1 Title Page

LIN-MD-64

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

STATISTICAL ANALYSIS PLAN - Clinical Study Report

FOR IBS-C PARTICIPANTS

Final: [redacted]

Amendment #1: [redacted]

Amendment #2: 20 February 2024

2 Table of Contents

2.1 List of Tables

2.2 List of Figures

3 List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BM	bowel movement
BP	blood pressure
CI	confidence interval
CSBM	complete spontaneous bowel movement
eCRF	electronic case report form
eDiary	electronic diary
ECG	electrocardiogram, electrocardiographic
EOS	End- of- Study
EOT	End- of- Treatment
ESS	effective sample size
FC	functional constipation
IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome with constipation
IWRS	interactive web response system
LLN	lower limit of normal
mITT	modified intent-to-treat
OC	observed cases
p-BSFS	pediatric Bristol Stool Form Scale
PCS	potentially clinically significant
PID	participant identification
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
RM	rescue medication

SAE	serious adverse event
SAP	statistical analysis plan
SBM	spontaneous bowel movement
SD	standard deviation
SI	*Le Système International d'Unités* (International System of Units)
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal

4 Introduction

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and/or specified in the amended protocol of Study LIN-MD-64 (version dated Jun-2020) for irritable bowel syndrome with constipation (IBS-C) participants only. Specifications of tables, figures, and data listings for IBS-C participants are contained in a separate document.

The statistical analyses of the efficacy and safety for functional constipation (FC) participants as specified in amended protocol of LIN-MD-64 (version dated Jun-2020) are documented in a separate statistical analysis plan.

The design elements that are only for IBS-C participants in study LIN-MD-64 are discussed in this SAP. The IBS-C portion of Study LIN-MD-64 is a Phase 3 multicenter, randomized, double-blind, parallel-group, confirmatory safety and efficacy study of linaclotide therapy (145 µg or 290 µg daily) in pediatric participants, 7 to 17 years of age, with a diagnosis of irritable bowel syndrome with constipation (IBS-C) [ie, who fulfill the Rome III criteria for child/adolescent IBS and modified Rome III criteria for child/adolescent functional constipation (FC)]. A total of at least 100 IBS-C participants are planned to be randomized in a 1:1 ratio to receive either 145 µg or 290 µg linaclotide. Randomization of IBS-C participants will be stratified by age group only (7 to 11 years of age versus 12 to 17 years of age) with a minimum of 40% of participants within each age group.

The study will include a total of 8 visits and will be up to 20 weeks in duration: a 2-to 4-week Screening Period, a 2- to 3-week Preintervention Period, followed by a 12-week double-blind Study Intervention Period and 1-week Postintervention Period. The raw datasets of study LIN-MD-64 capture Preintervention Period as Pretreatment Period, Study Intervention Period as Treatment Period, and Postintervention Period as Posttreatment Period. Participants will not receive study intervention (i.e. study treatment) during the Screening/Preintervention Period and the Postintervention Period.

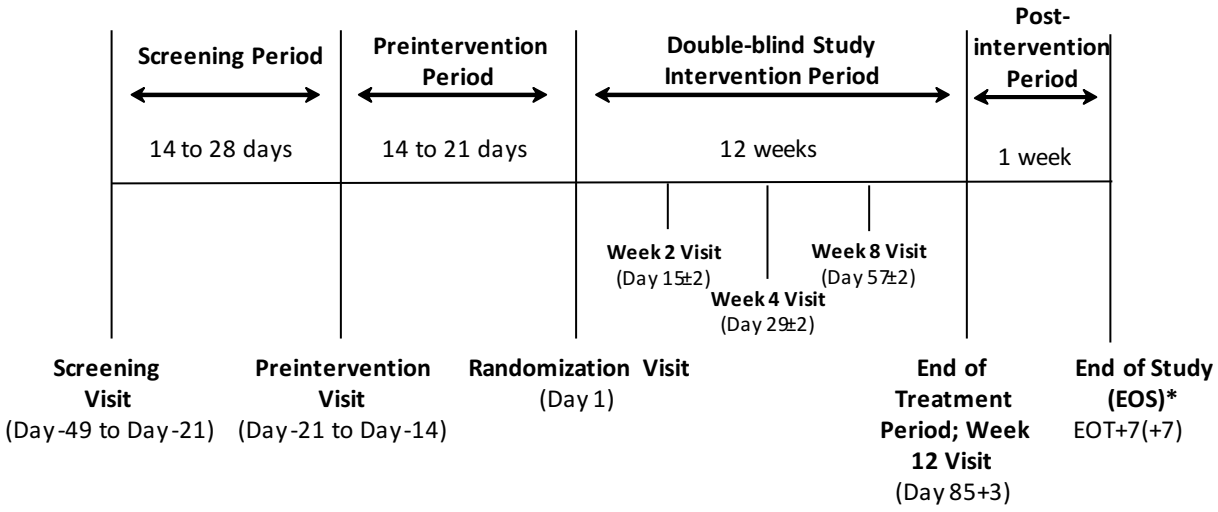
Participants who enter into the long-term safety study, LIN-MD-66, before the End-of-Study (EOS) Visit are not required to have the EOS visit in LIN-MD-64.

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

Approximately 140 sites from the United States of America, Canada, and the Europe and Middle East are expected to participate in the study to enroll FC participants. Only study sites in North America will randomize IBS-C participants.

Figure 4-1 is the schematic of the study design.

Figure 4-1. LIN-MD-64 Study Schema



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

The schedule of evaluations for Study LIN-MD-64 IBS-C participants is presented in Table 4-1.

