# Title Page

**Protocol Title:** A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Sequential, Ascending, Multidose Study to Evaluate the Safety and Efficacy of Linaclotide in Pediatric Participants (Age 2 to 5 Years) with Functional Constipation

**Protocol Number:** LIN-MD-67

**Amendment Number:** 1

**Product:** linaclotide

**Brief Protocol Title:** Linaclotide Safety and Efficacy in 2 to 5-Year-Old Participants with Functional Constipation

**Development Phase:** 2

Sponsor Name and Legal Registered Address:
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Refer to the final page of this protocol for electronic signature and date of approval.

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## Protocol Amendment Summary of Changes

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| *Amendment 1* | *May 2020* |
| *Original Protocol* | *May 2019* |

### Amendment 1 (May 2020)

The purpose of Global Protocol Amendment 1 is to include an assessment of modified Rome III criteria at the end of treatment as an 'other' efficacy endpoint, to include a fecal impaction assessment at Visit 3 prior to randomization and dosing, and to provide additional clarification and updates to the LIN-MD-67 protocol (dated 01 May 2019).

The following is a summary of changes made in Global Protocol Amendment 1. Strikethrough text denotes text removed and bolded text denotes added text. Additional administrative edits were also made, but not specifically noted (e.g., corrected spelling, punctuation, grammar, abbreviation, and style errors) including global edits required for consistency.

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| Protocol Section(s) | Description of Changes | Rationale for Changes |
|---|---|---|
| Section 1.1 Synopsis | • EMEA was removed from the following sentence: Up to 40 sites from the United States~~,~~ **and** Canada ~~and EMEA~~ are expected to participate in the study. | • To reflect current information |
| Section 1.3 Schedule of Activities (SoA) | • An assessment of modified Rome III criteria at EOT was added<br>• IWRS verification was added to the EOT Visit<br>• A fecal impaction assessment at Randomization (Visit 3) was added for all participants. A footnote describing this has also been added and numbering of the subsequent footnotes has been updated accordingly.<br>• Footnote 'o' was revised as follows: '…and the global change items will be completed ~~beginning at~~ **from one week after** randomization through End of Study' | • To assess participants for fulfilling modified Rome III criteria at end of treatment as an 'other' efficacy endpoint.<br>• For clarification<br>• To ensure participants don't have fecal impaction prior to receiving study intervention<br>• To allow an appropriate amount of time from randomization to complete the weekly assessment |
| Section 2 Introduction | • **'Australia'** was added to the list of countries where linaclotide is approved for treatment of IBS-C and CIC.<br>• Text added to include the pediatric Phase 2 study LIN-MD-63 results. | • To reflect current information |
| Section 2.2.1 Adult Linaclotide Program | • The following sentence was deleted: ~~A summary of these studies and major conclusions are provided in Section 10.9~~.<br>• Text added to include the recently completed Phase 3b study MCP-103-312. | • To reflect current information |
| Section 2.2.2 Pediatric Linaclotide Program | • A summary of results for the recently completed LIN-MD-63 study in pediatric IBS-C participants was added. | • To reflect current information |
| Section 2.2.3.2 GC-C mRNA Expression | • Corrected the study number for Study MCP-103-311 | • Correction of typo |
| Section 4.1 Overall Design | • The word 'modified' was added to the following sentence: 'Study LIN-MD-67 is a Phase 2 randomized, double-blind, placebo-controlled, sequential, ascending multidose study with a 4-week Study Intervention Period in participants, 2 to 5 years of age, who meet **modified** Rome III criteria for childhood FC.'<br>• Europe was removed from the following sentence: Up to 40 sites from the United States~~,~~ **and** Canada ~~and Europe~~ are expected to participate in the study. | • For clarification<br>• To reflect current information |



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| Protocol Section(s) | Description of Changes | Rationale for Changes |
|---|---|---|
| Section 4.3 Justification for Dose | • Corrected the study number for Study MCP-103-311<br>• The source for Figure 4-2 was added | • Correction of typo<br>• For clarification |
| Section 5.2 Exclusion Criteria | • '**Vital sign assessment**' was included in exclusion criteria 1.01 and edits were made to exclusion criteria 1.05 and 1.09 to add clarity.<br>• Exclusion criterion 1.04 was revised to add '**fecal impaction at Visit 3**' as an exclusion criterion. | • For clarification<br>• To ensure participants don't have fecal impaction prior to dosing |
| Section 6 Study Intervention | • The following sentence was deleted: ~~The study intervention does not have marketing authorization in the EU for the pediatric indication~~. | • Removed since EU sites will not be included in the study |
| Section 6.3 Measures to Minimize Bias: Randomization and Blinding | • Revised the study number from 301 to 267<br>• Revised the site number from 00001-99999 to 10001-19999 | • To reflect what's being used in the study |
| Section 6.5.1 Prohibited Interventions and Washout Before the Study | • Added linaclotide to the list of prohibited medicines with a 14-day washout period | • To provide additional clarity |
| Section 6.5.2 Rescue Medication | • The following text regarding rescue medication options was deleted: ~~Participants outside of the United States and Canada will have a choice of at least one of the following medications: senna (oral), mineral oil enema (rectal), or sodium picosulphate (oral) that will be dispensed according to the SOA (Section 1.3).~~ | • Removed since only sites from the US and Canada will participate in the study. |
| Section 7.1.1 Removal of Individual Participants from Therapy or Assessment | • Text referring to signs of drug-induced liver injury was moved to newly added Appendix 9: Liver Safety: Suggested Actions and Follow-up Assessments. | • To align with the liver appendix template |
| Section 8 Study Assessments and Procedures | • The following text was added: '**Additional details regarding study conduct during the novel coronavirus pandemic are provided in Appendix 10**.' | • To add a reference to newly added Appendix 10. |
| Section 8.1 Efficacy Assessment | • The following text was deleted: '~~The relationship of the caregiver to the participant should be recorded in the eCRF~~.' | • To reflect current information |

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| Protocol Section(s) | Description of Changes | Rationale for Changes |
|---|---|---|
| Section 8.1.2 Other Efficacy Assessments | • Added an assessment of modified Rome III criteria at the end of the study intervention period<br>• The wording of the global change item question was revised along with the starting time of the assessment | • To assess participants for fulfilling modified Rome III criteria at both screening and at end of treatment<br>• To reflect current information |
| Section 8.2.1 Physical Examinations | • Added a fecal impaction assessment at randomization (Visit 3) prior to dosing | • To ensure participants don't have fecal impaction prior to receiving study intervention |
| Section 8.2.3 Electrocardiograms | • Revised text to clarify method for recording ECGs. | • To provide additional clarity |
| Section 8.3.6 Potential Hy's Law Cases | • Details regarding liver safety assessments and follow-up for potential Hy's law cases were moved to newly added Appendix 9: Liver Safety: Suggested Actions and Follow-up Assessments | • To align with the liver appendix template |
| Section 9.1. Statistical Endpoints | • Added the 'other' efficacy endpoint of **'Proportion of participants who no longer fulfill modified Rome III criteria for functional constipation at the end of the Study Intervention Period.'** | • To assess whether participants no longer meet modified Rome III criteria at the end of the study intervention period as an 'other' efficacy endpoint. |
| Section 9.4.1.1 Key Efficacy Endpoints | • The following text was added: 'Stool consistency **for each caregiver-observed BM** will be measured daily in the eDiary using the 7-point ordinal BSFS'<br>• The following text was added: 'The participant's daily straining score **for each caregiver-observed BM** will be derived based on the average of non-missing responses of the two straining questions.' | • For clarification<br>• For clarification |
| Section 9.4.1.2 Other Efficacy Endpoints | • Added text for the other efficacy endpoint of '**Proportion of participants who no longer fulfill modified Rome III criteria for functional constipation at the end of the Study Intervention Period.'** | • To reflect how fulfillment of modified Rome III criteria is being assessed in the study |
| Section 9.4.2.2 Clinical Laboratory Assessments | • The following text was added: 'The numerator will be the total number of participants with **available non-PCS baseline values and** at least 1 PCS postbaseline value …' | • For clarification |



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| Protocol Section(s) | Description of Changes | Rationale for Changes |
|---|---|---|
| Section 10.1.11 Study Documentation | • The following text was deleted: '~~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~~).' | • Removed since EU sites will not be included in the study |
| Section 10.1.6.3 DSMB | • Added **'or ad hoc if needed'** | • For clarification |
| Section 10.2 Appendix 2: Clinical Laboratory Tests | • %Reticulocytes was removed from Table 10-1<br>• Footnote 'a' was revised to refer to Appendix 9: Liver Safety: Suggested Actions and Follow-up Assessments for liver chemistry stopping criteria and required actions and follow-up assessments | • To reflect what's being assessed in the study<br>• To align with the liver appendix template |
| Section 10.3 Appendix 3: Adverse Events | • Text updated to align with the timing of AE collection in the body of the protocol<br>• Text regarding reporting of potential Hy's Law cases was moved to newly added Appendix 9: Liver Safety: Suggested Actions and Follow-up Assessments | • To reflect current information<br>• To align with the liver appendix template |
| Section 10.6 Appendix 6: Study Tabular Summary | • 'EMEA' was removed from the Planned Country of Investigational Sites as follows: United States~~,~~ **and** Canada~~, and EMEA~~ | • To reflect current information |
| Section 10.7 Appendix 7: Instructions for Dosing | • Additional text was added regarding instructions for dosing and the capsule strengths to be used for dosing. | • To provide additional clarity |
| Section 10.8.1 Screening (Visit 1) | • The following procedure was added to the Screening Visit: **'Complete modified Rome III assessment'.**<br>• **'Lumbosacral'** was added to the physical exam description. | • For clarification and update to reflect current information |
| Section 10.8.3 Randomization (Visit 3, Day 1) | • A fecal impaction assessment was added to the randomization visit (Visit 3) as shown: **'Perform a fecal impaction assessment prior to randomization. If fecal impaction is present, the participant will not be eligible for the study.'** | • To ensure participants don't have fecal impaction prior to receiving study intervention |
| Section 10.8.5 Week 4/EOT (Visit 5) | • The following was added to the EOT Visit: '**IWRS verification'**<br>• **'Lumbosacral**' was added to the physical exam description<br>• The following procedure was added to the EOT Visit: **'Complete modified Rome III assessment.'** | • For clarification<br>• For clarification<br>• To assess participants for fulfilling modified Rome III criteria at the end of treatment as an 'other' efficacy endpoint. |



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| Protocol Section(s) | Description of Changes | Rationale for Changes |
|---|---|---|
| Section 10.9 Appendix 9: Liver Safety: Suggested Actions and Follow-up Assessments | • Appendix 9: Liver Safety: Suggested Actions and Follow-up Assessments was added. | • To provide liver safety information in a consolidated location and to align with the liver appendix template |
| Section 10.10 Appendix 10: Study Conduct During the Novel Coronavirus Pandemic: Pre-randomization | • Appendix 10: Study Conduct During the Novel Coronavirus Pandemic: Pre-randomization was added | • To provide information on study conduct during the novel coronavirus pandemic |

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# 1. Protocol Summary

## 1.1. Synopsis

**Protocol Title:** A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Sequential, Ascending, Multidose Study to Evaluate the Safety and Efficacy of Linaclotide in Pediatric Participants (Age 2 to 5 Years) with Functional Constipation

**Protocol Number:** LIN-MD-67

**Amendment Number:** 1

**Brief Title:** Linaclotide Safety and Efficacy in 2 to 5-Year Old Participants with Functional Constipation

**Study Phase:** 2

**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 dis-impaction (ie, removal of the rectal fecal mass), followed by maintenance treatment and eventually a weaning phase. Multiple pharmacological agents are available for the treatment of FC in children. Despite chronic pharmacological treatment, approximately 40% of children with FC referred to a pediatric gastroenterologist remain symptomatic after 5 years and 20% of children still have symptoms after 10 years. In some cases, symptoms may persist into adolescence or adulthood despite medical treatment. Potential reasons for ineffectiveness of treatment include suboptimal dosage regimens, poor compliance with treatment, or the use of drugs with action mechanisms that do not address the underlying pathophysiological etiology.

Despite the fact that children with FC are commonly prescribed various and miscellaneous pharmacologic agents for FC, it is notable that there are no approved products indicated for FC in children or well controlled trials of these frequently prescribed agents. Thus, effective treatments are needed to provide symptomatic relief in children and adolescents with FC, with the evidence for safety and efficacy of these based on the results of adequate and well-controlled studies in children.

For the primary and key secondary endpoints in the Phase 2 dose-ranging LIN-MD-62 study in children, 6 to 17 years of age, with FC, none of the 3 linaclotide doses (A [low dose], B [medium

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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 towards efficacy at the higher doses was observed for the primary endpoint of change from baseline in 4-week overall spontaneous bowel movement (SBM) frequency rate (SBMs/week). Overall, linaclotide was well tolerated across all doses in participants, 6 to 17 years of age. The safety profile was consistent with prior adult linaclotide chronic idiopathic constipation (CIC) studies.

As linaclotide was well tolerated across all doses tested in 6 to 17-year old participants treated in LIN-MD-62, LIN-MD-67 is being initiated in younger children with the primary objective of evaluating the dose response, safety, and efficacy of 4 weeks of linaclotide in pediatric participants, 2 to 5 years of age, with FC.

**Objectives and Endpoints:**

The objective of LIN-MD-67 is to evaluate the dose response, safety, and efficacy of 4 weeks of study intervention with linaclotide compared with placebo in pediatric participants, 2 to 5 years of age, with FC.

