Statistical Analysis Plan for Study LIN-MD-66

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

Date: 19 July 2022

Version 2.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) provides a technical and detailed elaboration of the statistical analyses of the safety and efficacy data as outlined and specified in protocol amendment 2 of Study LIN-MD-66 (approved on 30-Apr-2021). Specifications of tables, figures and data listings are contained in a separate document.

Statistical analysis and reporting will be provided separately for participants with functional constipation (FC) and participants with irritable bowel syndrome with constipation (IBS-C).

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) or later under the UNIX operating system.

2.0 Study Design and Objectives

2.1 Objectives, Hypotheses and Estimands

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

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

2.2 Study Design Overview

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

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

- Phase 2 completers are defined as pediatric participants who completed 4-week double-blind study intervention and end of treatment (EOT) Visit (Visit 5) in the Phase 2 studies AND
  - Completed the end of study (EOS) (Visit 6) in Study LIN-MD-62 or
  - Completed the EOS (Visit 6) in Study LIN-MD-63. However, this EOS Visit in LIN-MD-63 is not required for participants who enroll into LIN-MD-66 prior to that visit.
- Phase 3 completers are pediatric participants who completed 12-week double-blind study intervention in Study LIN-MD-64. Participants must have completed the EOT visit (Visit 7) and the EOS visit (Visit 8). However, this EOS visit in LIN-MD-64 is not required for participants who enroll into LIN-MD-66 prior to that visit.

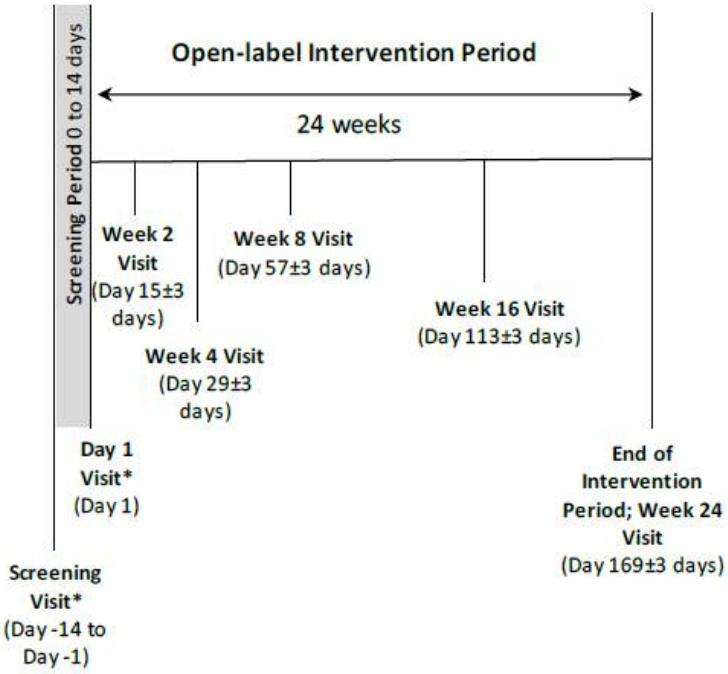
The present study will include a screening period and a 24-week (FC participants) or 52-week (IBS-C participants) study intervention period. For participants who enroll in LIN-MD-66 on the same day as their EOT Visit or EOS Visit in LIN-MD-64, the EOT Visit or EOS Visit, respectively, may be combined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

Participants who turn 18 years of age during study LIN-MD-63 or LIN-MD-64, or after completing the lead-in study, may be eligible if they enroll within 28 days (inclusive) of the last day of study intervention in the lead-in study (Study LIN-MD-64 [Visit 7] or

Study LIN-MD-63 [Visit 5]). Such participants will be dosed as 17-year-old participants; refer to the Intervention Groups and Study Duration section below for dosing.