Table 4-1. Schedule of Evaluations: Study LIN-MD-64 (IBS-C Participants)

Study Periods (Duration)	Screening (14-28 Days)	Preintervention (14-21 Days)	Study Intervention Period (12 weeks)					Postintervention (1 week)
Study Visit	Screening	Preintervention	Randomization	Week 2	Week 4	Week 8	Week 12 Visit/ End of Treatment (EOT)[a]	End of Study (EOS) Visit[b]
Visit Number	1	2	3	4	5	6	7	8
Study Day	-49 to -22	-21 to -14	1	15 (± 2)	29 (± 2)	57 (± 2)	85 (+3)[c]	EOT +7 (+7)
Parent/Caregiver Consent/Assentd	X							
Inclusion and Exclusion Criteria	X	X	X					
Rome III Assessment	X						X	
Assess Rome IV statuse			X					
IWRS	X	X	X[f]		X	X	X	
Medical History	X							
Lifestyle Modification Information Given to Participant/Caregiverg	X							
Physical Examinationh	X						X	
Fecal Impaction Assessmenti	X	X[j]	X[k]					
Height	X						X	
Vital Signs and Postural Vital Signsl	X	X	X	X	X	X	X	X
ECG	X						X	
Clinical Laboratory Testsm	X		X				X	
Serum Pregnancy Testingn	X							
Urine Pregnancy Testingo			X		X	X	X	
Urine Drug Screenp	X							
AE Evaluation	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X
Rescue Medication Dispensedq		X	X	X	X	X	X	
eDiary and Instructions Given to Participant/Caregiverr		X						

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

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

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

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

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

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

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

f. Eligibility report must be run prior to randomization.

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

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

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

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

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

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

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

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

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

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

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

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

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

t. Protocol permitted rescue medications only.

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

5 Objectives

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

6 Participant Populations

6.1 Screened Population

Screened Population will consist of all participants with IBS-C who undergo the Screening Visit (Visit 1) and receive a participant identification (PID) number.

6.2 Randomized Population

Randomized Population will consist of all participants in the Screened Population who are randomized to a study intervention group.

6.3 Modified Intent-to-Treat Population

The Modified Intent-to-Treat (mITT) Population will consist of all participants in the Randomized Population who receive at least 1 dose of double-blind study intervention. Participants will be summarized according to the randomized study intervention for all efficacy analysis variables/endpoints.

Significant non-compliance was identified at an investigational site (Site ID 10049). As a result of this finding, efficacy data for the participants randomized at this investigational site will be excluded from the statistical analyses. Safety data for these participants will be included in the statistical analyses. There were 3 participants that were randomized at this site, who will be excluded from mITT population.

An issue was discovered in July 2021 during the implementation of adding IBS-C participants in this study by the eDiary vendor, where the inclusion criterion (#2.012) related to abdominal pain was not displayed in the eligibility report. Because of this, 8 IBS-C participants (including the 3 participants at the above site 10049) were incorrectly randomized without meeting the abdominal pain criterion. As a result of this finding, these participants will be excluded from mITT population and efficacy data for these participants will be excluded from the statistical analyses. Safety data for these participants will be included in the statistical analyses.

6.4 Safety Population

The Safety Population will consist of all participants in the Randomized Population who receive at least 1 dose of double-blind study intervention.

Participants will be summarized according to the study intervention they actually received for all safety analysis variables/endpoints. If a participant received study intervention other than

randomized study intervention, actual study intervention received will be determined based on the study intervention received for the majority of the double-blind 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 subjects who require dose de-escalation, which is allowed once per participant to ensure safety and tolerability for study subjects. The actual study intervention will be listed for the participants in the listing related to study intervention dosing information.

7 Participant Disposition

The number and percentage of participants in 3 study populations (Randomized, mITT, and Safety) will be summarized overall, by study intervention group, country, and study center; the number of participants screened will be summarized overall, only by country, and study center.

Screen-failure participants (ie, participants who are screened but do not enter into the Preintervention Period), participants ineligible for randomization (ie, participants who enter into the Preintervention Period but are not randomized at Visit 3, also labeled as preintervention failures), and the associated reasons for failure as recorded in the electronic case report forms (eCRF) will be tabulated overall for all screened participants.

The number and percentage of participants who complete the study, complete the double-blind Study Intervention Period, complete the Postintervention Period, prematurely discontinue the study, prematurely discontinue the double-blind Study Intervention Period, and prematurely discontinue the Postintervention Period will be presented for each study intervention group and pooled across study intervention groups for the Randomized Population. The reasons for premature discontinuation from the double-blind Study Intervention Period and the Postintervention Period as recorded in the eCRF will be summarized (number and percentage) by study intervention group for the Randomized Population. All participants who prematurely discontinue during the Study Intervention Period or Postintervention period will be listed by discontinuation reason for the Randomized Population.

Please note that a participant is considered to have completed the study if he/she has completed 12 weeks of double-blind study intervention, End-of-Treatment visit, and the EOS visit. Participants who rollover to the long-term safety study, LIN-MD-66, before the EOS Visit will be considered to have completed the study if he/she has completed 12 weeks of study intervention and the End-of-Treatment Visit.

8 Demographics and Other Baseline Characteristics

Demographic parameters (age; age group [7-11 and 12-17 years (inclusive)]; race; ethnicity; sex) and baseline characteristics (weight; height; and body mass index, calculated as weight [kg]/(height [m])^2) will be summarized descriptively by study intervention group for the mITT, and Safety Populations. The above demographics parameters will also be summarized by age group (7-11 and 12-17 years (inclusive)) within the Safety Population.

Other baseline characteristics (including efficacy parameters related to the bowel habits and symptoms as discussed in Section 10) will be summarized descriptively by study intervention group for the mITT Population.