Key efficacy endpoints include:

- Change from baseline in 4-week overall SBM frequency rate (SBMs/week) during the Study Intervention Period of each cohort
- Change from baseline in 4-week stool consistency reported by the caregiver during the Study Intervention Period of each cohort
- Change from baseline in 4-week straining reported by the caregiver during the Study Intervention Period of each cohort
- Proportion of days with fecal incontinence during the Study Intervention Period (for participants who have acquired toileting skills during the daytime and nighttime or acquired toileting skills during daytime only) within each cohort

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:**

Study LIN-MD-67 is a Phase 2 randomized, double-blind, placebo-controlled, sequential, ascending multidose study with a 4-week study intervention period in participants, 2 to 5 years of age, with FC.

**Number of Participants:**

Up to 30 participants, 2 to 5 years of age, will be sequentially enrolled into LIN-MD-67; 8 participants each into Cohorts 1 to 3 and 6 participants in the final cohort. Participants will be randomly assigned to receive linaclotide or matching placebo as described below.

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**Number of Sites:**

Up to 40 sites from the United States and Canada are expected to participate in the study.

**Study Intervention Groups and Study Duration:**

The study will consist of up to 4 cohorts, each of which will be studied for 9 to 12 weeks in duration: 2 to 4-week Screening Period, a 2 to 3-week Preintervention Period, followed by a 4-week double-blind Study Intervention Period, and a 1-week Postintervention Period (Section 1.2).

Participants will not receive study intervention during the Screening/Preintervention Period and the Postintervention Period.

After at least 6 participants in Cohorts 1 to 3 complete at least 2 weeks of double-blind study intervention, an independent DSMB will review unblinded interim safety data. Based on this review, the DSMB will recommend whether the subsequent planned dose level should be tested. New participants will be recruited for each cohort.

Please refer to Figure 1-1 for assignment of participants to dose cohorts.

- Cohorts 1-3: 8 participants will be randomized at a ratio of 3:1 to receive linaclotide or matching placebo:
  - Cohort 1: linaclotide 18 µg or matching placebo once daily for 4-week Study Intervention Period.
  - Cohort 2: linaclotide 36 µg or matching placebo once daily for 4-week Study Intervention Period. The DSMB will have the option to recommend the lower dose of linaclotide [redacted] µg instead of the 36 µg dose, based on review of unblinded interim safety data from Cohort 1.
  - Cohort 3: linaclotide 72 µg or matching placebo once daily for 4-week Study Intervention Period. Participants will only be assigned to this cohort if the DSMB recommends proceeding to this 72 µg dose based on unblinded interim safety data from Cohort 2 with the linaclotide 36 µg dose.

- Final Cohort: 6 participants will be randomized at a ratio of 5:1 to receive linaclotide at the highest dose tested/determined to be safe or matching placebo for 4-week Study Intervention Period (ie, [redacted] 18, 36, 72 µg depending on the recommendation of the DSMB).

Data and Safety Monitoring Board (DSMB): Yes

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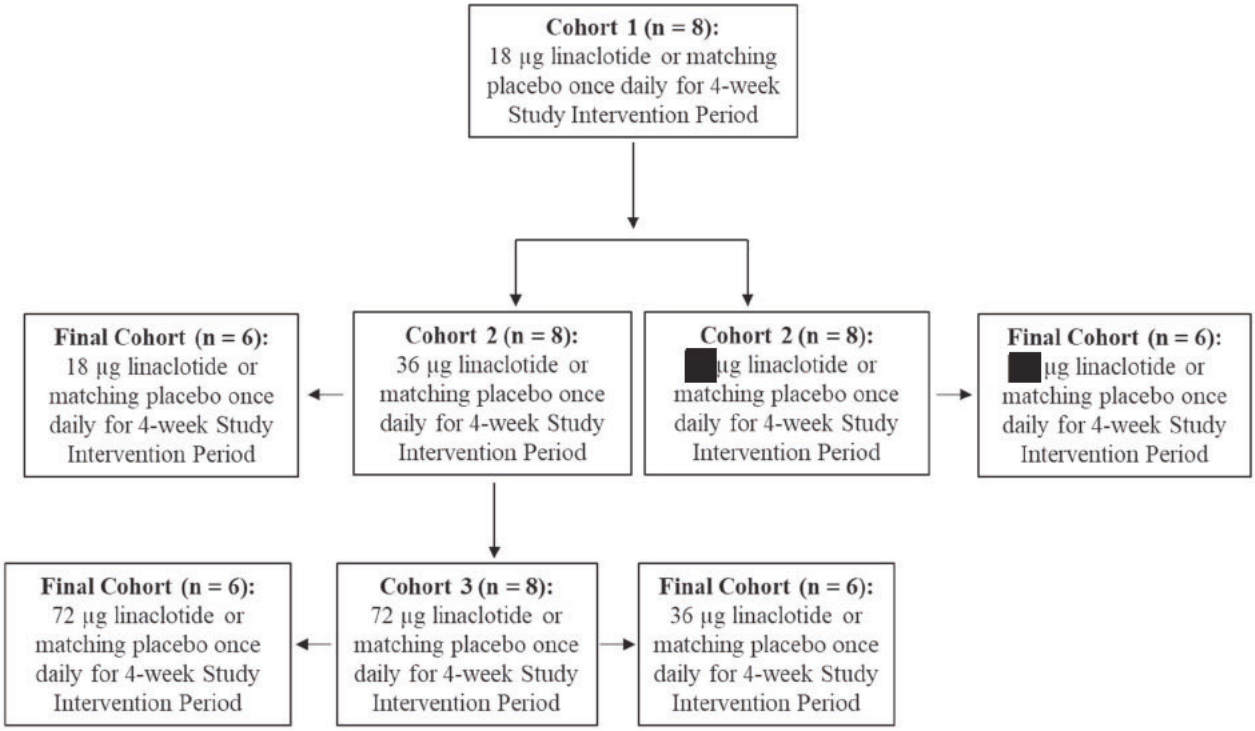
**Figure 1-1 Assignment of Participants to Dose Cohorts**

Sponsor decision on how to proceed with the study is based on DSMB feedback following review of all available safety data prior to each subsequent cohort.

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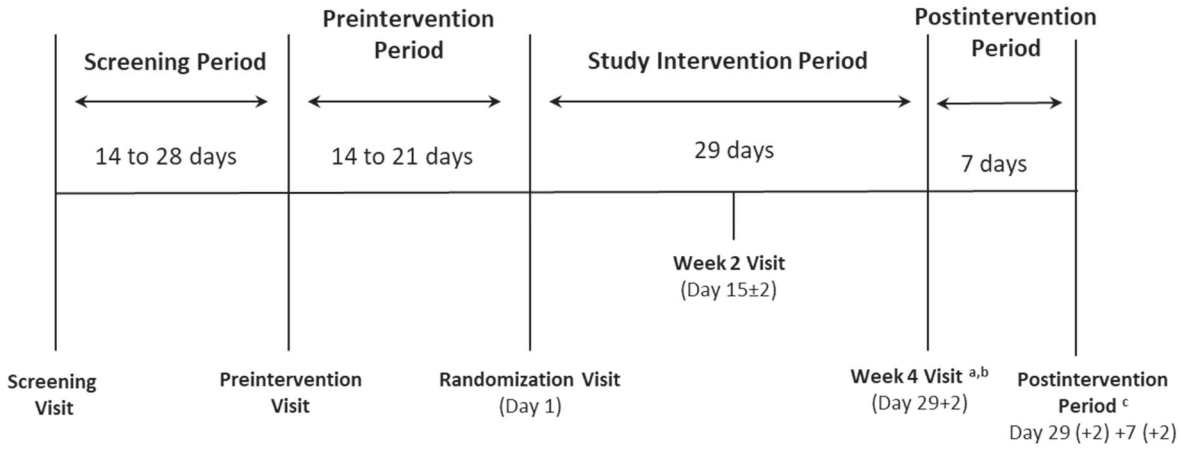
## 1.2. Schema

Study duration will be 9 to 12 weeks for each cohort with 4 weeks of study intervention as described below.




Note: There is no Day 0.

[a] The participant must complete at least 4 weeks (28 days) of double-blind study intervention before Week 4 Visit. The last dose of study intervention will be administered at the study site for the Visit 5 (Week 4) visit on Day 29 (+2) at approximately the same time as on other days of study intervention administration. The participant should arrive at the study site in fasted state. On the same day, a PK sample will also be taken at the same time as other safety laboratory assessments required at this visit (Section 8.5.1).

[b] All randomized participants who prematurely discontinue from the study, regardless of cause, must be seen for the assessments to be completed at this EOT Visit (Week 4/Visit 5).

[c] The Postintervention Visit has to be at least 7 days after the Week 4 visit.

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## 1.3. Schedule of Activities (SoA)

| Schedule of Evaluations LIN-MD-67 | | | | | | |
|---|---|---|---|---|---|---|
| **Study Periods (Duration)** | **Screening (14-28 Days)** | **Preintervention (14-21 Days)** | **Study Intervention (29 Days)** | | | **Postintervention (7 Days)** |
| | **Screening[a]** | **Preintervention** | **Randomization[b]** | **Week 2** | **Week 4/EOT[c,d]** | **1 Week Postintervention Visit End of Study** |
| **Study Visit** | **1** | **2** | **3** | **4** | **5** | **6** |
| **Study Day** | | | **1** | **15 (± 2)** | **29 (+ 2)** | **Week 4/EOT + 7 (+2)** |
| Parent/LAR/Caregiver Consent[e] | X | | | | | |
| Inclusion and Exclusion Criteria | X | X | X | | | |
| Modified Rome III Assessment | X | | | | X | |
| Assess Rome IV status[f] | | | X | | | |
| IWRS | X | X | X | | X | |
| PK Random Assignment in IWRS[g] | | | X | | | |
| Medical History | X | | | | | |
| Lifestyle Modification Information Given to Caregiver | X | | | | | |
| Physical Examination[h] | X | | | | X | |
| Fecal Impaction Assessment[i] | X | X[i] | X[j] | | | |
| Height | X | | | | | |
| Vital Signs, Postural Vital Signs[k] | X | X | X | X | X | X |
| ECG | X | | | | X | |
| Clinical Laboratory Tests[l] | X | | | | X | |
| PK Sample[g] | | | | | X[m] | |
| AE Evaluation | X | X | X | X | X | X |
| Prior and Concomitant Medications | X | X | X | X | X | X |
| Dispense Rescue Medication[n] | | X | X | X | X | |
| eDiary and Instructions Given to Caregiver[o] | | X | | | | |
| eDiary Eligibility Report[p] | | | X | | | |
| eDiary Compliance[o] | | | X | X | X | X |
| Study intervention administered in the clinic | | | X[b] | | X[c] | |
| Study intervention dispensed | | | X | | | |
| IP and Rescue Medication Compliance and Accountability | | | X | X | X | X[q] |

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[a] During the Screening Period, caregivers will receive information regarding lifestyle modifications. There should be at least a 2-week interval between discussing the lifestyle modifications during the Screening Period and the participant's entry into the Preintervention Period.

[b] Study intervention will be administered in the study site after confirming the participant has fasted for at least 2 hours during the Randomization Visit (Day 1) after running the Eligibility report. IWRS will be contacted to obtain the study intervention (bottle number) to be dispensed. Participants may eat 30 minutes after dosing (the requirement for study intervention to be administered 30 minutes prior to the meal will not apply for the first dose).

[c] The participant must complete at least 4 weeks (28 days) of study intervention before returning for Visit 5 (Week 4). The last dose of study intervention will be administered at the study site at the Visit 5 (Week 4) visit on Day 29 (+2) at approximately the same time as on other days of study intervention administration. Caregivers will be instructed when the participants should fast to ensure they have fasted for at least 2 hours before receiving their last dose of study intervention (Section 10.8.3)

[d] All randomized participants who prematurely discontinue from the study, regardless of cause, are required to be seen for the assessments completed at EOT (Visit 5, Week 4), except for PK sample collection.

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

[f] Prior to dosing, the investigator or appropriate site staff member will assess if Rome IV criteria for Child FC was met and record the outcome in the eCRF. Eligibility for the study is not based on this assessment.

[g] Participants in Cohorts 1-3 will be randomized on Study Day 1 (Visit 3) at a 1:3 ratio to either a predose or postdose PK sample respectively. The 6 additional participants in the final cohort will be randomized at a 1:2 ratio to either a pre-dose or post-dose PK sample, respectively (Section 8.5.1).

[h] Physical examinations will be performed by medically qualified site personnel at Screening (Visit 1) and Week 4 (Visit 5) and may be repeated at the investigator's discretion. If fecal impaction (as defined in footnote h below) is documented during an optional repeat physical examination, the study physician must be notified.

[i] Fecal impaction is defined as a hard mass in the lower abdomen identified on physical examination or a dilated rectum filled with a large amount of stool on rectal examination. If a rectal examination is performed, the medically qualified site personnel should assess for and document the presence of anal wink and normal anal tone. A fecal impaction assessment is only performed at the Preintervention Visit (Visit 2) if a fecal impaction was documented during the fecal impaction assessment at Screening (Visit 1). If there is no fecal impaction at the Preintervention Visit (Visit 2), the participant may enter the Preintervention Period after adhering to any washout requirements. If fecal impaction is present upon re-examination, the participant will not be eligible for the study.

[j] A fecal impaction assessment is performed at the Randomization Visit (Visit 3) prior to randomization and dosing for all participants. If there is no fecal impaction at the Randomization Visit (Visit 3) (as defined in footnote i above), the participant may enter the Randomization Period. If fecal impaction is present upon examination, the participant will not be eligible for randomization.

[k] 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. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting. At all visits, postural vital signs must be obtained after participants have been in a supine position for at least 2 to 3 minutes, followed by a standing position for at least 1 minute. Temperature may be recorded as oral, rectal or tympanic (ear). If possible, temperature should be obtained using the same method at each visit.