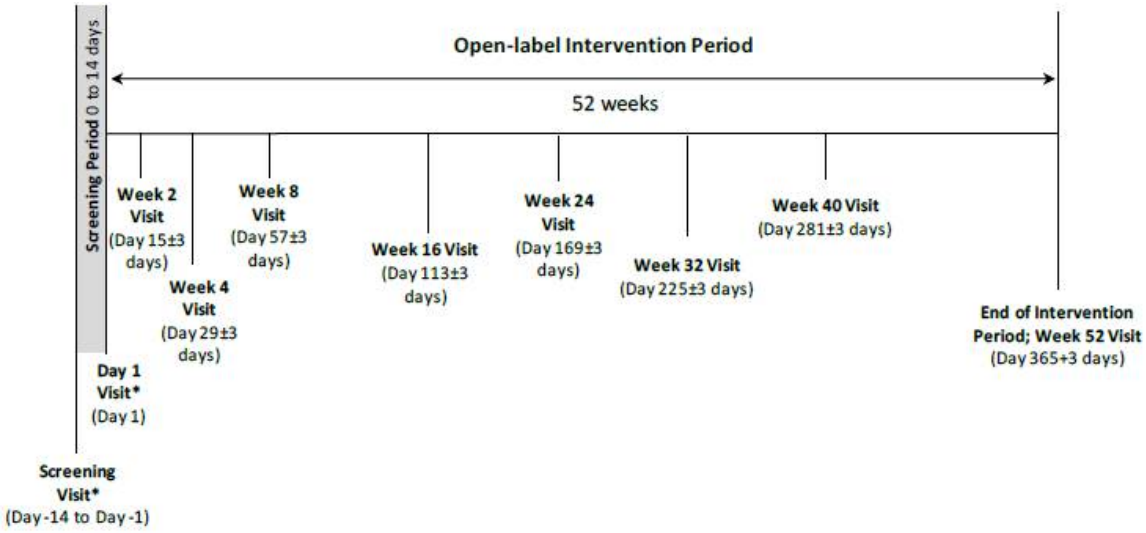
The study schematics for FC and IBS-C participants are shown in Figure 1 and Figure 2, respectively.

Figure 1. Study Schematic for FC Participants



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

Figure 2. Study Schematic for IBS-C Participants



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

2.3 Treatment Assignment and Blinding

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

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

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

- LIN-MD-63 completers will receive open-label linaclotide 290 µg once daily except for the LIN-MD-63 completers who had received ≤ 145 µg linaclotide or placebo. These participants will have the option to receive open-label linaclotide 145 µg once daily.
- LIN-MD-64 completers will have the option to either remain on the same blinded linaclotide dose they were receiving during the lead-in study LIN-MD-64 or receive open-label 290 µg linaclotide.
  - LIN-MD-64 completers who choose to remain on the same blinded linaclotide dose received during the lead-in study LIN-MD-64 will continue to receive blinded linaclotide 145 or 290 µg once daily.
  - LIN-MD-64 completers who choose to receive open-label linaclotide therapy will receive linaclotide 290 µg once daily.

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

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

Table 1. Dose Reductions

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

2.4 Sample Size Determination

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

3.0 Endpoints

3.1 Efficacy Endpoint

There is one other efficacy endpoint in this study:

- The achievement of no longer fulfilling Rome III criteria at the end of study intervention period

3.2 Safety Endpoints

The safety parameters will include:

- adverse events (AEs)
- clinical laboratory parameters
- vital signs
- electrocardiograms (ECGs)
- height
- weight

4.0 Analysis Populations

For this long-term safety study, only 1 analysis population, i.e., Safety Population, is considered. The Safety Population is defined as all enrolled participants who received at least one dose of study intervention in this study. Participants will be summarized according to the study intervention they actually received.

If a participant received study intervention other than the original assigned study intervention, actual study intervention received will be determined based on the study intervention received for the majority of the study intervention period. If there is a tie, the higher dose will be considered the actual study intervention for that participant. This is also relevant for participants who require dose de-escalation/escalation in this long-term safety study.

5.0 Subject Disposition

Number of participants screened for the study will be provided.

The summary of study disposition during study intervention period will be provided by study intervention group for overall and for each age group (6 to 11 years and 12 to 18 years in FC; 7 to 11 years and 12 to 18 years in IBS-C) separately for FC and IBS-C participants for the following:

- Number of participants enrolled (at Visit 2/Day 1) (Note: This frequency count will be used as the denominator to calculate the percentages described below)
- Number and percentage of participants received placebo in the Lead-in Study
- Number and percentage of participants treated
- Number and percentage of participants completed the study drug
- Number and percentage of participants prematurely discontinued study drug (all reasons)

6.0 Study Drug Duration and Compliance

For the safety population, duration of treatment will be summarized for each study intervention group overall and for each age group (6 to 11 years and 12 to 18 years in FC and 7 to 11 years and 12 to 18 years in IBS-C) separately for FC and IBS-C participants. Duration of treatment is defined for each participant as last dose date minus first dose date + 1 in this study. Duration of treatment will be summarized using the number of participants treated, mean, standard deviation, median, minimum and maximum. In addition, the number and percentage of participants in each treatment duration category (defined below) will be summarized.