Continuous variables will be summarized by number of participants, mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

Abnormalities in participants' medical and surgical histories will be coded using the Medical Dictionary for Regulatory Activities, version 23.0 or newer. The number and percentage of participants with abnormalities in medical and surgical histories in each system organ class and preferred term will be summarized by study intervention group for the Safety Population.

Prior medication is defined as any medication 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 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.

Both prior and concomitant medications will be coded by drug name and therapeutic class. The use of prior and concomitant medications will be summarized by the number and percentage of participants in each study intervention group for the Safety Population. If a participant took a specific medication multiple times or took multiple medications within a specific therapeutic class, that participant would be counted only once for the coded drug name or therapeutic class.

The World Health Organization (WHO) Drug Dictionary, version Global B3 March 2020 or newer, will be used to classify prior and concomitant medications by therapeutic class and drug name.

Unique participants reporting significant protocol deviations will be summarized in total and by study intervention group for the Randomized Population.

9 Extent of Exposure and Study Intervention Compliance

9.1 Extent of Exposure

Exposure to the study intervention for the Safety Population during the double-blind Study Intervention Period will be summarized for study intervention duration, calculated as the number of days from the date of the first dose of study intervention to the date of the last dose of study intervention, inclusive. Descriptive statistics (number of participants, mean, SD, median, minimum, and maximum) will be presented by study intervention group.

Patient-years, defined as exposure to the study intervention in years, will be summarized by study intervention for the Safety Population.

9.2 Measurement of Treatment Compliance

Dosing compliance for the double-blind Intervention Period is defined as number of capsules actually taken by a participant during that period divided by the number of capsules prescribed for that period multiplied by 100. This information will be obtained from the study intervention record of the participant's eCRF.

The number of capsules expected to be taken for the double-blind Intervention 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 treatment compliance will be presented by study intervention group between 2 consecutive visits, as well as for the whole double-blind Intervention Period for the Safety Population.

9.3 eDiary Compliance

Participants will complete the electronic diary (eDiary) twice daily, once in the morning and once in the evening. Participant's eDiary compliance will be assessed based on the number of days with fully completed morning and evening assessments in a specific period. Morning or evening assessments will be considered fully completed if the participant responded to each question in the corresponding eDiary. eDiary compliance will be summarized for the Preintervention Period, double-blind Intervention Period, Postintervention Period, and for each week within each period based on the mITT Population.

Compliance for each participant/interval will be calculated using the following formula:

$$\%\text{Compliance} = \frac{100 * \#\text{ of days with completed morning and evening assessments within the interval}}{\#\text{ of expected days within the interval}}$$

On randomization day, the morning diary and/or clinic diary will be included in Preintervention Period and the evening diary will be included in the double-blind Intervention Period. On the day after last dose date, the morning diary will be included in the double-blind Intervention Period and the evening diary will be included in the Postintervention Period.

10 Efficacy Analyses

The efficacy analyses will be based on the mITT Population. All efficacy assessments will be determined by responses entered in the eDiary (morning eDiary, evening eDiary, or weekly eDiary) and eCRF (as appropriate).

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

An SBM is a BM that occurs in the absence of laxative, suppository, or enema use on the calendar day of the BM or the calendar day before the BM. A complete spontaneous bowel movement (CSBM) is an SBM that is associated with a sense of complete evacuation.

The baseline SBM and CSBM weekly rates, stool consistency, straining, and abdominal symptoms (abdominal pain and bloating) will be derived as discussed in Section 16.3.5 from 14 days prior to randomization and up to randomization (as appropriate). A participant's baseline stool consistency and straining cannot be assessed if the participant does not have at least 1 SBM during the Preintervention Period. For participants who report no SBMs during a study period, the stool consistency and straining assessments will be considered missing for that study period in the analyses. Participants with missing baseline stool consistency and straining will be excluded from the respective stool consistency and straining analyses that involve change from baseline.

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

An observed cases (OC) approach to missing postbaseline data will be applied. Efficacy responses following onset of dose de-escalation will not be included for primary analyses. Supplemental summaries will be provided for primary and secondary endpoints by study intervention dose sequence incorporating the responses following the onset of dose de-escalation. No statistical testing will be performed to compare linaclotide doses. No multiplicity adjustment will be applied in this study for IBS-C participants.

10.1 Primary Efficacy Endpoint

The primary efficacy endpoint for IBS-C pediatric participants is 6/12 weeks APS (abdominal pain and SBM) + 2 responder. A 6/12 weeks APS + 2 responder is a participant that meets the

weekly APS + 2 responder criteria for at least 6 out of the 12 weeks of the intervention period. A weekly APS +2 responder is a participant who has an increase of at least 2 in the SBM weekly rate from baseline, AND a decrease of at least 30% in the mean abdominal pain score (combination daytime and nighttime) from baseline, during that study intervention week. Details on the derivations of SBM rate and abdominal pain score are provided in Section 16.3.4 and Section 16.3.5, respectively.

10.1.1 Main Analysis Approach

The primary efficacy endpoint will be summarized by counts and percentages by study intervention group for the mITT population.

Based on the review that the IBS-C disorder and the patient response to linaclotide treatment being similar between the adult and pediatric subjects, the primary statistical analysis is comprised of a partial extrapolation approach utilizing a Bayesian method. Following this approach, information is borrowed from the adult IBS-C population in Phase 2b study MCP-103-202 and Phase 3 registration studies LIN-MD-31 and MCP-103-302 (Carlin and Louis 2009). To enable this approach, the proposed IBS-C pediatric portion of study LIN-MD-64 will utilize the primary efficacy endpoint, 6/12 weeks APS + 2 responder to align with the adult registration studies where APC (abdominal pain and complete SBM) +1 responder is one of the primary efficacy endpoints.