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

[m] Participants will arrive in a fasted state for this visit to receive their last dose of study intervention before or after assigned PK sample is collected. PK samples should be collected at the same time as clinical labs. This visit should be scheduled at approximately same time as when participants take their daily dose.

[n] Protocol-permitted rescue medication will be dispensed in IWRS where applicable. The parent/caregiver/guardian/LAR may choose a different protocol-permitted rescue medication at any subsequent visit, where available. Additional protocol-permitted rescue medications may be dispensed as needed at any subsequent visits, where available.

[o] At the Preintervention Visit, caregivers will be trained on the use of the eDiary and instructed to complete the daily evening assessment. At subsequent visits, study site staff will verify compliance with the eDiary and remind caregivers to complete their assessments daily. The global severity items will be completed beginning at the Preintervention Period through End of Study, and the global change items will be completed from one week after randomization through End of Study.

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

[q] Protocol-permitted rescue medications only.

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# 2. Introduction

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

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

## 2.1. Study Rationale

Functional constipation is a common healthcare problem in children of all ages, with a worldwide prevalence ranging between 0.7% and 29.6% (Koppen 2018). Symptoms include infrequent, hard stools, and painful defecation and affected children may have abdominal pain and fecal incontinence, which is usually the result of fecal impaction leading to overflow incontinence. These symptoms can have a severe impact on a child's quality of life and may lead to school absenteeism and substantial costs related to healthcare utilization. Initial 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.

There are no approved products for FC in children. Thus, effective treatments are needed to provide symptomatic relief in children and adolescents with FC, with the evidence for the safety and efficacy of these based on the results of adequate and well-controlled studies in children.

For the primary and key secondary endpoints in the Phase 2 dose-ranging LIN-MD-62 study in children, 6 to 17 years of age, none of the 3 linaclotide doses (A [low dose], B [medium dose], and C [high dose]) indicated clear improvement over placebo (p-value ≥ 0.1502) based on the ITT population. However, a numerical trend towards efficacy at the higher doses was observed



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for the primary endpoint of change from baseline in 4-week overall SBM frequency rate (SBMs/week). In addition, the safety profile was consistent with prior adult linaclotide studies in CIC.

As linaclotide was well tolerated across all doses tested in 6 to 17-year old participants treated in LIN-MD-62, LIN-MD-67 is being initiated in younger children with the primary objective of evaluating the dose response, safety, and efficacy of 4 weeks of linaclotide in pediatric participants, 2 to 5 years of age, with FC.

## 2.2. Background

### 2.2.1. Adult Linaclotide Program

Linaclotide has been developed by the sponsors, Allergan Sales, LLC and Ironwood Pharmaceuticals Inc., and is approved at 72 µg and 145 µg for the treatment of CIC and 290 ug for the treatment of IBS-C in adults. The adult linaclotide clinical development program 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.

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

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

### 2.2.2. Pediatric Linaclotide Program

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

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

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

There were no reported AESIs (ie, significant volume depletion and/or significant electrolyte abnormalities and/or ECG abnormalities that were considered by the investigator or sponsor to be related to diarrhea) or deaths. There were 2 SAEs (suicidal ideation and vomiting), each reported in 1 participant, in the 12 to 17 years of age group, neither were considered related to study intervention. Moreover, in the younger pediatric participants, 6 to 11 years of age, no SAEs or AEs leading to discontinuation were reported.

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

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

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

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

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

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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. Nonclinical 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 – 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



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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 years old to 7 years old without supplemental fluid administration. Based on these nonclinical results, the Linzess PI (Jan 2017) 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, from birth to <24 months, 24 months to <6 years, 6 years to <12 years, and 12 years to <18 years.

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

### 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 participants 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.

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

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



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profiles that are effective in providing relief for the variety of symptoms associated with FC in pediatrics.

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

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

# 3. Objectives and Endpoints

The objective of LIN-MD-67 is to evaluate the dose response, safety, and efficacy of 4 weeks of study intervention with linaclotide compared with placebo in pediatric participants, 2 to 5 years of age, with FC.

Key efficacy endpoints include:

- Change from baseline in 4-week overall SBM frequency rate (SBMs/week) during the Study Intervention Period of each cohort
- Change from baseline in 4-week stool consistency reported by the caregiver during the Study Intervention Period of each cohort
- Change from baseline in 4-week straining reported by the caregiver during the Study Intervention Period of each cohort
- Proportion of days with fecal incontinence during the Study Intervention Period (for participants who have acquired toileting skills during the daytime and nighttime or acquired toileting skills during daytime only) within each cohort

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

Study LIN-MD-67 is a Phase 2 randomized, double-blind, placebo-controlled, sequential, ascending multidose study with a 4-week Study Intervention Period in participants, 2 to 5 years of age, who meet modified Rome III criteria for childhood FC.

Up to 30 participants, 2 to 5 years of age, will be sequentially enrolled into LIN-MD-67; eight participants each into Cohorts 1 to 3 and six participants in the final cohort. Participants will be randomly assigned to receive linaclotide or matching placebo as described below.

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**Number of Sites:**

Up to 40 sites from the United States and Canada are expected to participate in the study.

**Study Intervention Groups and Study Duration:**

The study will consist of up to 4 cohorts, each of which will be 9 to 12 weeks in duration: 2 to 4-week Screening Period, a 2 to 3-week Preintervention Period, followed by a 4-week double-blind Study Intervention Period, and a 1-week Postintervention Period (Section 1.2).

Participants will not receive study intervention during the Screening/Preintervention Period and the Postintervention Period.

After at least 6 participants in Cohorts 1 to 3 complete at least 2 weeks of double-blind study intervention, an independent DSMB will review unblinded interim safety data. Based on this review, the DSMB will recommend whether the subsequent planned dose level should be tested. New participants will be recruited for each cohort.

Please refer to Figure 4-1 for assignment of participants to dose cohorts.

- Cohorts 1-3: 8 participants will be randomized at a ratio of 3:1 to receive linaclotide or matching placebo:
  - Cohort 1: linaclotide 18 µg or matching placebo once daily for 4-week Study Intervention Period.
  - Cohort 2: linaclotide 36 µg or matching placebo once daily for 4-week Study Intervention Period. The DSMB will have the option to recommend the lower dose of linaclotide [redacted] µg instead of the 36 µg dose, based on review of unblinded interim safety data from Cohort 1.
  - Cohort 3: linaclotide 72 µg or matching placebo once daily for 4-week Study Intervention Period. Participants will only be assigned to this cohort if the DSMB recommends proceeding to this 72 µg dose based on unblinded interim safety data from Cohort 2 with the linaclotide 36 µg dose.

- Final Cohort: 6 participants will be randomized at a ratio of 5:1 to receive linaclotide at the highest dose tested/determined to be safe or matching placebo for 4-week Study Intervention Period (ie, [redacted] 18, 36, 72 µg depending on the recommendation of the DSMB).

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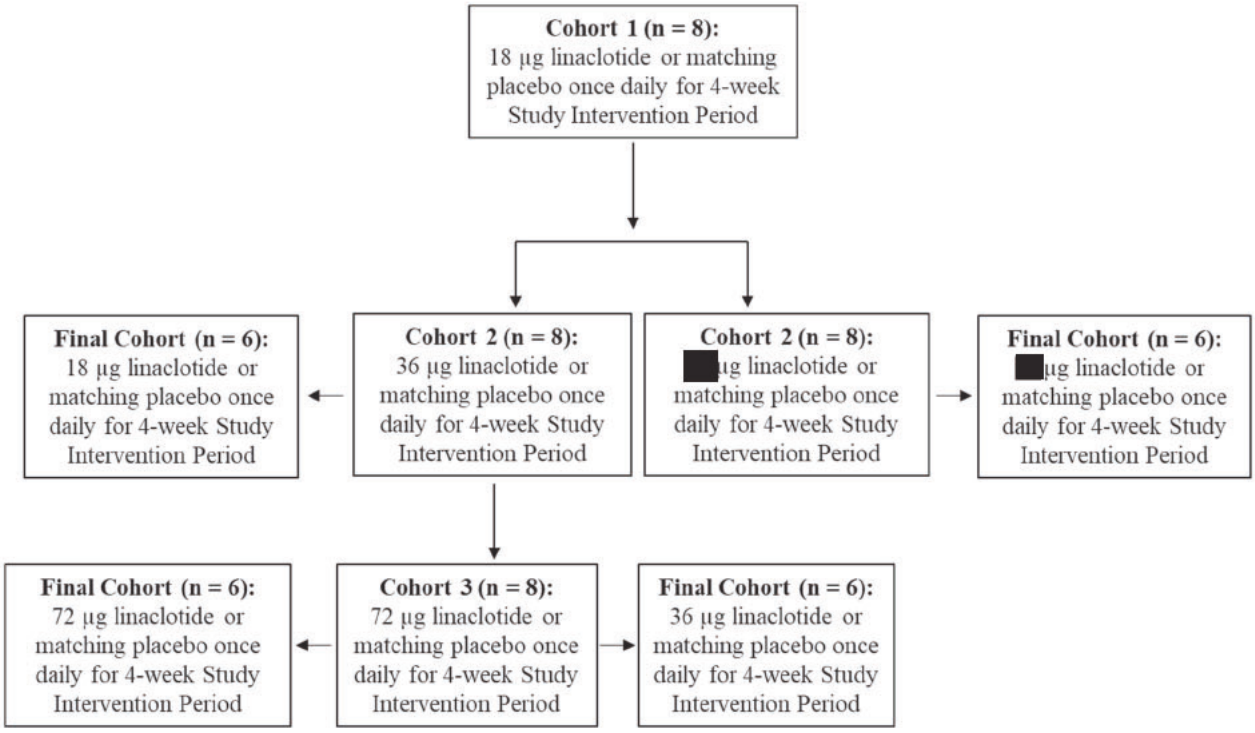
**Figure 4-1 Assignment of Participants to Dose Cohorts**

Sponsor decision on how to proceed with the study is based on DSMB feedback following review of all available safety data prior to each subsequent cohort.




## 4.2. Scientific Rationale for Study Design

The purpose of this Phase 2 study is to investigate the potential therapeutic dose(s) of linaclotide in the target pediatric subset of participants, 2 to 5 years of age, with FC. Given the current contraindication under 6 years of age, as well as the lack of clinical data in this younger age group, a sequential, ascending multidose escalation design was selected.

## 4.3. Justification for Dose

Results from LIN-MD-62 suggested a lack of body weight normalized dose response in pediatric patients of age 6 to 17 years (Figure 4-2), which was also observed in adults (Studies MCP-103-201, LIN-MD-01, MCP-103-303, and MCP-103-309; Figure 10–1 in Appendix 11, Section 10.11). In addition, study MCP-103-311 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. These data support a flat dosing approach for pediatric participants aged 2 to 5 years in the current dose range finding study.

The safety profile in the first completed pediatric linaclotide study in FC, LIN-MD-62, was consistent with prior adult linaclotide studies in CIC. There were no new safety signals observed



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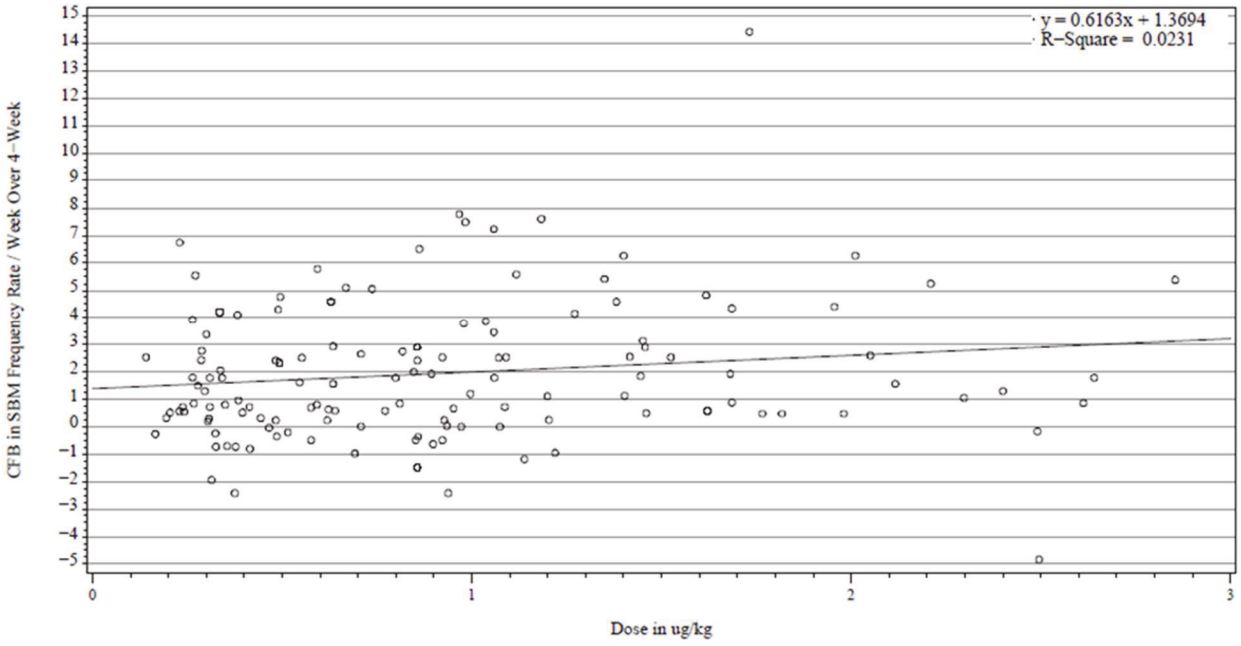
in the pediatric participants, and linaclotide was well tolerated across all doses and age groups. For participants in the 6 to 11 years age group in LIN-MD-62, the highest dose tested was 2 µg/kg. The linaclotide dose selected for Cohort 1 in the current LIN-MD-67 study, 18 µg, is consistent with the highest µg /kg dose tested in LIN-MD-62 in the 6 to 11 years age group (not to exceed 1.8 µg /kg) given minimum weight requirement for eligibility is 10kg. Dose escalation between cohorts will be implemented based on the review of all available safety/tolerability data by an independent DSMB.