- FC participants: ≤ 4 weeks, > 4 - ≤ 8 weeks, > 8 - ≤ 12 weeks, > 12 - ≤ 18 weeks, > 18 - ≤ 24 weeks, > 24 weeks
- IBS-C participants: ≤ 4 weeks, > 4 - ≤ 8 weeks, > 8 - ≤ 12 weeks, > 12 - ≤ 20 weeks, > 20 - ≤ 28 weeks, > 28 - ≤ 36 weeks, > 36 - ≤ 44 weeks, > 44 - ≤ 52 weeks, > 52 weeks

Additionally, total continuous exposure with any linaclotide doses across the lead-in studies and Study LIN-MD-66 will also be summarized. Participants who received linaclotide, completed the lead-in study, and enrolled in Study LIN-MD-66 within 28 days from last study intervention will be considered to have continuous exposure. The continuous exposure of linaclotide will be calculated as the sum of the exposure from the lead-in study and from Study LIN-MD-66. The number and percentage of participants in each treatment duration category (defined below) will be summarized.

- FC participants: ≥ 4 weeks, ≥ 12 weeks, ≥ 24 weeks, ≥ 30 weeks, ≥ 36 weeks
- IBS-C participants: ≥ 4 weeks, ≥ 12 weeks, ≥ 24 weeks, ≥ 36 weeks, ≥ 48 weeks, ≥ 52 weeks, ≥ 64 weeks

Treatment compliance is defined as the number of capsules actually taken by a participant divided by the number of capsules expected for the same period multiplied by 100. The information period will be based on the information from 'Exposure Form' of the participant's electronic case report form (eCRF). The number of capsules expected to be

taken in a specific treatment period will be calculated by multiplying the number of days in that period by the number of capsules to be taken per day.

Descriptive statistics for study drug compliance will be presented by study intervention group using the safety population, for overall and for each age group (6 to 11 years and 12 to 18 years in FC; 7 to 11 years and 12 to 18 years in IBS-C) separately for FC and IBS-C participants.

7.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

Demographics, baseline characteristics, medical history, and prior and concomitant medications will be summarized for the safety population by study intervention group, for overall and for each age group (6 to 11 years and 12 to 18 years in FC; 7 to 11 years and 12 to 18 years in IBS-C) separately for FC and IBS-C participants. Categorical variables will be summarized with the number and percentage of participants; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum and maximum).

7.1 Demographics and Baseline Characteristics

Demographic variables include:

- Age (based on informed consent date)
- Age group (6 to 11 years and 12 to 18 years in FC; 7 to 11 years and 12 to 18 years in IBS-C)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)

Baseline characteristics variables include:

- Weight (kg)
- Height (cm)
- Body mass index (calculated as weight [kg]/ height[m]^2)

The baseline is defined as the baseline of the lead-in study if participants enroll into LIN-MD-66 within 28 days of last dose date of the lead-in study, or the last non-missing assessment made before the first dose of the study intervention in this study if participants enroll into LIN-MD-66 after 28 days of the last dose date of the lead-in study.

7.2 Medical History

Medical and surgical history data will be coded using Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report.

Medical and surgical histories in each SOC and preferred term will be summarized by study intervention group using the safety population, for overall and for each age group (6 to 11 years and 12 to 18 years in FC; 7 to 11 years and 12 to 18 years in IBS-C) separately for FC and IBS-C participants. Medical and surgical histories include medical condition prior to Day 1 visit (Visit 2), whether ongoing or resolved.