The assumptions and details of the proposed Bayesian analysis are discussed below.

1. META-ANALYSIS of PLACEBO EFFECT in ADULTS: Utilizing the three adult studies, MCP-103-202, MCP-103-302, and LIN-MD-31, a meta-analysis was conducted to obtain an estimate for adult placebo effect related to 6/12 weeks APS + 2 responder rate The estimated 6/12 Weeks APS + 2 responder rate for placebo was 0.16 and upper bound of 95% confidence interval (CI) of the placebo responder rate was 0.18.
2. PRIOR for LINACLOTIDE TREATMENT: Utilizing the three adult studies, MCP-103-202, MCP-103-302, and LIN-MD-31, a meta-analysis of the adult studies was conducted to obtain an adult prior distribution for linaclotide 290 ug responder rate. All subjects administered 266 ug to 300 ug in these contributing studies were included and considered for linaclotide 290 ug. Since this responder rate is bounded between [0,1], the prior distribution of linaclotide responder rate (θ) can be approximated by the Beta distribution. In this case, α (aggregate number of adult responders) and β (aggregate number of adult non-responders

   $\theta \sim \text{Beta}(\alpha, \beta)$,

where α 340 and β 550 based on meta-analysis of 3 adult contributing studies (MCP-103-202, LIN-MD-31 and MCP-103-302).

In this Bayesian analysis, this distribution forms the prior for the pediatric responder rate in linaclotide treated subjects for each linaclotide arm (145 ug and 290 ug).

3. LIKELIHOOD FUNCTION: Let N be the sample size of IBS-C participants in LIN-MD-64 and for each θ Pr(Pediatric subject is a responder), let X be the observed number of pediatric patients who are responders in LIN-MD-64. Then, given θ, X will have a binomial likelihood function, which can also be simply expressed as follows:

$$X \mid \theta \sim \text{Binomial}(N, \theta)$$

4. DOWNWEIGHT PRIOR: Due to the large number of adult subjects, a down weighting factor, w, bounded (0,1), is prespecified, such that the prior in step 2 becomes

$$\theta \sim \text{Beta}(w*\alpha, w*\beta)$$

Down-weighting in this manner will allow each adult patient to be 'worth' the fraction w of a new pediatric patient. An alternative way of expressing this 'worth' and describing the impact of the weights would be to describe an effective sample size (ESS). ESS is calculated as $(\alpha + \beta)*w$ and is interpreted as the amount of new samples that the adult data will be equivalent to in an analysis.

5. POSTERIOR for TREATMENT EFFECT: The posterior distribution for linaclotide responder rate utilizing IBS-C pediatrics data in Step 3 is also a Beta distribution with down-weighted prior in Step 4:

$$\Theta \mid X \sim \text{Beta}(X + w*\alpha, N - X + w*\beta)$$

6. For each linaclotide dose arm, calculate the Bayesian probabilities (Bayesian powers) of the pediatric posterior (i.e., pediatric responder rate based on pediatric posterior distribution in Step 5) in two ways as below:
   (a) demonstrating superiority to the adult placebo effect, based on the 2.5 percentile of the posterior distribution exceeding the upper bound 0.18 of 95% CI of the adult placebo effect calculated in Step 1
   (b) demonstrating superiority to the adult placebo effect, based on the 2.5 percentile of the posterior distribution exceeding the adult pooled placebo estimate of 0.16 as calculated in Step 1.

7. Repeat Steps 4 to 6 for a range of values of “w”; plot Bayesian probability as function of “w” as specified in Step 6. Range of w is prespecified as (0.0067, 0.0200), corresponding to an ESS for adult data providing the informational equivalent of approximately 6 to 20 pediatric subjects.

10.1.2 Supplemental Analysis

The following supplemental and sensitivity analyses on the primary endpoint will be performed:

- The primary efficacy endpoint will be summarized by counts and percentages and 95% Exact binomial CI by study intervention group for the mITT population.
- The proportion of responders will be compared to 0.18 (the upper bound of the 95% CI of the adult placebo rate from the meta-analysis) based on a one-sample proportion exact test, and the corresponding p-value will be provided for the pooled linaclotide dose groups and for each individual linaclotide dose group.
- Bayesian probabilities of the pediatric posterior in Step 6 (Section 10.1.1) will also be calculated with a non-informative prior (i.e., Beta(1, 1)) for linaclotide treatment.
- The primary efficacy endpoint will also be summarized by counts and percentages by study intervention incorporating all efficacy responses including the responses following onset of dose-de-escalation.

Weekly responder rates (counts and percentages) will be provided for APS+2 responders by study intervention group. The 95% Exact binomial CI for weekly responder rate at week 12 will be presented.

Additional Sensitivity Analyses with Different Missing Data Handling Methods

For any postbaseline analysis week, if participant has less than 4 completed diary days (i.e., completed both morning and evening diaries) in an analysis week, participant's corresponding week's analysis value for SBM or abdominal pain (AP) combination score will be considered missing and the postbaseline missing week during the intervention period will be imputed as follows.

- Missing weekly SBM or AP combination scores will be imputed using multiple imputation (MI) assuming missing at random. Subjects with missing weekly values will be characterized as responders or non-responders based on the derived weekly SBM or AP combination scores from MI datasets. The imputed endpoints will be analyzed using each of the 30 datasets. SAS PROC MIANALYZE will be used to generate the final percentages and 95% CI for the responder rate based on normal approximation using Rubin's rule.