**Figure 4-2** **Change from Baseline in 4-week Overall SBM Frequency Rate by Dose in µg/kg (ITT Population, LIN-MD-62)**




Abbreviations: CFB = change from baseline; ITT = intent-to-treat; SBM = spontaneous bowel movement
Source: Figure 14.2-1.3 of the LIN-MD-62 CSR

Assuming that the DSMB recommends proceeding to the next subsequent higher dose cohort, the following doses are planned to be tested in an ascending cohort design in the current study:

- Cohort 1: 18 µg (not to exceed 1.8 µg /kg, assuming minimum body weight of 10 kg*)
- Cohort 2: 36 µg (not to exceed 3.6 µg /kg, assuming minimum body weight of 10 kg*)
- Cohort 3: 72 µg (not to exceed 7.2 µg /kg, assuming minimum body weight of 10 kg*)

*10 kg =10% for 2-year old based on the CDC Stature for Age and Weight for Age percentiles in 2 to 20-year old boys (See Section 5.1, Inclusion Criteria 1.02)

Please refer to Section 4.1 and Figure 1-1 for assignment of participants to dose cohorts.

After at least 6 participants in each of the serial Cohorts 1 to 3 complete at least 2 weeks of double-blind study intervention, an independent DSMB will review unblinded interim safety



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data. Based on this review, the DSMB will recommend whether the subsequent planned dose level should be tested. New participants will be recruited for each cohort.

## 4.4. End of Study Definition

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

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

## 4.5. End of Cohort Definition

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

# 5. Study Population

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

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

## 5.1. Inclusion Criteria

The targeted participant population will include male and female participants, 2 to 5 years of age.

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

| | |
|---|---|
| **1.** | **Age and Weight** |
| **1.01** | Male and female participants must be ages 2 to 5 years, (inclusive) at the time the parent/guardian/LAR has provided signed consent |
| **1.02** | Participant weighs ≥ 10 kg at the time the parent/guardian/LAR has provided signed consent |
| **2.** | **Type of Participant and Disease Characteristics** |

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| | |
|---|---|
| **2.01** | Participant meets modified Rome III criteria for FC: For at least 2 months before Screening (Visit 1) (for participants aged ≥ 4 years old), or for at least 1 month before Screening (Visit 1) (for participants aged < 4 years old), the participant has had 2 or fewer defecations (with each defecation occurring in the absence of any laxative, suppository, or enema use during the preceding 24 hours) per week.<br>In addition, at least once per week, participant must meet 1 or more of the following:<br>a. History of retentive posturing or excessive volitional stool retention<br>b. History of painful or hard bowel movements (BMs)<br>c. Presence of a large fecal mass in the rectum<br>d. History of large diameter stools that may obstruct the toilet<br>e. At least one episode of fecal incontinence per week after the acquisition of toileting skills |
| **2.02** | Participant is willing to discontinue any laxatives used before the Preintervention Visit in favor of the protocol- permitted rescue medicine. |
| **2.03** | Participant has an average of fewer than 3 SBMs per week during the 14 days before the randomization day and up to the randomization (including the clinic eDiary assessments reported before administration of first dose of double-blind study intervention on the randomization day). An SBM is defined as a BM that occurs in the absence of laxative, enema, or suppository use on the calendar day of the BM or the calendar day before the BM |
| **2.04** | Caregiver is compliant with eDiary requirements by completing daily assessments for 10 out of the 14 days immediately preceding the Randomization Visit. |
| **3.** | **Informed Consent** |
| **3.01** | Parent/guardian/LAR and caregiver must provide written informed consent before the initiation of any study-specific procedures |
| **3.02** | Caregiver who will be completing the eDiary is able to read and/or understand the assessments in the eDiary device and must undergo training |

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## 5.2. Exclusion Criteria

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

| 1. | **Medical Conditions** |
|---|---|
| **1.01** | Participant has clinically significant findings on a physical examination, vital sign assessment, ECG, or clinical laboratory tests at Screening (Visit 1), as determined by the investigator, based on consideration of whether the finding could represent a safety concern or a condition that would be exclusionary, could prevent the participant from performing any protocol assessments, or could confound study assessments. |
| **1.02** | Caregiver reports the participant had more than 1 loose, mushy stool (eDiary-recorded stool consistency of 6 on the Bristol Stool Form Scale [BSFS]) or any watery stool (eDiary-recorded stool consistency of 7 on the BSFS) with any SBM that occurred in the absence of laxative use on the calendar day of the BM or the calendar day before the BM during the 14 days before the randomization day and up to the randomization (including the daily eDiary assessment reported before administration of first dose of double-blind study intervention on the randomization day) |
| **1.03** | *For participants aged ≥ 4 years old*: Participant meets Rome III criteria for Child/Adolescent IBS: At least once per week for at least 2 months before Screening (Visit 1), the participant has experienced abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with 2 or more of the following at least 25% of the time:<br>a. Improvement with defecation<br>b. Onset associated with a change in frequency of stool<br>c. Onset associated with a change in form (appearance) of stool |
| **1.04** | Participant has (a) fecal impaction at Visit 2 after failing outpatient clean-out during the Screening Period or (b) fecal impaction at Visit 3. |
| **1.05** | Participant has required manual dis-impaction any time prior to randomization or dis-impaction during in-patient hospitalization (for impaction) within 1 year prior to randomization |
| **1.06** | Participant currently has both unexplained and clinically significant alarm symptoms (lower GI bleeding [rectal bleeding or heme-positive stool], iron-deficiency anemia, or any unexplained anemia, or weight loss) and systemic signs of infection or colitis, or any neoplastic process |

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| | |
|---|---|
| **1.07** | Participant has had surgery that meets any of the following criteria:<br>a. Surgery to remove a segment of the GI tract at any time before Screening (Visit 1)<br>b. Surgery of the abdomen, pelvis, or retroperitoneal structures during the 6 months before the Screening Visit<br>c. An appendectomy or cholecystectomy during the 60 days before Screening (Visit 1)<br>d. Other major surgery during the 30 days before Screening (Visit 1) |
| **1.08** | Participant has an acute or chronic condition that, in the investigator's opinion, would limit the participant's ability to complete or participate in this clinical study |
| **1.09** | Participant has a known or suspected mechanical bowel obstruction or pseudo-obstruction. |
| **1.10** | Participant has a known allergy or sensitivity to the study intervention or its components or other medications in the same drug class |
| **1.11** | Participant has any of the following conditions:<br>a. Celiac disease, or positive serological test for celiac disease or the condition is suspected but has not been ruled out by endoscopic biopsy<br>b. Cystic fibrosis<br>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 Screening (Visit 1)<br>d. Down's syndrome or any other chromosomal disorder<br>e. Active anal fissure (ie, participant reports having streaks of blood on the stool or on toilet paper and/or pain/crying with bowel movement within 2 weeks prior to Screening). (Note: Anal fissures that have resolved at least 2 weeks prior to screening would not be exclusionary.) However, if in the investigator's opinion, an anal fissure(s) may be the primary cause of participant's modified Rome III FC criteria, the participant would not be eligible to participate in the study.<br>f. Anatomic malformations (eg, imperforate anus, anal stenosis, anterior displaced anus)<br>g. Intestinal nerve or muscle disorders (eg, Hirschprung disease, visceral myopathies, visceral neuropathies)<br>h. Neuropathic conditions (eg, spinal cord abnormalities, neurofibromatosis, tethered cord, spinal cord trauma)<br>i. Lead toxicity, hypercalcemia<br>j. Neurodevelopmental disabilities (early-onset, chronic disorders that share the essential feature of a predominant disturbance in the acquisition of cognitive, |

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| | |
|---|---|
| | motor, language, or social skills, which has a significant and continuing impact on the developmental progress of an individual) producing a cognitive delay that precludes comprehension and completion of the daily eDiary or other study-related questionnaires (Note: Participants are excluded if the person who will be completing the daily eDiary or other study-related questionnaires meets this criterion.)<br>k. Inflammatory bowel disease<br>l. Childhood functional abdominal pain syndrome<br>m. Childhood functional abdominal pain<br>n. Poorly treated or poorly controlled psychiatric disorders that might influence his or her ability to participate in the study<br>o. Lactose intolerance that is associated with symptoms which could confound the assessments in this study<br>p. History of cancer other than treated basal cell carcinoma of the skin. (Note: Participants with a history of cancer are allowed provided that the malignancy has been in a complete remission before the Randomization Visit. A complete remission is defined as the disappearance of all signs of cancer in response to treatment.) |
| **2.** | **Prior/Concomitant Therapy** |
| **2.01** | Participant used a protocol-specified prohibited medicine before the start of the Preintervention Period or failed to meet the stable-dose requirements of certain medications |
| **2.02** | Participant used rescue medication on the calendar day before the Randomization Visit and on the day of the Randomization Visit until randomized |
| **2.03** | Breastfeeding is allowed unless the mother is taking protocol-specified prohibited medicines (Section 6.5.1) |
| **3.** | **Prior/Concurrent Clinical Study Experience** |
| **3.01** | Participant received a study intervention during the 30 days before Screening (Visit 1) or is planning to receive study intervention (other than that administered during this study) |
| **4.** | **Other** |
| **4.01** | The participant has a condition or is in a situation which, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study. |

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| | |
|---|---|
| **4.02** | Participant's parent/guardian/LAR or caregiver has been directly or indirectly involved in the conduct and administration of this study as an investigator, study coordinator, or other study staff member. In addition, any participant, parent/guardian/LAR or caregiver who has a first-degree family member, significant other, or relative residing with him/her directly or indirectly who is involved in this study |
| **4.03** | *For participants aged ≥ 4 years old*: Participant has a history of non-retentive fecal incontinence |

**Rationale for Inclusion and Exclusion Criteria**

The inclusion and exclusion criteria are meant to identify a population of pediatric participants that is well characterized as having FC who fulfill modified Rome III criteria for childhood FC.

## 5.3. Lifestyle Considerations

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

- **Adequate fluids**: The investigator will discuss the fluid intake necessary to maintain a hydrated state (intake requirements may vary amongst children - eg, child athletes, children in hot climates).
- **A high-fiber diet**: Adequate intake values for fiber range from 19 to 25 g/day for children 1 to 8 years of age. High-fiber foods include beans, whole grains, fruits, and vegetables. Start slowly, adding just several grams of fiber a day over the Screening Period to reduce the amount of gas and bloating that can occur in someone who is not used to consuming high-fiber foods.
- **Increased physical activity**: Participants should be physically active throughout the day. Caregivers of participants should encourage active play that includes a variety of activity types.
- **Adequate time for bowel movements**:
    - For participants who have acquired toileting skills prior to Screening (Visit 1) encourage the child to sit on the toilet for 5 to 10 minutes twice daily within 30 minutes after a meal (breakfast and dinner). Follow the routine every day, even during holidays and vacations.
    - For participants who have started toilet training prior to Screening (Visit 1) but are not yet toilet trained, encourage the child to continue with same toilet training regimen (defined as sitting on the toilet for 5 to 10 minutes twice daily within 30 minutes after a meal (breakfast and dinner) during the study. Participants should not change the toileting behavior during the study as changes in toileting skills may





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impact bowel habits and accurate reporting of bowel movements and fecal incontinence.

- Parents/caregivers will be requested not to start the toilet training process with their child during the child's participation in the study. Changes in toileting skills may impact bowel habits and accurate reporting of bowel movements and fecal incontinence

## 5.4. Screen Failures

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

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

# 6. Study Intervention

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

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

A rationale for selection of the doses is provided in Section 4.3 (Justification for Dose).

## 6.1. Study Intervention(s) Administered

Linaclotide in the form of capsules will be packaged in bottles and provided by the sponsor. Study intervention will be administered at the study site during the Randomization Visit and at EOT (Visit 5) after confirming the participant has fasted for at least 2 hours. Participants may eat 30 minutes after dosing; the requirement is for study intervention to be administered 30 minutes before any meal at approximately the same time each day, with the exception of the first dose at Day 1 (Randomization Visit) and last dose at EOT (Week 4/Visit 5) when participants will receive the last dose of linaclotide or placebo in the clinic. At this EOT (Week 4/Visit 5) visit, participants will arrive in a fasted state for this visit to receive their last dose of study intervention before or after assigned PK sample. Confirmation will be recorded in the source



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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 or Placebo |
|---|---|
| **Dosage Formulation** | Capsules (refer to Study Reference Manual for capsule strength information) |
| **Dose Strength** | Refer to Section 4.1 for dose information |
| **Route of Administration** | Oral; capsule contents are to be sprinkled into 20 mL of bottled water, and 5 mL of this solution is dosed to the participant using an oral syringe. Instructions for dosing are provided in Appendix 7. |
| **Dosing Instructions** | Single dose, once daily at approximately the same time each day, 30 minutes before any meal |
| **Packaging and Labeling** | All bottles will be labeled with the protocol number, storage information, and warning language ("Caution: New Drug—Limited by Federal Law to Investigational Use, Keep out of Reach of Children") |
| **Manufacturer** | Forest Laboratories Ireland, Limited |

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

### 6.1.1. Selection and Timing of Dose for Each Participant

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

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

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

## 6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study intervention must be stored



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in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the study reference manual or other specified location.
5. Study interventions in bottles containing capsules must be stored at the study site in an appropriate secure area (eg, a locked cabinet in a locked room) at 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F - 86°F). Keep the product in the original container. Do not subdivide or repackage. Protect from moisture. Do not remove desiccant from the container. Keep bottles tightly closed in a dry place.
6. The investigator or designee is responsible for recording the receipt and use of all study interventions supplied and for ensuring the supervision of the storage and allocation of these supplies. All unused study interventions and protocol-permitted rescue medication must be returned; and, whenever study interventions are returned, unit counts must be performed. All study interventions must be accounted for. At the end of the study, all unused or empty study intervention containers should be returned to the sponsor or the local distributor at the address provided in the Study Reference Manual.

