures will be performed:

- Obtain vital signs (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 urine pregnancy test for female participants of childbearing potential
- Review any AEs occurring since the last visit
- Review concomitant medications
- Review linaclotide compliance and accountability
- Remind participant and caregiver to bring the bottles of linaclotide to the next visit
- Contact IWRS to obtain study intervention
- Dispense 3 bottles of linaclotide

10.10.11. Week 52/EOT (Visit 10) for IBS-C Participants

All enrolled participants who prematurely discontinue from the study, regardless of cause, are required to return for the EOT study assessments.

During Week 52/EOT (Visit 10), the following procedures will be performed:

- Perform a complete 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, vital signs (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 urine pregnancy test for female participants of childbearing potential
- Review any AEs occurring since the last visit.

- Review concomitant medications
- Review linaclotide compliance and accountability
- Return study intervention

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 may be rescreened.

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.

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