The following tipping-point analysis will be performed assuming missing-not-at-random as another sensitivity analysis to evaluate the impact of missingness assumption for the analysis result.

- The achievement of the primary efficacy endpoint requires a participant to meet the weekly APS + 2 responder criteria for at least 6 out of the 12 weeks of the intervention period. For participants with missing data on weekly SBM or AP combination scores, the missingness may or may not affect the responder status in the primary endpoint. For example, if a participant already met the weekly APS + 2 responder criteria for 6 weeks and had missing data for 3 weeks, the participant would achieve the primary endpoint, regardless of the missing data. On the other hand, if a participant met the weekly APS + 2 responder criteria for 2 weeks, did not meet the weekly APS + 2 responder criteria for 7 weeks, and had missing data for the other 3 weeks, the participant would not achieve the primary endpoint, regardless of the missing data. In this analysis, the participants with missing data that potentially impacts the responder status will be sequentially imputed as responders (i.e., from 0 to the total number of participants with missing data that potentially impacts the responder status) and the series of 95% Exact binomial CI will be presented.

10.1.3 Estimand Framework

Population

The target population is participants with IBS-C, ages 7-17 years old, satisfying the inclusion and exclusion criteria as specified in Sections 5.1 and 5.2 of the protocol (Version June-2020), respectively.

The analysis population is mITT as discussed in Section 6.3.

Variable

The variable is the primary efficacy endpoint defined in Section 10.1, which is 6/12 weeks APS (abdominal pain and SBM) + 2 responder as derived from twice daily responses in eDiary (morning and evening). SBM is derived based on responses for BM and rescue medication in the eDiary twice daily (morning and evening). Abdominal pain score is also derived based on responses in the eDiary twice daily for abdominal pain.

Accounting for Intercurrent Events in the Primary Efficacy Analyses

The following intercurrent events are considered for the primary efficacy analyses. All the intercurrent events are handled based on the composite strategy.

- The BMs for the participants who took a laxative, enema, or suppository on the calendar day of the BM or the calendar day before the BM will not be considered as SBMs for the analysis.
- Participants who discontinue prematurely during but prior to the completion of the double-blind Study Intervention Period will have their eDiary data included up to the morning diary following the last dose date for primary endpoint. The early discontinued participants will be considered non-responders for the following weeks for primary endpoint.
- eDiary responses following the onset of dose de-escalation will not be included. The participants with dose de-escalation will be considered non-responders for the subsequent study intervention weeks (after the onset of dose de-escalation) for the primary endpoint based on the randomized study intervention group.
- A participant has to have at least 4 completed diary days per study intervention week to be considered a responder for that week and otherwise, the participant will be considered non-responder for that week. A completed diary day is a day in which both morning and evening eDiary entries are filled out by a study participant.

Population-level Summary

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

A Bayesian analysis will be performed for the primary efficacy endpoint using adult IBS-C data (borrowed from studies MCP-103-202, MCP-103-303, and LIN-MD-31) to inform the prior distribution of response in pediatric IBS-C patients. The 2.5 percentile of posterior distribution for the APS + 2 responder rate for linaclotide 145 µg or 290 µg will be compared separately with the pooled placebo APS + 2 responder rate and with the upper limit of 95% CI of the pooled placebo responder rate from contributing adult studies as discussed in Section 10.1.1.

10.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

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

Change From Baseline in 12-Week SBM Frequency Rate During the Study Intervention Period

Assessments of BM characteristics that determine occurrences of SBM (ie, BM frequency and RM use) will be measured by using the eDiary completed twice daily (morning and evening) on the eDiary device.

The 12-week SBM frequency rate (SBMs/week) during the study intervention period will be derived based on total number of SBMs a participant reported during this period in the morning and evening assessments on the eDiary. The details of the derivation of SBM frequency rate are provided in Section 16.3.4.

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

Abdominal pain will be measured twice daily, once in the morning and once in the evening eDiary, using a 5-point scale. The 12-week abdominal pain score during the study intervention

period will be derived for each participant based on the reported abdominal pain scores in morning and evening eDiary assessments during this period. The details of the derivation of abdominal pain score are provided in Section 16.3.5.

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

Stool consistency will be measured twice daily, once in the morning and once in the evening eDiary, using the 7-point ordinal p-BSFS for each BM. The 12-week stool consistency score during the study intervention period will be derived based on the responses in morning and evening eDiary assessments during this period. If the participant has no SBM during the baseline period, the stool consistency (p-BSFS score) during the baseline period will be missing and the participant will be excluded from the change from baseline analysis for this secondary endpoint. The details of the derivation of stool consistency are provided in Section 16.3.6.

6/12 Weeks SBM + 2 Responder

A 6/12 weeks SBM + 2 responder is a participant who meets the weekly SBM + 2 responder criteria for at least 6 out of the 12 weeks of the study intervention period. A weekly SBM + 2 responder is a participant who had an increase of at least 2 in the SBM weekly rate from baseline during that study intervention week. A participant has to have at least 4 completed diary days in analysis week to be considered as responder for that week and otherwise, will be considered as non-responder for that analysis week.

6/12 Weeks Abdominal Pain Responder

A 6/12 weeks abdominal pain responder is a participant who meets the weekly abdominal pain responder criteria for at least 6 out of the 12 weeks of the study intervention period. A weekly abdominal pain responder is a participant who had a decrease of at least 30% in the mean abdominal pain score from baseline during that study intervention week. A participant has to have at least 4 completed diary days in analysis week to be considered as responder for that week and otherwise, will be considered as non-responder for that analysis week.

10.2.1 Main Analysis Approach

Descriptive statistics for continuous secondary endpoints in terms of mean, median, standard deviation, standard error of mean, minimum, and maximum will be provided by study intervention group. For responder endpoints, counts and percentages will be provided by study intervention group.