## 6.3. Measures to Minimize Bias: Randomization and Blinding

After a parent/LAR/caregiver sign the permission/consent at Screening (Visit 1), study personnel will register the participant in the IWRS, and the system will assign the participant a sequential PID number. The first participant entered in the system at each study site will be assigned the first number in the sequence by the system.

- Component 1: Study number (3 digits) = 267
- Component 2: Site number (5 digits) = 10001-19999
- Component 3: Participant number (3 digits) = 001-999

The randomization number encodes the participant's assignment to 1 of the 2 study intervention groups of the study, according to the randomization schedule generated prior to the study by the statistics department at the sponsor. Each participant will be dispensed blinded study intervention, labeled with his/her unique PID number, throughout the study.

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

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### 6.3.1. Blinding and Unblinding

#### 6.3.1.1. Blinding

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

#### 6.3.1.2. Unblinding

Any unblinding at the study site level should be done only in an emergency that requires for the study intervention to be identified for the medical management of the participant. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study 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 study 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. Study intervention codes may be broken by Global Patient Safety and Epidemiology for regulatory reporting purposes. In such cases, the study staff will be kept blinded and the participant will not need to be disqualified from the study. The unblinding of the bioanalytical representatives is to be carried out in a secure manner following the sponsor's standard operating procedures. Extreme care will be taken to ensure no other individuals outside the bioanalytical team will be unblinded.

***For IWRS Unblinding***

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

## 6.4. Study Intervention Compliance

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

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

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.



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## 6.5. Prior and Concomitant Therapy

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

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

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

### 6.5.1. Prohibited Interventions and Washout Before the Study

**Prohibited Medications**

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

**1-Day Washout**

1. Any over-the-counter or prescription laxative, suppository, or enema (eg, polyethylene glycol, lactulose, Fleet enema) and any herbal or natural agent that might be taken for constipation. (Note: The use of fiber, bulk laxatives, stool softeners [surfactants such as docusate], and probiotics is acceptable, provided that the participant has been on a stable dose for 30 days before Screening (Visit 1) and plans to continue stable dosing for the duration of the study)

2. Any medicine used to treat diarrhea (eg, bismuth subsalicylate, kaolin)

**14-Day Washout**

1. Drugs with known pharmacologic activity at 5-HT4, 5-HT2b or 5-HT3 receptors (eg, cisapride, tegaserod, prucalopride, ondansetron, tropisetron, granisetron, dolasetron, mirtazapine)
2. Any of the following treatments, either alone or in combination: plecanatide, lubiprostone, colchicine, linaclotide, and misoprostol
3. Prokinetic agents (eg, metoclopramide, itopride, domperidone)

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4. Anticholinergic agents (eg, dicyclomine, flavoxate, scopolamine, hyoscyamine, propantheline, oxybutynin, tolterodine, solifenacin, darifenacin, trospium). (Note: inhaled ipratropium and tiotropium are permitted)
5. Bile acid sequestrants (eg, cholestyramine, colestipol)
6. Cholinomimetic agents (eg, bethanechol, pyridostigmine, tacrine, physostigmine). (Note: intraocular cholinomimetic agents such as pilocarpine are permitted)
7. Antipsychotic agents (eg, risperidone, haloperidol, droperidol, chlorpromazine, perphenazine, all phenothiazines, quetiapine, olanzapine, clozapine), unless the participant has been on a stable dose for 30 days before Screening (Visit 1) and plans to continue stable dosing for the duration of the study. (Note: paliperidone is permitted without restriction)
8. Antidepressants, unless the participant has been on a stable dose for 30 days before Screening (Visit 1) and plans to continue stable dosing for the duration of the trial. Specifically included are the following:
    a. Tricyclic antidepressants (eg, amitriptyline, imipramine, nortriptyline)
    b. Monoamine oxidase inhibitors (eg, furazolidone, isocarboxazid, pargyline phenelzine, selegiline, tranylcypromine)
    c. Selective serotonin reuptake inhibitors (eg, fluoxetine, sertraline, paroxetine, escitalopram, citalopram, vilazodone)
    d. Serotonin-norepinephrine-reuptake inhibitors (eg, levomilnacipran, duloxetine, venlafaxine, desvenlafaxine succinate)
    e. Other antidepressants (eg, trazodone, bupropion)
9. Calcium-channel blocker verapamil, unless the participant has been on a stable dose for 30 days before Screening (Visit 1) and plans to continue stable dosing for the duration of the study. (Note: all other calcium-channel blockers [eg, nifedipine, diltiazem, amlodipine, felodipine, nicardipine, nimodipine, nisoldipine] are permitted and may be used without restriction).
10. Oral and parenteral antibiotics; however, 1 standard regimen (up to 10 days) of oral antibiotics is permitted during the Study Intervention and Postintervention Period*s*
11. Any study intervention or imported drugs that have not been approved for human use
12. All narcotics (eg, tramadol, codeine, morphine, propoxyphene, loperamide, diphenoxylate, paregoric), either alone or in combination. Note: narcotics used as anesthesia for a colonoscopy require a 5-calendar day wash-out prior to the participant entering into the Preintervention Period. Dextromethorphan, the cough suppressant in many over-the-counter cold and cough medicines, is allowed.
13. Any medication to treat attention-deficit/hyperactivity disorder, unless the participant has been on a stable dose for ≥ 30 days before Screening (Visit 1) and plans to continue stable dosing for the duration of the study
14. Any medicine that is known to cause diarrhea (eg, acarbose)

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

### 6.5.2. Rescue Medication

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

When there is more than one option available, the participants will choose a rescue medication(s) at the Preintervention Visit (Visit 2) and study site staff will register the rescue medication in IWRS, where applicable. The study site must contact the IWRS (if applicable) at all subsequent study visits to obtain the protocol-permitted rescue medication to be dispensed to the participant at each visit as needed.

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

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

## 6.6. Dose Modification

Dose modifications will not be allowed during this study. However, the investigator may allow a participant to stop taking study intervention for up to 3 days because of an AE. If the investigator believes that the participant is unable to resume dosing after 3 days or requires a suspension of dosing on more than 1 occasion, the investigator is required to contact the Study Physician to discuss the participant's continued participation in the study.

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# 7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

## 7.1. Discontinuation of Study Intervention

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

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

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

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

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

### 7.1.1. Removal of Individual Participants from Therapy or Assessment

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

- An SAE considered by the investigator or the sponsor to be possibly related or related to study intervention,
- An AESI (evidence of significant volume depletion and/or significant electrolyte and/or ECG abnormalities that are considered by the investigator or sponsor to be related to diarrhea) related to the study intervention (ie, intervention-related AESIs) see Section 8.3.1,

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

- The presence of intentional overdose or intentional misuse per investigator discretion

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- 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 participant to consider study withdrawal), see Section 6.1.1
- 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

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 the best interest of the participant.

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

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

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

### 7.1.2. Criteria for Consideration of Study Discontinuation

Dosing and enrollment will be immediately paused for all participants at all sites and a thorough review will be initiated after any one of the following conditions has been met in participants who have received study intervention at any time in the study:

- Any life-threatening SAE that is considered by the investigator or the sponsor to be possibly related or related to the study intervention.

- Any SAE resulting in death that is considered by the investigator or the sponsor to be possibly related or related to the study intervention.

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In the event of a pause in enrollment and dosing, the Data Safety and Monitoring Board (DSMB) will be notified and their recommendation on an appropriate course of action will be sought. This may include resuming enrollment, continuing a hold on enrollment, resuming the study intervention, amending the protocol or stopping the study (Section 10.1.6.3). The decision to restart or to stop the study will be made by the sponsor, following a thorough review of all clinical, laboratory, DSMB recommendations and other available safety data.

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

## 7.2. Participant Discontinuation/Withdrawal from the Study

- A participant/parent/LAR may withdraw from the study at any time at their request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- If the participant/parent/LAR 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/parent/LAR withdraws from the study, they may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

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

## 7.3. Lost to Follow-Up

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

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

- The site must attempt to contact the participant/parent/LAR and reschedule the missed visit as soon as possible and counsel them 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/parent/LAR (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or

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local equivalent methods). These contact attempts will be documented in the participant's study record.

- Should the participant/parent/LAR continue to be unreachable, he/she will be considered to have withdrawn from the study.

# 8. Study Assessments and Procedures

A detailed listing of study assessments by day is presented in Appendix 8.

- 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 12 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the sample.
- Additional details regarding study conduct during the novel coronavirus pandemic are provided in Appendix 10.

## 8.1. Efficacy Assessments

An observer-reported outcome (ObsRO) instrument assessing key signs and symptoms of FC for use in children (2 to 5 years of age) with FC was developed by Allergan and Ironwood Pharmaceuticals based on extensive qualitative research with caregivers of children with FC, as well as feedback from pediatric gastroenterologists, measurement experts, and health authorities. The ObsRO instrument was developed for completion by caregivers on an electronic diary (eDiary). Data collected in the eDiary will be used to derive the efficacy endpoints.

All efficacy assessments will be determined by responses entered in the eDiary by the caregiver. The caregiver is identified as the individual who completes the eDiary and should be the same individual throughout the course of the study and must be able to read and understand the eDiary



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as a condition for study participation (Inclusion Criterion 3.02). At the start of the Preintervention Period, caregivers will receive full training in the use and completion of the eDiary at the study visit in which they are given the eDiary device. If the caregiver completing the diary changes, the study team should be notified and should document the date when it changed and who the new caregiver is. The new caregiver must also provide written informed consent before the initiation of any study-specific procedures.

### 8.1.1. Key Efficacy Assessments

The key efficacy assessments, which will be used to determine the efficacy parameter of SBM frequency, are the items assessing BM frequency and rescue medication use. Caregivers will report their child's BM frequency (the number of BMs) by responding to the following:

**Bowel Movement Frequency**

**Rescue medication use**

**Stool Consistency (Bristol Stool Form Scale)**

If the caregiver was present for the BM, he/she will be asked to rate the child's observed stool consistency for each BM he/she was present for.

Stool consistency will be based on the BSFS. The BSFS is a widely used measurement of stool consistency (Lewis 1997). Caregivers will use the BSFS 7-point ordinal scale to rate their child's stool consistency as follows:

- "Choose the option that is most like the Xth (eg, 1st, 2nd, 3rd, ...) bowel movement you were with the child for"
    - Type 1: Separate hard lumps, like nuts (hard to pass)
    - Type 2: Sausage-shaped, but lumpy
    - Type 3: Like a sausage but with cracks on its surface
    - Type 4: Like a sausage or snake, smooth and soft
    - Type 5: Soft blobs with clear cut edges (easy to pass)
    - Type 6: Fluffy pieces with ragged edges, a mushy stool
    - Type 7: Watery, no solid pieces. Entirely liquid
    - 99 - I don't know



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**Straining With BM**

If the caregiver was present for the BM, they will be asked to rate the amount of straining they observed when the child passed the BM. They will be asked this for every bowel movement for which they were present.

[redacted]

**Fecal Incontinence (For Participants Who Have Acquired Toileting Skills Only)**

Caregivers of children who have acquired toileting skills for bowel movements will be asked about their child's fecal incontinence episodes.

[redacted]

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### 8.1.2. Other Efficacy Assessments

**Modified Rome III Criteria**

Modified Rome III criteria will be assessed by the investigator at the Screening Visit (Visit 1) and at the end of the study intervention period at the EOT Visit (Visit 5). A participant will be considered as fulfilling modified Rome III criteria if a "yes" response is recorded to the overall question of whether the participant meets modified Rome III criteria for functional constipation. For the EOT assessment, these criteria will be assessed over the 4-week double-blind study intervention period. In the event a participant discontinues the study prematurely, these criteria will be assessed over the duration of time the participant received double-blind study intervention.

**Global Items**

Assessments of global change in symptoms and global severity of symptoms will be completed weekly in the eDiary.

The global items consist of 2 items, 1 assessing global change in the child's symptoms and 1 assessing the global severity of the child's symptoms. Both global items will be completed weekly on the eDiary by the caregiver. The global severity item will be completed beginning at the Preintervention Period through the End of Study and the global change item will be completed from 1 week after randomization through the End of Study.



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**Global Change Item**

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

**Global Severity Item**

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

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

All AEs will be monitored until symptom resolution or until the condition stabilizes. A DMSB will oversee AEs and safety of the overall study (Section 10.1.6.3).

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

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### 8.2.1. Physical Examinations

A complete physical examination will be done at screening and at the Week 4/EOT Visit by a professionally trained physician or health professional listed on Form FDA 1572 or the Delegation of Authority log and licensed to perform physical examinations. Physical examinations may be repeated at the investigator's discretion. If fecal impaction is documented during an optional repeat physical examination, the study physician must be notified.

Any new physical examination abnormalities for the post-baseline physical examination or worsening of the change from Screening (Visit 1) will be reported as an AE.