7.3 Prior and Concomitant Medications

The medication data will be coded using the World Health Organization (WHO) Drug Dictionary, version Global B3 March 2020 or newer. Prior medication is defined as any medication taken prior to the start of study intervention regardless of stop date of the medication. Concomitant medication is defined as any medication taken after the start of study intervention regardless of the start date of the medication. Any prior medications stopped more than 30 days before the date of the first dose of study intervention and any concomitant medications started after the date of the last dose of study intervention will not be presented in the summary tables but will be included in the participant data listings.

Prior and concomitant medications will be coded using the Anatomical Therapeutic Chemical code (4th level, or most specific level available if 4th level is unavailable).

The number and percentage of participants reporting prior or concomitant medications will be summarized, for overall and for each age group (6 to 11 years and 12 to 18 years in FC; 7 to 11 years and 12 to 18 years in IBS-C) by study intervention group, ATC class and code, and preferred drug name using the safety population separately for FC and IBS-C participants. If more than one medication is coded to the same preferred drug name for the same participant, the participant will be counted only once for that preferred drug name.

8.0 Efficacy Analyses

Rome III criteria will be assessed by the investigator at the Screening Visit (Visit 1), and at the end of the study intervention period at the EOT Visit (Visit 7 for FC participants and Visit 10 for IBS-C participants) as an additional efficacy assessment. The counts and percentages will be provided for participants who no longer fulfill Rome III criteria at the screening visit and the end of study intervention period in this study. No missing data will be imputed, and data as observed will be summarized. Fulfillment of Rome III criteria data will be presented in the listing.

9.0 Safety Analyses

9.1 General Considerations

All safety analyses or summaries will be performed by study intervention group using the safety population, for overall and for each age group (6 to 11 years and 12 to 18 years in FC; 7 to 11 years and 12 to 18 years in IBS-C) separately for FC and IBS-C participants.

For each safety parameter (laboratory, vital signs, body weight, height, and ECG), the baseline will be defined as below:

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

Safety data analyses will be provided descriptively based on the observed safety data, without data imputation for missing safety parameters.

9.2 Adverse Events

Adverse events (AEs) will be summarized and presented using primary MedDRA System Organ Classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study report.

9.2.1 Treatment-Emergent Adverse Events

An AE will be considered a treatment emergent adverse event (TEAE) if:

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

However, an AE that occurs more than 30 days after the last dose of study intervention in LIN-MD-66 will not be counted as a TEAE.

An AE will be considered a treatment emergent serious adverse event (TESAE) if it is a TEAE that additionally meets any serious adverse event (SAE) criterion.

9.2.2 Adverse Event Overview

Overall summary of TEAEs will be provided on a per-participant level for TEAEs, treatment-related TEAEs, TESAEs, deaths, and TEAEs leading to study intervention discontinuation.

If there is more than one event for the same participant, the participant will be counted only once.

9.2.3 Treatment-Emergent Adverse Events by SOC and/or PT

The number and percentage of participants reporting TEAEs will be tabulated by SOC and preferred term; and by SOC, preferred term, and severity.

The number and percentage of participants reporting treatment-related TEAEs will be tabulated by SOC and preferred term.

If more than one event is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the greatest severity for the summarization by severity.

If the severity of a TEAE is missing, the maximum severity will be assigned to the event for the summarization by severity. The value will be displayed as missing in the data listing.

If the relationship to the study intervention is missing for a TEAE, the event will be considered related to the study intervention for the summarization. The value will be displayed as missing in the data listing.

Listings of all the AEs will be presented.

9.2.4 Treatment-Emergent Adverse Events Exposure-Adjusted Incidence Rate (EAIR)

The EAIR provides exposure adjusted rates for the first occurrence of an event. It is an adjusted incidence rate calculated as 100 times the number of subjects with the specific event divided by the total time at risk (in year) among subjects included in the analysis. For a specific event, subjects with multiple occurrences of the event in the specific analysis period will only be counted once in the numerator. The time at risk for a subject without the specific event is the treatment duration, whereas the time at risk for a subject with the event is defined as the treatment duration up to the start date (inclusive) of the first occurrence of the event (date of first onset of the event – date of first dose + 1). The total time at risk in years (denominator) is calculated as dividing the sum of time at risk in days over all subjects included in the analysis by 365.25. The EAIR per 100 patient-years, calculated as [numerator/denominator]*100, is interpreted as the expected number of subjects with at least one occurrence of the specific event per 100 patient-years of exposure to the study drug.