10.2.2 Supplemental Analysis

Weekly responder rates (counts and percentages) will be provided separately for abdominal pain weekly responders and SBM+2 weekly responders by study intervention group. By-week summary (mean, median, SD, standard error of mean, minimum, and maximum) will be provided for change from baseline in SBM frequency rate, abdominal pain, and stool consistency separately.

The descriptive statistics (mean, median, SD, standard error of mean, minimum, and maximum for continuous endpoints and counts and percentages for responder endpoints) will also be provided by study intervention sequence incorporating efficacy responses following onset of dose-de-escalation for secondary efficacy endpoints.

10.3 Other Efficacy Endpoints

The other efficacy endpoints are as follows:

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

6/12 Weeks APS + 1 Responder

A 6/12 weeks APS + 1 responder is a participant that meets the weekly APS + 1 responder criteria for at least 6 out of the 12 weeks of the intervention period. A weekly APS +1 responder is a participant who has an increase of at least 1 in the SBM weekly rate from baseline, AND a decrease of at least 30% in the mean abdominal pain score (combination daytime and nighttime) from baseline, during that study intervention week. This responder endpoint will be derived similar to the primary endpoint as discussed in Section 10.1. The proportion of participants

satisfying responder criteria for at least 6 out of 12 weeks during the study intervention period will be presented by study intervention group.

9/12 Weeks SBM + 2 Responder

A 9/12 weeks SBM + 2 responder is a participant that meets the weekly SBM + 2 responder criteria for at least 9 out of the 12 weeks of the intervention period. A weekly SBM +2 responder is a participant who has an increase of at least 2 in the SBM weekly rate from baseline during that study intervention week. A participant has to have at least 4 completed diary days in analysis week to be considered as responder for that week and otherwise, will be considered as non-responder for that analysis week.

The proportion of participants satisfying responder criteria for at least 9 out of 12 weeks during the study intervention period will be presented by study intervention group.

9/12 Weeks Abdominal Pain (Combined Daytime and Nighttime Symptoms) Responder

A 9/12 weeks abdominal pain responder is a participant who meets the weekly abdominal pain responder criteria for at least 9 out of the 12 weeks of the study intervention period. A weekly abdominal pain responder is a participant who had a decrease of at least 30% in the mean abdominal pain score from baseline during that study intervention week. A participant has to have at least 4 completed diary days in analysis week to be considered as responder for that week and otherwise, will be considered as non-responder for that analysis week.

The proportion of participants satisfying responder criteria for at least 9 out of 12 weeks during the study intervention period will be presented by study intervention group.

9/12 Weeks APS + 2 Responder

A 9/12 weeks APS + 2 responder is a participant that meets the weekly APS + 2 responder criteria for at least 9 out of the 12 weeks of the intervention period. A weekly APS +2 responder is a participant who has an increase of at least 2 in the SBM weekly rate from baseline, AND a decrease of at least 30% in the mean abdominal pain score (combination daytime and nighttime) from baseline, during that study intervention week. This responder endpoint will be derived similar to the primary endpoint as discussed in Section 10.1. The proportion of participants satisfying responder criteria for at least 9 out of 12 weeks during the study intervention period will be presented by study intervention group.

Proportion of Participants with an SBM within 24 Hours of First Dose of Study Intervention

A participant is a 24-hour responder if the participant has at least 1 SBM within 24 hours of first dosing of study intervention. Any SBM reported in the evening diary on randomization day and in the morning diary at the day after first dose date (i.e., Day 2) will be considered a SBM within 24 hours. The proportion of participants satisfying responder criteria will be presented by study intervention group.

Change From Baseline in Other Efficacy Endpoints Related to Bowel Habits and Abdominal Symptoms

The derivations of straining, abdominal pain (daytime and nighttime), bloating (daytime, nighttime, and combined daytime and nighttime symptoms), and CSBM frequency rates (CSBMs/week) during the Study Intervention Period are discussed in Section 16.3.7, Section 16.3.5, Section 16.3.8, and Section 16.3.4, respectively.

Descriptive statistics (mean, median, SD, standard error of mean, minimum, and maximum) will be presented by study intervention group.

Change from Baseline in 12-week Percent of Abdominal Pain (Combined Daytime and Nighttime Symptoms)-Free Days During Study Intervention Period

The percent of abdominal pain-free days during the analysis period will be derived as the number of days with abdominal pain (combined daytime and nighttime symptoms) scores of 0 divided by the total number of days with non-missing abdominal pain scores in the period (baseline or study intervention period) multiplied by 100. If a participant has reported abdominal pain score (any non-zero value from 1 to 4) in at least one eDiary (morning or evening) on a specific day during the analysis period, that day will not be counted as abdominal pain-free day during that analysis period.

Descriptive statistics (mean, median, SD, standard error of mean, minimum, and maximum) will be presented by study intervention group.

Proportion of Participants Who No Longer Fulfill Rome III Criteria for IBS-C at the End of the Study Intervention Period

The details of the derivation of this endpoint are discussed in Section 16.3.9. The proportion of participants who no longer fulfill Rome III criteria for IBS-C at the end of the study intervention period will be presented by study intervention group.

Participant-Completed Global Change Items and Global Severity Items at Each Week During Study Intervention Period

The details of participant-completed global change item scores and global severity item scores are discussed in Section 16.3.10. For each of the participant-completed global change items (pooping problems, tummy problems, and tummy pain) and global severity items (pooping problems, tummy problems, and tummy pain), counts and percentages for each category within each individual item will be provided by study intervention group at each week during the study intervention period.