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

In addition to the physical examination, a fecal impaction assessment will be performed for all participants at both Screening (Visit 1) and Randomization (Visit 3) prior to randomization and 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 Screening (Visit 1), 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). After the participant has received treatment for the impaction, the investigator must re-evaluate the participant for the presence of fecal impaction at the Preintervention Visit (Visit 2). If there is no fecal impaction at the Preintervention Visit, the participant may enter the Preintervention Period after adhering to any washout requirements (Section 10.8.2). If fecal impaction is present upon re-examination, the participant will not be eligible for the study (ie, they have failed their out-patient clean-out regimen).
- If fecal impaction is present upon examination at Randomization (Visit 3), the participant will not be eligible to be randomized into the study.

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### 8.2.2. Vital Signs

Vital signs and postural vital signs will be obtained and documented as noted in the SOA (see Section 1.3). Vital signs will be assessed as follows:

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. Temperature may be recorded as oral, rectal or tympanic (ear). If possible, temperature should be obtained using the same method throughout the course of the study.

At all visits, postural vital signs must be obtained after participants have been in a supine position for at least 2 to 3 minutes, followed by a standing position for at least 1 minute.

### 8.2.3. Electrocardiograms

A standard 12-lead ECG will be performed at Screening (Visit 1) and at the Week 4/EOT Visit. ECGs will be performed and electronically transmitted to a central ECG laboratory for analysis according to the instructions provided by the central ECG laboratory. Measurements (in msec) will be recorded for the following parameters: heart rate, RR interval, PR interval, QRS duration, and uncorrected QT interval. QTcB (Bazett-corrected QT interval) and QTcF (Fridericia-corrected QT interval) will be calculated.

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

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

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

### 8.2.4. Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- At Screening (Visit 1), the investigator will assess the clinical significance of any values outside the reference ranges provided by the laboratory, and participants with abnormalities judged to be clinically significant will be excluded from the study.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The



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laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significant during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical safety physician.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the SoA and the laboratory manual.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.
- Participants with clinically significant electrolyte abnormalities that are considered to be secondary to diarrhea (ie, an AE of special interest) must be reported to the sponsor within 24 hours on an SAE form if considered to be serious. Non-serious events do not require submission on an SAE form; rather, these events only need to be entered into the eCRF (Section 10.3). If the AE is assessed as causally related to the use of study intervention, the participant should be discontinued from the study; however, the study physician and investigator may discuss individual participants and AEs to make this determination (Section 10.3).
- A central laboratory will be used to evaluate all blood samples, which will be collected, processed, and stored according to the instructions provided by the laboratory.

## 8.3. Adverse Events and Serious Adverse Events

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

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following



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up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

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

Examples of AEs are as follows:

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

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

### 8.3.1. Adverse Events of Special Interest (AESIs)

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

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

At each visit, participants are to be queried regarding any AEs or SAEs that have occurred since the previous visit. Participants will be asked to volunteer information with a nonleading question such as, “How do you feel since your last visit?” Study site personnel will record all pertinent information in the participant’s eCRF. All 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 SoA (Section 1.3), and as observed or reported spontaneously by study participants.

All AEs from the signing of the ICF until 30 days after the last dose of study intervention will be collected at the timepoints specified in the SoA (Section 1.3), and as observed or reported spontaneously by study participants.

Medical occurrences that begin before the start of study intervention, but after obtaining informed consent will be recorded in the AE section of the eCRF.

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All SAEs and serious AESIs of special interest will be recorded and reported to the sponsor or designee within 24 hours on an SAE form, as indicated in Section 10.3. Non-serious AESIs do not require submission on an SAE form; rather, these events only need to be entered into the eCRF. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

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

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

After the initial AE/ SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE/ SAE and non-serious AEs of special interest (as defined in Section 10.3) 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 and AESI data to the sponsor within 24 hours of receipt of the information.

### 8.3.5. Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.



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

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

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

### 8.3.6. Potential Hy's Law Cases

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

- ALT or AST ≥ 3 × upper limit of normal [ULN] AND
- Total bilirubin ≥ 2 × ULN AND
- ALP < 2 × ULN

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

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

### 8.3.7. Medication Errors

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

- Wrong study drug
- Wrong dose (including dosing regimen, strength, form, concentration, amount)
- Wrong route of administration



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- 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

An important consideration is whether oral bioavailability of linaclotide is similar in children as in adults or whether systemic exposure may be higher in children. Sparse PK sampling will therefore be included in this study to assess the PK of linaclotide in children. Sparse PK blood samples will be collected at the pre-specified times to determine plasma concentration of linaclotide and its active metabolite (MM-419447).

### 8.5.1. Blood Pharmacokinetic Sampling Procedure

Participants in Cohorts 1-3 will be randomized on Study Day 1 (Visit 3) at a 1:3 ratio to either a pre-dose or post-dose PK sample and the 6 participants in the final cohort will be randomized at a 1:2 ratio to either a pre-dose or post-dose PK sample, respectively, to be completed before or after the last dose of study intervention at Visit 5 (Week 4) for determination of linaclotide and active metabolite (MM-419447) concentrations in plasma. One blood sample will be collected from each participant at Visit 5 (Week 4) before or after the last dose of study intervention, along with all laboratory blood samples at same time. Postintervention PK sample will be collected at 1 to 8 hours post-dose.

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Blood samples will be collected in 2-mL Vacutainer tubes containing $K_2$EDTA as an anticoagulant. Blood samples will be processed, stored, and shipped as directed in the Study Manual.

All participants will be instructed to hold their last dose of linaclotide/placebo for Visit 5 (Week 4) and will take their dose at the site that day in a fasted state. Every attempt should be made to ensure that the dosing time during Visit 5 (Week 4) is consistent with the time linaclotide has been taken during the course of the study intervention. Sites will also be instructed to encourage caregivers to schedule Visit 5 (Week 4) early in the study once the participant is randomized as the participants will need to take linaclotide in a fasted state (Section 10.8.3). Sites will also document the date and time of the dose administered prior to the PK sample collection.

#### 8.5.2. Pharmacokinetic Sample Bioanalysis

Plasma concentrations of linaclotide and its active metabolite (MM-419447) will be determined using a validated liquid chromatography-tandem mass spectrometry method.

## 8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

## 8.7. Genetics

Not applicable

## 8.8. Biomarkers and Other Assessments

Biomarkers are not evaluated in this study.

## 8.9. Health Economics

Not applicable.

# 9. Statistical Considerations

## 9.1. Statistical Endpoints

Key efficacy endpoints include:

- Change from baseline in 4-week overall SBM frequency rate (SBMs/week) during the Study Intervention Period of each cohort
- Change from baseline in 4-week stool consistency reported by the caregiver during the Study Intervention Period of each cohort
- Change from baseline in 4-week straining reported by the caregiver during the Study Intervention Period of each cohort

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- Proportion of days with fecal incontinence during the Study Intervention Period (for participants who have acquired toileting skills during daytime and nighttime or acquired toileting skills during daytime only) within each cohort

Other efficacy endpoints include:

- Proportion of participants who no longer fulfill modified Rome III criteria for functional constipation at the end of the Study Intervention Period.
- Proportion of participants with each individual item score for the global change in symptoms and the global severity of symptoms at each week during the Study Intervention Period.

## 9.2. Sample Size Determination

Up to 30 participants, 2 to 5 years of age, will be sequentially enrolled into LIN-MD-67; 8 participants each into Cohorts 1 to 3 will be randomly assigned with 3:1 allocation ratio either to linaclotide dose or matching placebo and 6 additional participants in the final cohort will be randomly assigned with 5:1 allocation ratio either to linaclotide dose or matching placebo. Participants will be randomly assigned to receive linaclotide or matching placebo as described in Section 4.1.

Sample size in this study is not driven by any statistical consideration. Instead, this study is designed to enroll sufficient pediatric participants to observe the clinical response trends and monitor safety.

## 9.3. Populations for Analyses

Four analysis populations will be defined as follows:

- Screened population includes all participants who undergo Screening (Visit 1) and receive a PID number.
- Randomized population includes all participants in the Screened population who are randomized to a study intervention group.
- Safety population includes all participants in the Randomized population who receive at least 1 dose of double-blind study intervention. Participants will be summarized according to the study intervention they actually receive for all safety analysis variables/endpoints.
- Modified intent-to-treat (mITT) population includes all participants in the Randomized population who receive at least 1 dose of double-blind study intervention and who had at least 1 postbaseline entry on BM characteristic assessments that determine occurrences of SBMs (ie, BM frequency and rescue medication use). Participants will be summarized according to the randomized study intervention for all efficacy analysis variables/endpoints.

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## 9.4. Statistical Analyses

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

### 9.4.1. Efficacy Analyses

All efficacy analyses will be performed based on the mITT population.

Baseline values for efficacy parameters related to daily eDiary responses will be derived from the eDiary in the Preintervention Period, specifically the period of time from 14 days before randomization up to the time of randomization. The numerator of the baseline weekly SBM rate will be derived based on the total number of caregiver-observed SBMs a participant had during this period. Caregiver-observed SBMs are defined as SBMs reported in the eDiary for which the caregiver identified being with the child for.

Baseline stool consistency reported by the caregiver based on daily assessments will be calculated as a mean of the participant's non-missing BSFS scores from each caregiver-observed SBM during this period. Baseline straining score reported by the caregiver will be calculated as a mean of the participant's non-missing daily average straining score [redacted] from caregiver-observed SBMs during this period. A participant's baseline stool consistency and straining reported by the caregiver cannot be assessed if the participant does not have at least 1 caregiver-observed SBM during the Preintervention Period. For participants with no caregiver-observed SBMs reported in the eDiary during a study period, the consistency and straining assessments reported by caregiver will be considered missing for that study period in the analyses. Participants with missing baseline consistency and straining reported by the caregiver will be excluded from the respective consistency and straining change from baseline analyses.

Baseline value for the global severity in symptoms will be based on the last non-missing assessment on or before the date of first dose of study intervention.

An observed-cases approach to missing postbaseline data will be applied. The descriptive statistics for efficacy endpoints including placebo and the corresponding linaclotide dose in each cohort will be provided to evaluate the main objective of this study. No statistical testing will be performed to compare linaclotide dose with placebo. No multiplicity adjustment will be applied in this dose-ranging study.

Descriptive statistics for continuous endpoints in terms of mean, median, standard deviation, standard error of mean, minimum, and maximum will be provided for placebo and corresponding linaclotide dose within each cohort. For categorical endpoints, count and percentages will be provided for placebo and corresponding linaclotide dose within each cohort.

If any cohort has linaclotide dose similar to the other cohort, summary statistics will be provided for these efficacy parameters combining the participants from similar dose cohorts. Any additional analysis will be discussed further in Statistical Analysis Plan.



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#### 9.4.1.1. Key Efficacy Endpoints

**Change from baseline in 4-week overall SBM frequency rate (SBMs/week) during the Study Intervention Period of each cohort**

The numerator of the SBM rate (SBMs/week) during the Study Intervention Period of each cohort will be derived based on the total number of SBMs reported by a caregiver as being directly observed during this period in the eDiary. Additional analysis will also be performed based on the total number of SBMs reported during the Study Intervention Period (including SBMs not directly observed by the caregiver) and the corresponding baseline SBM frequency rate will be determined based on the total number of SBMs reported during the Preintervention period.

**Change from Baseline in 4-Week Stool Consistency Reported by the Caregiver During the Intervention Period of Each Cohort**

Stool consistency for each caregiver-observed BM will be measured daily in the eDiary using the 7-point ordinal BSFS. A participant's BSFS score for the Study Intervention Period will be the average of the non-missing BSFS scores from the caregiver-observed SBMs during the 4-week Study Intervention Period. If no caregiver-observed SBMs are present at baseline, the baseline BSFS score reported by caregiver will be missing and, therefore, that participant will not be included in the change from baseline stool consistency analysis.

**Change from Baseline in 4-Week Straining Reported by the Caregiver During Study Intervention Period for Each Cohort**

Straining for each caregiver-observed BM will be collected daily in the eDiary device, using a 4-point scale based on two questions as discussed in Section 8.1.1. The participant's daily straining score for each caregiver-observed BM will be derived based on the average of non-missing responses of the two straining questions. The participant's straining score in the 4-week Study Intervention Period will be the average of the non-missing daily average straining scores from the caregiver-observed SBMs during the 4-week Study Intervention Period for each cohort. If a participant has no caregiver-observed SBMs at baseline, then the baseline straining score reported by the caregiver will be missing and, therefore, that participant will not be included in the change from baseline straining analysis.

**Proportion of days with fecal incontinence during study intervention period (for participants who have acquired toileting skills during daytime and nighttime or acquired toileting skills during daytime only) within each cohort**

Fecal incontinence will be collected daily in the eDiary. Any "yes" response for the question [redacted] will be counted as presence of fecal incontinence in the corresponding day (Section 8.1.1).

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#### 9.4.1.2. Other Efficacy Endpoints

**Proportion of participants who no longer fulfill modified Rome III criteria for functional constipation at the end of the study intervention period**

Modified Rome III criteria will be assessed by the investigator at the Screening Visit (Visit 1) and at the end of the study intervention period at the EOT Visit (Visit 5). A participant will be considered as fulfilling modified Rome III criteria if a "yes" response is recorded to the overall question of whether the participant meets modified Rome III criteria for functional constipation. For the EOT assessment, these criteria will be assessed over the 4-week double-blind study intervention period. In the event a participant discontinues the study prematurely, these criteria will be assessed over the duration of time the participant received double-blind study intervention (Section 8.1.2).