The EAIR per 100 patient-years will be provided for each AE category in the AE overview summary and for the TEAE summary by SOC and PT.

9.2.5 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

Summary tables will be provided for participants with TESAEs and participants with TEAEs leading to study discontinuation if 5 or more participants reported such events.

SAEs (including deaths) and AEs leading to study drug discontinuation will be listed.

9.2.6 Adverse Events of Special Interest

The adverse events of special interest (AESIs) including 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 will be monitored throughout this study.

The number and percentage of participants with AESIs during the study will be tabulated by preferred term.

AESIs will also be provided in a listing.

9.2.7 Diarrhea Treatment Emergent Adverse Events

The TEAE summary by SOC and PT will be provided for those subjects who had a TEAE of diarrhea, regardless of whether these TEAEs occurred concurrently.

The following information will be summarized for the subjects who had a diarrhea TEAE. Each diarrhea TEAE for each subject shall be counted as a separate event for the summaries described in the first 2 bullets below.

- The number and percentage of subjects with a 1 or more diarrhea TEAE events, with 2 or more diarrhea TEAE events, and with 3 or more diarrhea TEAE events.
- The number and percentage of diarrhea TEAEs with an end date, and ongoing at the end of the study.
- Descriptive statistics for the time to onset of the first diarrhea TEAE. The number and the percentage of subjects with diarrhea TEAE will be summarized by time to onset of first occurrence using the following time intervals: Day 1, Day 2, Day 3-7, Week 2 to Week 11 (for each week), and Week 12 and later.
- The longest duration of diarrhea TEAEs within a subject will be summarized. For those subjects with at least one diarrhea TEAE ongoing at the end of the study, the subject will be counted in the 'Ongoing' category. The number and the percentage of subjects classified according to their longest diarrhea duration or ongoing will be summarized by the following duration intervals: 1 day, 2 days, 3-7 days, 8-14 days, 15-28 days, >28 days, and ongoing. The descriptive statistics for the duration of the longest duration of diarrhea TEAE with an end date for subjects will be presented.

9.3 Analysis of Laboratory Data

Descriptive statistics for clinical laboratory values (in International System of Units [SI] units) and changes from the baseline values at each assessment time point will be presented by study intervention group for the following clinical laboratory parameters.

Hematology: Platelet count, red blood cell (RBC) count, hemoglobin, hematocrit, RBC indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration), white blood cell count with differential (Neutrophil, Lymphocytes, Monocytes, Eosinophils, Basophils), and

Chemistry: Blood urea nitrogen, creatinine, glucose, potassium, sodium, bicarbonate, magnesium, phosphate, total protein, calcium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, direct and indirect bilirubin, total cholesterol, chloride, albumin, and

Urinalysis: Specific gravity and pH

Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in Table B-1 in Appendix B. The number and percentage of participants who have at least one PCS post-baseline clinical laboratory value will be tabulated. The percentages will be calculated based on the denominator of the number of participants with available non-PCS baseline values and at least one post-baseline value and the numerator of the number of participants with non-PCS baseline value and at least one PCS post-baseline value. A supportive listing of participants with post-baseline PCS values will be provided.

In addition, a tabular display showing all AEs that occurred in participants who had PCS postbaseline clinical laboratory values will be provided.

Shift tables from baseline to the end of Intervention Period for clinical laboratory parameters listed above will be presented by study intervention group for the following categories: low, normal, and high, which are provided by lab vendor.

Potential Hy's Law Cases

Potential Hy's Law criteria within a 24-hour window is defined by a post baseline elevation of ALT or AST ≥ 3×ULN, along with TBL ≥ 2×ULN and a non-elevated ALP < 2×ULN, all based on blood draws collected within a 24-hour period.

Participants who meet the potential Hy's Law criteria from the first dose of study intervention to within 30 days after the last dose of study intervention will be summarized. Supportive tabular displays will also be provided.

9.4 Analysis of Vital Signs

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

Vital sign values will be considered to be PCS values if they meet both the observed-value criteria and the change-from-baseline-value criteria as defined in Table B-2 in Appendix B. The number and percentage of participants who have PCS postbaseline vital sign values will be tabulated. The percentages will be calculated relative to the number of participants who have available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided for the Safety Population.