Observer-Completed Global Change Item and Global Severity Item at Each Week During Study Intervention Period

The observer-completed global change item and global severity item will be assessed on a weekly basis in the eDiary, for the 7 - 11 years of age group only as discussed in Section 16.3.11. Counts and percentages of the global change item and the global severity item will be provided by study intervention group at each week during the study intervention period.

10.4 Subgroup Analysis for Efficacy endpoints

Primary and secondary efficacy endpoints will be summarized in a similar way as discussed for main analysis approach for the following subgroups (within each subgroup category) based on the mITT Population. Subgroups will be interpreted with caution due to possible limited sample size within each subgroup category.

- Age group (7-11 years group, 12-17 years group)
- Race (white, non-white)
- Gender (male, female)

11 Safety Analyses

The safety analysis will be performed using the Safety Population. The safety parameters will include adverse events (AEs) and clinical laboratory parameters, vital sign (including postural), electrocardiographic (ECG) parameters, height, and weight. For each safety parameter of the clinical laboratory, vital signs, height, weight, and ECG parameters, the last non-missing safety assessment before the first dose of study intervention will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by number of participants and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants. The safety summaries will be provided by study intervention group.

11.1 Adverse Events

Adverse events will be coded by system organ class and preferred term using the *Medical Dictionary for Regulatory Activities,* version 23.0 or newer.

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; 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 30 days after the last dose of study intervention 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 SAE criterion.

The number and percentage of participants reporting TEAEs in each study intervention group will be tabulated by descending percentage in any group, by system organ class and preferred term, and further categorized by severity and causal relationship to the study intervention. 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 greatest severity and strictest causality for the summarization by severity and causal relationship. The above summaries of TEAEs, further categorized by severity and causal relationship will also be provided within each age group. If there are 5 or less participants with severe or related TEAEs in any study intervention group, the

corresponding age group summaries for TEAEs by severity or causal relationship will not be provided.

The incidence of common (≥ 5% of participants in any study intervention group) TEAEs will be summarized by system organ class, preferred term, and study intervention group.

Summary tables will be provided for participants with TESAEs, AEs of special interest, and participants with AEs leading to discontinuation.

For all screened participants, separate listings will be presented for participants who died, participants with SAEs, participants with AEs leading to premature discontinuation, and participants with AEs of special interest (AESI). AEs during the Postintervention Period will also be included in the listings. A listing of all AEs will also be presented.

11.2 Clinical Laboratory Parameters

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 laboratory parameters:

Hematology:	Absolute and differential white blood cell count, erythrocyte count, hemoglobin, hematocrit, platelet count, red blood cell count, and red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration)
Chemistry:	Sodium, potassium, calcium, chloride, bicarbonate, magnesium, phosphate, glucose, blood urea nitrogen, creatinine, total protein, alkaline phosphatase (ALP), albumin, total bilirubin (TBL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol
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 11-1. The number and percentage of participants who have PCS postbaseline clinical laboratory values will be tabulated by study intervention for the double-blind Intervention Period. The percentages will be calculated relative to the number of participants with available non-PCS baseline values and at least 1 postbaseline assessment for the double-blind Intervention Period. The numerator will be the total number of participants with available non-PCS baseline values and at least 1 PCS postbaseline value for the double-blind Intervention Period. A supportive tabular display of participants with PCS postbaseline values will be provided, including the PID number, baseline

and all postbaseline (including non-PCS) values. In this listing, any participant with PCS value (if any) during the Post-intervention period will also be included.

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 double-blind 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.

Table 11-1. 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- 17 (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
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
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.

11.3 Vital Signs

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

Vital sign values will be considered PCS if they meet both the observed-value criteria and the change-from-baseline criteria listed in Table 11-2. The number and percentage of participants with PCS postbaseline values will be tabulated by study intervention group for the double-blind Intervention Period and Postintervention Period separately. The percentages will be calculated relative to the number of participants with available non-PCS baseline values and at least 1 postbaseline assessment in the specific period. The numerator will be the total number of participants with available non-PCS baseline values and at least 1 PCS postbaseline value during the specific period. A supportive tabular display of participants with PCS postbaseline values will be provided, including the PID number, baseline and all postbaseline (including non-PCS) values.

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

Table 11-2. 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 systolic blood pressure from supine to standing at observed time point is at least 10 mmHg greater than the decrease in systolic blood pressure 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 diastolic blood pressure from supine to standing at observed time point is at least 10 mmHg greater than the decrease in diastolic blood pressure 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]
Systolic Blood Pressure, mm Hg (Supine)	High	Age 6-11 (inclusive): ≥ 140 Age 12-17 (inclusive): ≥ 155	Increase of ≥ 20
	Low	Age 6-11 (inclusive): ≤ 80 Age 12-17 (inclusive): ≤ 90	Decrease of ≥ 20
Diastolic Blood Pressure, mm Hg (Supine)	High	Age 6-11 (inclusive): ≥ 95 Age 12-17(inclusive): ≥ 105	Increase of ≥ 15
	Low	Age 6-11 (inclusive): ≤40 Age 12-17 (inclusive): ≤ 45	Decrease of ≥ 15
Pulse Rate, bpm (Supine)	High	Age 6-11 (inclusive): ≥ 140 Age 12-17 (inclusive): ≥ 120	Increase of ≥ 15
	Low	Age 6-11 (inclusive): ≤ 50 Age 12-17 (inclusive): ≤ 40	Decrease of ≥ 15
Weight, kg	High	—	Increase of ≥ 5%
	Low	—	Decrease of ≥ 5%

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

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

* Change from supine value standing value supine value

11.4 Electrocardiogram

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

Electrocardiographic parameter values are considered PCS if they meet or exceed the higher-limit PCS criteria listed in Table 11-3. The number and percentage of participants with PCS postbaseline ECG values will be tabulated by study intervention group for the double-blind invention period. The percentages will be calculated relative to the number of participants with available non-PCS baseline values and at least 1 postbaseline assessment for the double-blind Intervention Period. The numerator is the total number of participants with available non-PCS baseline values and at least 1 PCS postbaseline value for the double-blind Intervention Period. A supportive tabular display of participants with PCS postbaseline values will be provided, including the PID number, baseline, all postbaseline (including non-PCS) values, and change from baseline. In this listing, any participant with PCS value (if any) during Postintervention Period will also be included.