**Proportion of participants with each individual item score for the global change in symptoms and the global severity of symptoms at each week during the study intervention period**

The global change in symptoms and the global severity of symptoms will be assessed on a weekly basis in the eDiary with a 7-point scale and a 5-point scale respectively as discussed in Section 8.1.2.

### 9.4.2. Safety Analyses

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

Safety summaries will be provided for each cohort separately. If any cohort has a similar linaclotide dose with another cohort, the safety summaries will also be provided combining participants from the similar dose cohorts, as appropriate.

#### 9.4.2.1. Adverse Events

An AE will be considered a TEAE if:

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

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

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

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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 within each cohort separately.

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

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

Listings of all AEs, SAEs, AESIs, and AEs leading to discontinuation by participant will be presented.

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

#### 9.4.2.2. Clinical Laboratory Assessments

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

The criteria for potentially clinically significant (PCS) laboratory values will be detailed in the SAP. The number and percentage of participants who have PCS postbaseline clinical laboratory values within the corresponding cohort during the double-blind study intervention period 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 for the double-blind Study Intervention Period of the corresponding cohort. The numerator will be the total number of participants with available non-PCS baseline values and at least 1 PCS postbaseline value during the double-blind Study Intervention Period of the corresponding cohort. A supportive listing of participants with PCS postbaseline values will be provided for the safety population.

#### 9.4.2.3. Vital Signs

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

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

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the specific period of the corresponding cohort. A supportive listing of participants with PCS postbaseline values will be provided for the safety population.

#### 9.4.2.4. Electrocardiograms

Descriptive statistics for ECG parameters (ie, ventricular heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc) at baseline and changes from baseline values at each assessment time point will be presented by study intervention group within each cohort. 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 within the corresponding cohort. The criteria for PCS ECG values will be detailed in the SAP. The percentages will be calculated relative to the number of participants with available non-PCS baseline values and at least one postbaseline assessment for the double-blind Study Intervention Period within the corresponding cohort. The numerator will be the total number of participants with available non-PCS baseline values and at least one PCS postbaseline value during the double-blind Study Intervention Period of the corresponding cohort. A supportive listing of participants with PCS postbaseline values will be provided for the safety population.

### 9.4.3. Pharmacokinetic Analyses

Individual plasma concentrations of linaclotide and its active metabolite (MM-419447) will be listed by participant. Summary statistics of plasma concentrations for each analyte will be provided by dose group and time after the most recent dose if there are sufficient data to perform such an evaluation. In addition, population PK parameters of linaclotide and MM-419447 may be calculated via population PK modeling if data permits.

### 9.4.4. Subgroup Analyses

Subgroup analyses (if planned) will be defined in the SAP.

## 9.5. Interim Analyses

No interim analyses are planned.

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# 10. Supporting Documentation and Operational Considerations

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

### 10.1.1. Regulatory and Ethical Considerations

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

### 10.1.2. Financial Disclosure

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

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### 10.1.3. Informed Consent Process

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

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

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

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

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

### 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.

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### 10.1.6. Data Quality Assurance

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

#### 10.1.6.1. Data Monitoring

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



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

#### 10.1.6.2. Data Recording and Documentation

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

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

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

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

#### 10.1.6.3. Data and Safety Monitoring Board (DSMB)

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

### 10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study.



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### 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, and its partner, Ironwood, have 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



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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), or the integrity and authenticity of the study data should be reported to the sponsor within 24 hours, if possible.

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

### 10.1.11. Study Documentation

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

- For sites in the United States, a completed and signed Form FDA 1572. If, during the course of the study, any changes are made that are not reflected on Form FDA 1572, a new Form FDA 1572 must be completed and returned to the sponsor for submission to the FDA
- A fully executed contract
- For sites in the United States, the curricula vitae for the investigator and all sub-investigators listed on Form FDA 1572, including a copy of each physician's license
- A copy of the original IRB/IEC approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals. All subsequent modifications must be submitted and approved by the IRB/IEC, as stated in Section 10.1.1.
- A copy of the IRB/EC-approved parent/LAR, Caregiver ICFs
- A copy of the HIPAA authorization form, or other local privacy applicable forms
- A list of the IRB/IEC members or the US Department of Health and Human Services general assurance number
- The Investigator's Statement page in this protocol signed and dated by the investigator
- For sites in the United States, financial disclosure agreement completed and signed by the investigator and all subinvestigators listed on Form FDA 1572. The investigator and all subinvestigators will provide an updated financial disclosure agreement to the sponsor 1 year after the completion of the study

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## 10.2. Appendix 2: Clinical Laboratory Tests

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

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

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

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 and blood samples, which will be collected, processed, and stored according to the instructions provided by the laboratory.

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.

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**Table 10–1 Protocol-Required Safety Laboratory Assessments**

| Laboratory Assessments | Parameters | | | |
|---|---|---|---|---|
| Hematology | Platelet count<br>Red blood cell (RBC) count<br>Hemoglobin<br>Hematocrit | RBC indices:<br>MCV<br>MCH<br>MCHC | | White blood cell (WBC) count with differential (absolute):<br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils |
| Clinical Chemistry[a] | Blood urea nitrogen (BUN) | Potassium | AST | Total, direct and indirect bilirubin |
| | Creatinine | Sodium<br>Bicarbonate<br>Magnesium<br>Phosphate<br>Total protein<br>Total bilirubin | ALT | Total protein<br>Total cholesterol<br>chloride,<br>albumin |
| | Glucose non-fasting | Calcium | ALP | |
| Routine Urinalysis | • Specific gravity<br>• pH, glucose, protein, blood, ketones Microscopic examination (if blood or protein is abnormal) | | | |
| Other Screening Tests | • All study-required laboratory assessments will be performed by a central laboratory | | | |

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

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

**Definition of AE**

| AE Definition |
|---|
| • An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.<br>• 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.<br>For the purpose of the site's data collection responsibilities, any untoward event that was reported from the time written consent was obtained until 30 days after the last known dose of study intervention is to be considered an AE. Particular attention must be given to the AE of diarrhea, which was the most frequently reported AE in the adult linaclotide program. Details about AE reporting are provided below.<br>Examples of AEs are as follows:<br>• Changes in the general condition of the participant<br>• Subjective symptoms offered by or elicited from the participant<br>• Objective signs observed by the investigator or other study site personnel<br>• All diseases that occur after signing the informed consent, including any change in severity or frequency of preexisting disease<br>• All clinically relevant abnormalities in laboratory values or clinically relevant physical findings that occur during the study schedule<br>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.<br>**AE of Special Interest (AESI)**<br>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.<br>The following AESI(s) have been identified for the study intervention(s) in this protocol: significant volume depletion and/or significant electrolyte abnormalities and/or ECG abnormalities that are considered by the investigator or sponsor to be related to diarrhea. The investigator should contact the Study Physician if there is any question whether the criterion for an AESIs has been met.<br>All serious AESIs must be reported to the sponsor on an SAE form within 24 hours as noted below for SAEs.<br>Non-serious AESI do not require submission on an SAE form; rather, these events only need to be entered into the eCRF. |

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

**Potential Hy's Law Cases**

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

**Events Meeting the AE Definition**

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease); for example:
  - The test result is associated with accompanying symptoms, and/or
  - The test result requires additional diagnostic testing or medical/surgical intervention, and/or
  - The test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
  - The test result is considered to be an AE by the investigator or sponsor.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

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| 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.<br>• 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.<br>• The following disease-related events (DREs) are common in participants with FC and can be serious/life threatening:<br>o Abdominal bloating<br>o Straining<br>o Sense of incomplete evacuation<br>o Fecal incontinence<br>If the investigator considers these manifestations to have a reasonable possibility of relationship to the study intervention(s), then they should be reported as AEs or SAEs.<br>• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE<br>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)<br>• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen |

**Definition of SAE**

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**<br>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. |

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| |
|---|
| **c. Requires inpatient hospitalization or prolongation of existing hospitalization**<br>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.<br>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**<br>• The term disability means a substantial disruption of a person's ability to conduct normal life functions.<br>• 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:**<br>• 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.<br>Examples of such events include invasive or malignant cancers, intensive intervention in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. |

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

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**Recording and Follow-Up of AE and/or SAE**

**AE and SAE Recording**

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

**Assessment of Intensity**

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

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

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

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| Assessment of Causality |
|---|
| • The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE.<br>• 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.<br>• The investigator will use clinical judgment to determine the relationship.<br>• 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.<br>• The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment.<br>• 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.<br>• 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.**<br>• 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.<br>• The causality assessment is one of the criteria used when determining regulatory reporting requirements. |

**Reporting of SAEs**

| SAE Reporting |
|---|
| • All SAEs will be recorded and reported to the sponsor within 24 hours on an SAE form.<br>• The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.<br>• Email is the preferred method to transmit SAE information. The email address is IR-Clinical-SAE@allergan.com.<br>• Facsimile transmission of the SAE information is also acceptable. The fax number is +1-714-796-9504 (backup number is +1-714-246-5295).<br>• 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.<br>• 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.<br>• Contacts for SAE reporting can be found on the protocol title page. |



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## 10.4. Appendix 4: Abbreviations

| | |
|---|---|
| AE | adverse event |
| AESI | adverse event of special interest |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| BM | bowel movement |
| BSFS | Bristol Stool Form Scale |
| CBC | complete blood count |
| CFR | Code of Federal Regulations |
| CC | chronic constipation |
| CIC | chronic idiopathic constipation |
| DILI | drug-induced liver injury |
| DSMB | Data and Safety Monitoring Board |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| eDiary | electronic diary |
| 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 |
| HEENT | head, ears, eyes, nose, and throat |
| 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 |

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| | |
|---|---|
| IV | intravenous |
| IWRS | interactive web response system |
| LAR | legally authorized representative |
| mITT | modified intent-to-treat |
| mRNA | messenger ribonucleic acid |
| MSP | medical safety physician |
| ObsRO | observer-reported outcome |
| PCS | potentially clinically significant |
| PID | participant identification |
| PK | pharmacokinetic |
| 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 |
| ULN | upper limit of normal |

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## 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) |
| Progressive disease | A disease process that is increasing in extent or severity (NCI) |
| Recovery | A healing process and/or an outcome implying relative health. The term is typically used in the context of direct and indirect effects of sickness or injury. (NCI) |
| Screen failure | The potential subject who does not meet one or more criteria required for participation in a trial |
| Site terminated by sponsor | An indication that a clinical study was stopped at a particular site by its sponsor (NCI) |
| Study terminated by sponsor | An indication that a clinical study was stopped by its sponsor (NCI) |
| Technical problems | A problem with some technical aspect of a clinical study, usually related to an instrument (NCI) |

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| CDISC Submission Value | CDISC Definition |
|---|---|
| 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) |

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## 10.6. Appendix 6: Study Tabular Summary

| Parameter Group | Parameter | Value |
|---|---|---|
| Trial information | Study Title | A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Sequential, Ascending, Multidose Study to Evaluate the Safety and Efficacy of Linaclotide in Pediatric Participants (Age 2 to 5 Years) with Functional Constipation. |
| | Clinical Study Sponsor | Allergan Sales LLC |
| | Study Phase Classification | 2 |
| | Study Indication | FC |
| | Study Indication Type | Study Intervention |
| | Study Type | Efficacy<br>Safety |
| | Study Length | 9 to 12 weeks per cohort |
| | Planned Country of Investigational Sites | United States and Canada |
| | Planned Number of Participants | up to 30 |
| | FDA-Regulated Device Study | No |
| | FDA-Regulated Drug Study | Yes |
| | Pediatric Study | Yes |
| Participant information | Diagnosis Group | Children, Ages 2 to 5 Years with Functional Constipation |
| | Healthy Participant Indicator | No |
| | Planned Minimum Age of Participants | 2 |
| | Planned Maximum Age of Participants | 5 |
| | Sex of Participants | Both |
| | Stable Disease Minimum Duration | 2 months (for participants aged ≥ 4 years old), or 1 month (for participants aged < 4 years old) |

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| Parameter Group | Parameter | Value |
|---|---|---|
| Treatments | Study Intervention Therapy or Treatment | linaclotide |
| | Intervention Type | drug |
| | Pharmacological Class of Invest. Therapy | GC-C agonist |
| | Dose per Administration | • Cohort 1: linaclotide 18 µg or matching placebo once daily for 4-week Study Intervention Period.<br>• Cohort 2: linaclotide 36 µg or matching placebo once daily for 4-week Study Intervention Period.<br>• Cohort 3: linaclotide 72 µg or matching placebo once daily for 4-week Study Intervention Period.<br>• Final Cohort highest dose of linaclotide tested/determined to be safe or matching placebo for 4-week Study Intervention Period. |
| | Dose Units | µg |
| | Dosing Frequency | single dose, once daily at approximately the same time each day, 30 minutes prior to any meal. |
| | Route of Administration | Oral |
| | Current Therapy or Treatment | None |
| | Added on to Existing Treatments | No |
| | Control Type | Placebo |
| | Comparative Treatment Name | NA |

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| Parameter Group | Parameter | Value |
|---|---|---|
| Study design | Study Type | Double-blind, placebo-controlled, Sequential, Ascending, Multidose Study to evaluate safety and efficacy |
| | Intervention Model | Sequential |
| | Planned Number of Groups | 8 participants each in Cohorts 1 to 3, 6 participants in final cohort, study intervention and placebo in each cohort |
| | Study is Randomized | Yes |
| | Randomization Quotient | 8 participants 3:1 linaclotide or placebo in Cohorts 1- 3; 6 participants 5:1 linaclotide or placebo in final cohort |
| | Study Blinding Schema | Double blind |
| | 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. |

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## 10.7. Appendix 7: Instructions for Dosing

Four capsule strengths will be provided:

- 36 µg capsules, which are used to prepare the [redacted] µg dose
- 72 µg capsules, which are used to prepare the 18 µg dose
- 145 µg capsules, which are used to prepare the 36 µg dose
- 290 µg capsules, which are used to prepare the 72 µg dose
- Placebo preparation is identical for all dose cohorts

Instructions for dose preparations are as follows: dose must be prepared at the time of administration and should not be prepared ahead of time and stored.