In addition, a tabular display showing all AEs that occurred in participants who had PCS postbaseline vital sign values will be provided.

9.5 Electrocardiogram

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

ECG parameter values are considered PCS if they meet or exceed the higher-limit PCS criteria listed in Table B-3 of the Appendix B. The number and percentage of participants with PCS postbaseline ECG values will be tabulated. The percentages will be calculated relative to the number of participants with available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with available non-PCS baseline values and at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided for the Safety Population.

In addition, a tabular display showing all AEs that occurred in participants who had postbaseline PCS ECG values will be provided.

A shift table from baseline to the end of Intervention Period in the Investigator's overall interpretation of the ECG will be presented by study intervention group for the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant. A tabular display showing participants with postbaseline clinically significant ECG abnormalities according to the Investigator's overall interpretation will be provided.

10.0 Interim Analyses

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

10.1 Data Monitoring Committee

An independent Data Safety Monitoring Board (DSMB) is reviewing safety data at defined intervals throughout the study. DSMB can also request ad hoc review if needed. The DSMB will communicate their recommendations to the sponsor after each meeting but will serve in an advisory capacity only. Further details of the DSMB (composition, policy, and procedures) are specified in a separate DSMB Charter.

11.0 Overall Type-I Error Control

There is no multiplicity adjustment since there is no statistical hypothesis in this study. No inferential testing will be performed.

12.0 Version History

Table 2. SAP Version History Summary

Version	Date	Summary
1.0	08 Nov 2021	Original version
2.0	19 Jul 2022	● Clarified study drug duration summary categories. ● Added summary for total continuous exposure of linaclotide across lead-in studies and long-term safety study. ● Modified TEAE definition to include any AE that occurs within 30 days (instead of 1 day) after the last dose of study intervention. ● Added Exposure-Adjusted Incidence Rate (EAIR) analysis for TEAE overview and TEAE by SOC and PT. ● Added additional analyses for Diarrhea TEAE. ● Included age of 18 years old in PCS criteria for clinical laboratory parameters, vital signs, and ECG parameters.

13.0 References

None.

Appendix A. Protocol Deviations

Unique participants reporting significant protocol deviations will be summarized by study intervention group using the safety population, for overall and for each age group (6 to 11 years and 12 to 18 years in FC; 7 to 11 years and 12 to 18 years in IBS-C) separately for FC and IBS-C participants.

A listing of any significant protocol deviations will be provided.

Appendix B. Potentially Clinically Important Criteria for Safety Endpoints

The potentially clinically significant criteria for clinical laboratory parameters, vital signs and ECG parameters are provided in the following sections.

Table B–1. Criteria for Potentially Clinically Significant Laboratory Results

Parameter	SI Unit	Lower Limit	Higher Limit
Chemistry			
Albumin	g/L	< 0.9 × LLN	> 1.1 × ULN
Alanine aminotransferase (ALT)	U/L	—	≥ 3 × ULN
Alkaline phosphatase	U/L	—	≥1.2 x ULN: 6-12 (inclusive), male & female; 13-15 (inclusive), male ≥ 3 × ULN:13-15 (inclusive), female; 16-18 (inclusive), male & female
Aspartate aminotransferase (AST)	U/L	—	≥ 3 × ULN
Bicarbonate	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Bilirubin, total	µmol/L	—	> 1.5 × ULN
Calcium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Chloride	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Cholesterol, Total	mmol/L	—	> 1.6× ULN
Creatinine	µmol/L	—	> 1.3 × ULN
Glucose, random, serum	mmol/L	< 0.8 × LLN	> 1.4 × ULN
Potassium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Protein, total	g/L	< 0.9 × LLN	> 1.1 × ULN
Sodium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Magnesium	mmol/L	< 0.9 x LLN	> 1.1 x ULN
Urea Nitrogen (BUN)	mmol/L	—	> 1.2 × ULN
Hematology			
Basophils, absolute cell count	10^9/L	—	> 3 × ULN
Eosinophils absolute cell count	10^9/L	—	> 3 × ULN
Lymphocytes absolute cell count	10^9/L	< 0.7 × LLN	> 1.3 × ULN
Monocytes, absolute cell count	10^9/L	< 0.5 × LLN	> 2.0 × ULN
Neutrophils, absolute cell count	10^9/L	< 0.8 × LLN	> 1.5 × ULN

Parameter	SI Unit	Lower Limit	Higher Limit
Hematocrit	Ratio	< 0.9 × LLN	> 1.1 × ULN
Hemoglobin	g/L	< 0.9 × LLN	> 1.1 × ULN
Platelet count	10^9/L	< 0.5 × LLN	> 1.5 × ULN
Red blood cell count	10^{12}/L	< 0.9 × LLN	> 1.1 × ULN
White blood cell count	10^9/L	< 0.7 × LLN	> 1.5 × ULN
Urinalysis			
pH	—	< 0.9 × LLN	> 1.1 × ULN
Specific gravity	—	—	> 1.1 × ULN

LLN = lower limit of normal value provided by the laboratory; SI = *Le Système International d'Unités* (International System of Units); ULN = upper limit of normal value provided by the laboratory

Table B-2. Criteria for Potentially Clinically Significant Vital Signs

Parameter	Flag	Criteria[a]	
		Observed Value	Change From Baseline
Systolic Blood Pressure, mmHg - Postural Vital Signs (Supine and Standing)		Decrease in systolic blood pressure of 20 mmHg or more from supine to standing [*Change from supine SBP ≤ -20]	Decrease in SBP from supine to standing at observed time point is at least 10 mmHg greater than the decrease in SBP from supine to standing at baseline [Postbaseline change from supine SBP – baseline change from supine SBP ≤ -10]
Diastolic Blood Pressure, mmHg Postural Vital Signs (Supine and Standing)		Decrease in diastolic blood pressure of 10 mmHg or more from supine to standing [Change from supine DBP ≤ -10]	Decrease in DBP from supine to standing at observed time point is at least 10 mmHg greater than the decrease in DBP from supine to standing at baseline [Postbaseline change from supine DBP – baseline change from supine DBP ≤ -10]
Pulse Rate, bpm - Postural Vital Signs (Supine and Standing)		Increase in heart rate of 20 beats per minute or more from supine to standing [Change from supine pulse rate ≥ 20]	Increase in heart rate from supine to standing at observed time point is at least 10 beats per minute greater than the increase in heart rate from supine to standing at baseline [Postbaseline change from supine pulse rate – baseline change from supine pulse rate ≥ 10]

Parameter	Flag	Criteria[a]	
		Observed Value	Change From Baseline
Systolic Blood Pressure, mm Hg (Supine)	High	Age 6-11 (inclusive): ≥ 140 Age 12-18 (inclusive): ≥ 155	Increase of ≥ 20
	Low	Age 6-11 (inclusive): ≤ 80 Age 12-18 (inclusive): ≤ 90	Decrease of ≥ 20
Diastolic Blood Pressure, mm Hg (Supine)	High	Age 6-11 (inclusive): ≥ 95 Age 12-18 (inclusive): ≥ 105	Increase of ≥ 15
	Low	Age 6-11 (inclusive): ≤40 Age 12-18 (inclusive): ≤ 45	Decrease of ≥ 15
Pulse Rate, bpm (Supine)	High	Age 6-11 (inclusive): ≥ 140 Age 12-18 (inclusive): ≥ 120	Increase of ≥ 15
	Low	Age 6-11 (inclusive): ≤ 50 Age 12-18 (inclusive): ≤ 40	Decrease of ≥ 15
Weight, kg	High	—	Increase of ≥ 5%
	Low	—	Decrease of ≥ 5%

bpm = beats per minute; DBP = diastolic blood pressure; SBP = systolic blood pressure

* Change from supine value = standing value – supine value.

a. A postbaseline value is considered potentially clinically significant if it meets both the observed-value and the change-from-baseline criteria.

Table B-3. Criteria for Potentially Clinically Significant Electrocardiograms

Parameter	Unit	Higher Limit
QRS interval	msec	QRS ≥ 115 msec (6-7 (inclusive) years) QRS ≥ 125 msec (8-15 (inclusive) years) QRS ≥ 150 msec (16-18 (inclusive) years)
PR interval	msec	PR > 225 msec (6-7 (inclusive) years) PR > 250 msec (8-18 (inclusive) years)
QTc(F)	msec	>480

QTc(F) = QT Corrected by Fridericia's formula