1. Pour exactly 20 mL of room-temperature bottled water into the provided medicine 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. Withdraw 5 mL into the provided oral syringe and discard this portion per instructions in the Study Reference Manual.
6. Withdraw a second portion of 5 mL into the oral syringe and administer dose to the participant, swallowing immediately.
7. Discard the remaining solution per instructions in the Study Reference Manual.
8. Rinse the syringe and medicine cup with bottled water.

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.

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## 10.8. Appendix 8: Study Schedule Supplement

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

### 10.8.1. Screening (Visit 1)

The Screening Period will occur 4 to 7 weeks before Randomization (Visit 3/Day 1) and last for 14 to 28 days during which time study procedures will be reviewed with the parent/guardian/LAR, and caregiver; and parent/guardian/LAR and caregiver consent will be obtained and documented (Section 10.1.3). After informed consent is obtained, participants will be registered in IWRS and assigned a unique PID number (Section 6.3). A review of inclusion/exclusion criteria and other screening assessments will be conducted to determine the participant's eligibility for enrollment (Sections 5.1 and 5.2).

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

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

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- 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
- Review any AEs occurring after informed consent is obtained

Additionally, during the Screening Period, caregivers will receive information about lifestyle modifications: increased water and fiber intake, increased physical activity, and consistent toileting habits. There should be at least a 2-week interval between discussing the lifestyle modifications during the Screening Period and the participant's entry into the Preintervention Period.

### 10.8.2. Preintervention Period (Visit 2)

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

Inclusion/exclusion criteria will be reviewed, caregivers will receive full training on the use and completion of the daily eDiary. IWRS registration will include rescue medication assignment (Section 6.5.2 ]). Caregivers will be instructed how to properly recognize signs of dehydration, how to administer oral rehydration therapy, and how to determine when the participant appears to be markedly ill or appears not to be responding to treatment for dehydration.

At the start of the Preintervention Period, caregivers will be trained in the use and completion of the eDiary including how to download eDiary responses and how to access the helpdesk if they encounter any problems using the eDiary. [redacted]

Caregivers will be instructed to have the participant fast for at least 2 hours before receiving their first dose of study intervention at the study site during the Randomization Visit (Visit 3/Day 1)) and before their last dose of study intervention at the study site during Visit 5 (Week 4). Water will be allowed.

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

- Review inclusion and exclusion criteria



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- IWRS verification
- Perform a fecal impaction assessment if fecal impaction was documented during screening (Section 10.8.1)
- Obtain vital signs (weight, temperature (oral, rectal, or tympanic), and respiratory rate) and postural vital signs (supine systolic and diastolic BP and pulse rate) (Section 8.2.2)
- Review any AEs occurring since the last visit
- Review concomitant medications
- Contact the IWRS, where applicable, for rescue medication to be dispensed to the participant.
- Remind caregiver to bring the bottle(s) of the rescue medication to the next visit.
- Instruct participants when to fast to ensure they have fasted for at least 2 hours before receiving the first dose of study intervention at the study site during the Randomization Visit; participants will be allowed to eat 30 minutes after dosing.
- Provide caregivers with the eDiary along with instructions

### 10.8.3. Randomization (Visit 3, Day 1)

Participants' eligibility to enter the Study Intervention Period must be confirmed prior to randomization by review of inclusion and exclusion criteria, including a fecal impaction assessment, adherence to instructions regarding the use of rescue medication and prohibited medications, meeting eligibility criteria captured in the eDiary device, including full compliance with eDiary on at least 10 of the 14 days immediately preceding Visit 3 and with clinic eDiary on the day of Randomization. The study coordinator will obtain the eDiary eligibility report to determine eDiary-related eligibility to be randomized. Once the participant's randomization eligibility is confirmed based on the eDiary eligibility report and other inclusion and exclusion criteria, the IWRS will randomize the participant. Study personnel will review the study procedures with the caregivers and instruct them to continue completing the eDiary entries every evening. Subsequent study visits will be scheduled keeping in mind that the last dose of study intervention will occur at Visit 5 and should occur at approximately same time as the other doses of study intervention during double-blind Study Intervention Period.

Randomization will occur on the first day of the Study Intervention Period. Based on randomization, participants will receive placebo or linaclotide. Participants will complete at least 4 weeks of treatment during the double-blind Study Intervention Period (ie, Study Intervention Period).

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

- Review inclusion and exclusion criteria, including review of eDiary-related criteria

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- IWRS verification
- Perform a fecal impaction assessment prior to randomization and dosing. If fecal impaction is present, the participant will not be eligible for the study.
- Obtain vital signs (weight, temperature (oral, rectal, or tympanic), and respiratory rate) and postural vital signs (supine systolic and diastolic BP and pulse rate) (Section 8.2.2)
- Review any AEs occurring since the last visit
- Review concomitant medications
- Review eDiary completion, including the Clinic eDiary
- Ensure participants have refrained from using rescue medicine on the prior calendar day and on the day of the Randomization (Visit 3) until the time of the clinic visit.
- Remind participants not to use rescue medicine for the remainder of the day and on the next calendar day after the Randomization Visit
- Run the eDiary Eligibility Report to confirm that the participant can be randomized.
- Review use of protocol-permitted rescue medication dispensed in IWRS where applicable. Participants may choose a different protocol-permitted rescue medication at any visit, where available. Additional protocol-permitted rescue medications may be dispensed as needed at any visit
- Prior to dosing, the investigator or appropriate site staff member will assess Rome IV criteria for childhood FC. Assessment result will be captured in the eCRF. Eligibility for the study is not based on this assessment
- Contact the IWRS to obtain the study intervention (bottle number) to be dispensed to the participant based on randomization and PK sample assignment.
- Prepare and administer the first dose of study intervention after completion of all Visit 3 assessments and after confirming the participant has fasted for at least 2 hours. Participants may resume eating 30 minutes after receiving their first dose of study intervention at the study site
- Dispense assigned study intervention for this study after the first dose has been administered. Provide study intervention reconstitution instructions for sprinkles to caregivers (Section 10.7).
- Record the date and time the first dose was administered

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- Remind caregiver to bring the bottle(s) of the study intervention and rescue medication to the next visit
- Encourage caregivers to schedule Visit 5 (Week 4) as the participants will need to take linaclotide in a fasted state.

### 10.8.4. Week 2 (Visit 4)

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

- Obtain vital signs (weight, temperature (oral, rectal, or tympanic), and respiratory rate) and postural vital signs (supine systolic and diastolic BP and pulse rate) (Section 8.2.2)
- Review any AEs occurring since the last visit
- Review concomitant medications
- Review use of protocol-permitted rescue medication dispensed in IWRS where applicable. Participants may choose a different protocol-permitted rescue medication at any visit, where available. Additional protocol-permitted rescue medications may be dispensed as needed at any visit
- Review study intervention and rescue medication compliance and accountability
- Review eDiary completion
- Remind participant and caregiver to bring the bottle(s) of the study intervention and rescue medication to the next visit
- Remind caregivers to have the participant fast for at least 2 hours before receiving their last dose of study intervention at the study site during the Week 4 (Visit 5) Visit.

### 10.8.5. Week 4/EOT (Visit 5)

Participants will arrive in a fasted state for this visit after completing at least 28 days of study intervention to receive their last dose of study intervention before or after PK sample. All randomized participants who prematurely discontinue from the study, regardless of cause, are required to be seen for the assessments completed at EOT (Visit 5, Week 4), except for PK sample collection. This visit should be scheduled at approximately the same time as when participants take their daily dose. During Week 4 (Visit 5), the following procedures will be performed:

- IWRS verification
- Perform a physical examination, including general appearance, skin, HEENT (head, ears, eyes, nose, and throat), neck, thorax/lungs, cardiovascular, abdomen, musculoskeletal, lymph

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nodes, neurologic (including mental status), and visual inspection of the lumbosacral and perianal region.

- Complete modified Rome III assessment
- Obtain vital signs (weight, temperature (oral, rectal, or tympanic), and respiratory rate) and postural vital signs (supine 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
- Review any AEs occurring since the last visit
- Review concomitant medications
- PK sample will be obtained in participants who will be completing the study intervention at this visit.
- Pre-dose or post-dose PK sampling should be obtained at the same time as clinical lab tests described above to avoid an extra needle stick.
- Pre-dose sample will be obtained from participants assigned to this group at the clinic before the administration of the last dose of study intervention. Post-dose PK sample will be obtained 1-8 hours after the last dose of study intervention in participants assigned to the post-dose PK group. The last dose of study intervention should be administered after confirming the participant has fasted for at least 2 hours. Participants may resume eating 30 minutes after receiving their last dose of study intervention at the study site.
- Obtain date and time of the dose of study intervention prior to PK sample collection
- Obtain standard 12-lead ECG (supine)
- Review use of protocol-permitted rescue medication dispensed in IWRS where applicable. Participants may choose a different protocol-permitted rescue medication at any visit, where available. Additional protocol-permitted rescue medications may be dispensed as needed at any visit
- Review study intervention and protocol-permitted rescue medication use and accountability
- Review eDiary completion
- Remind caregiver to bring the bottle(s) of the rescue medication to the next visit
- Return study intervention

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### 10.8.6. End of Study Visit /Postintervention Follow-up (1 week)

During EOS Visit (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 systolic and diastolic BP, and pulse rate) (Section 8.2.2)
- Review any AEs occurring since the last visit
- Review concomitant medications
- Review use of protocol-permitted rescue medication dispensed in IWRS where applicable.
- Review rescue medication compliance, accountability
- Return rescue medication
- Review eDiary completion and return eDiary device

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## 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



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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.

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## 10.10. Appendix 10: Study Conduct During the Novel Coronavirus Pandemic: Pre-randomization

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.

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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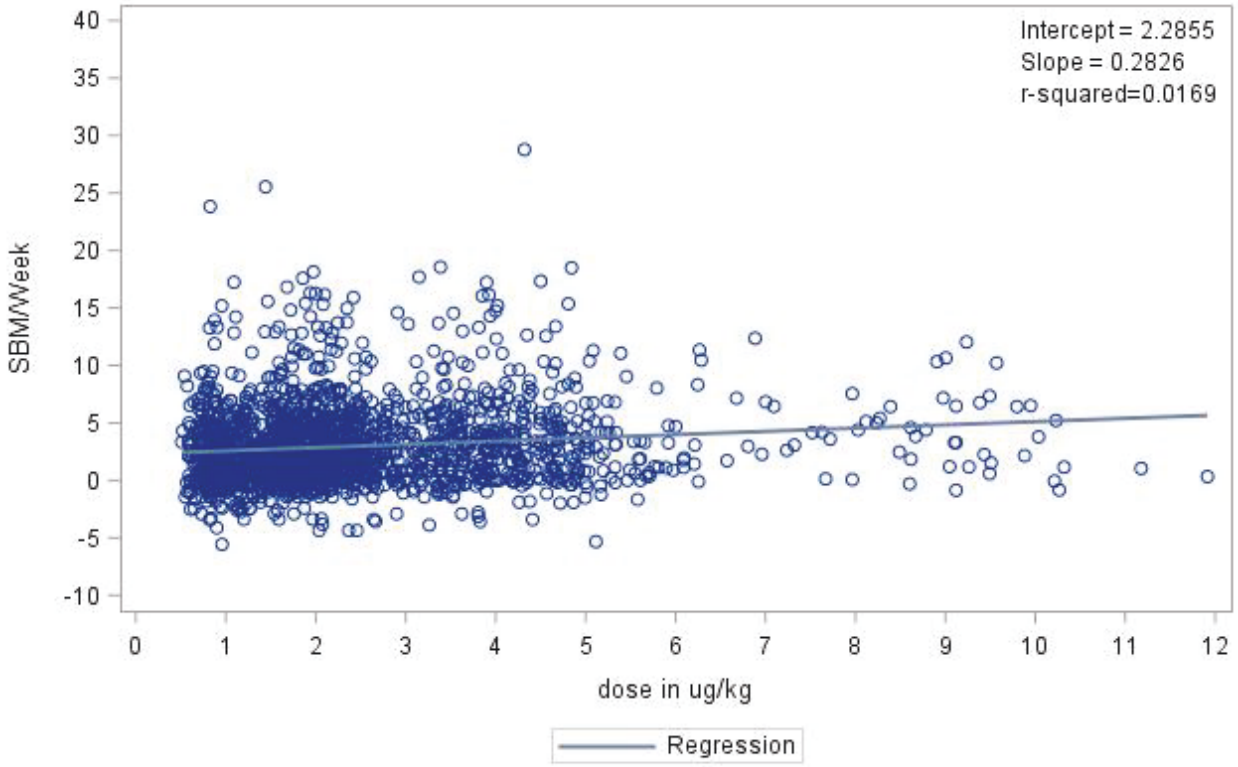
## 10.11. Appendix 11: Supporting Information from the Adult Linaclotide Program

**Figure 10–1** **Change from Baseline over the First 4 Weeks in Observed SBM/Week by Dose in µg/kg: ITT Population of Phase 2 and 3 Adult CIC Population**




Includes Studies MCP-103-201, Lin-MD-01, MCP-103-303, MCP-103-309
Data are from 1909 patients treated with 72, 145, and 290, and 579 ug linaclotide

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## 11. References

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