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 double-blind 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.

Table 11-3. 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 (16-17 (inclusive) years)
PR interval	msec	PR > 225 msec (6-7 (inclusive) years) PR > 250 msec (8-17 (inclusive) years)
QTc(F)	msec	>480

QTc(F) QT Corrected by Fridericia's formula

11.5 Other Safety Parameters

11.5.1 Potential Hy's Law

Potential Hy's Law criteria within a 24-hour window is defined by a post baseline elevation of ALT or AST ≥ 3x ULN, along with TBL ≥ 2x ULN and a non-elevated ALP < 2x 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 drug to within 30 days after the last dose of study intervention will be summarized. Supportive tabular displays will also be provided.

12 Health Outcomes Analyses

Not applicable.

13 Interim Analysis

For IBS-C participants in this study, no interim analysis is planned.

14 Determination of Sample Size

The sample size of at least 50 randomized participants per arm (at least 100 randomized participants in total) for IBS-C participants in this study was planned to inform the prescriber regarding the safe and efficacious use of linaclotide doses in this patient population. The planned sample size is not driven by any statistical consideration. This section provides the estimated Bayesian powers for the primary analysis of the primary endpoint in IBS-C portion of this study for the planned sample size.

Extrapolation from IBS-C adult studies (MCP-103-202 [Phase 2b], LIN-MD-31 [Phase 3], and MCP-103-302 [Phase 3]) was performed using Bayesian methodology with the primary efficacy endpoint of 6/12 week APS + 2 responder endpoint (as defined in Section 10.1). APS + 2 responder rates for treated individuals from the adult IBS-C population in Phase 2b study MCP-103-202 and Phase 3 pivotal studies LIN-MD-31 and MCP-103-302 were used to form a prior probability distribution for the pediatric APS + 2 response rate. This prior was down-weighted. Responder data from LIN-MD-64 were simulated using the down-weighted prior and the lower 2.5 percentile of posterior samples compared separately against the pooled placebo rate and the upper limit of 95% CI (2-sided) of pooled placebo rate from the adult contributing studies. The probabilities (Bayesian powers) that the lower 2.5 percentile of the linaclotide responder rate being greater than the pooled placebo rate from contributing adult studies, for different sample sizes and effective sample sizes (with associated down-weight factors) are provided in Table 14-1. Similarly the probabilities (Bayesian powers) that the lower 2.5 percentile of the linaclotide responder rate being greater than the upper limit of the 95% confidence interval of the placebo responder rate from contributing adult studies are also provided in Table 14-2.

With the consideration of a modest weight of 0.017 on the prior (equivalent to 15 new subjects from the adult IBS-C studies), the planned sample size of 50 IBS-C participants per arm should sufficiently describe the efficacy in pediatrics when contextualized using the pooled placebo rate from adult contributing studies.

The details of simulation codes to generate Bayesian powers in Table 14-1 and Table 14-2 are provided in Appendix 1.

Table 14-1. Bayesian Power Estimates by Sample Size and ESS (vs. the Responder Rate of the Adult Placebo Response, 0.16*)

	N/Arm=30	N/Arm=40	N/Arm=50
ESS=12 (w = 0.0135)	0.763	0.808	0.836
ESS=15 (w = 0.017)	0.865	0.873	0.854
ESS=18 (w = 0.020)	0.865	0.903	0.904
ESS=24 (w = 0.027)	0.943	0.954	0.964

ESS (Effective Sample Size) is calculated as the number of subjects used to derive the prior distribution multiplied by the down weight (w).

* Based on pooled adult placebo data from Phase 2b study MCP 103 202 and Phase 3 pivotal studies LIN MD 31 and MCP 103 302.

Table 14-2. Bayesian Power Estimates by Sample Size and ESS (vs. the Upper Limit of the 95% CI (2-sided) of the Adult Placebo Response, 0.18*)

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

ESS (Effective Sample Size) is calculated as the number of subjects used to derive the prior distribution multiplied by the down weight (w).

* Based on pooled adult placebo data from Phase 2b study MCP 103 202 and Phase 3 pivotal studies LIN MD 31 and MCP 103 302.

15 Statistical Software

Statistical analyses will be performed using version 9.4 (or newer) of SAS on a Linux operating system.

16 Data Handling Conventions

16.1 Visit Time Windows for Safety Analyses

Table 16-1 presents the visits assigned for safety analyses and the corresponding range of study intervention days (window) during which an actual visit may occur.

Table 16-1. Visit Time Windows

Derived Visit	*Scheduled Visit Day*[a]	*Window*
Baseline	Day 1	Days ≤ 1
Week 2 Visit	Day 15	Days [2, 21]
Week 4 Visit	Day 29	Days [22, 42]
Week 8 Visit	Day 57	Days [43, 70]
Week 12 Visit	Day 85	Days [Day 71, max (last dose day+1, Visit 7 date)]
Post-intervention Visit	Day 92	Days >= max (last dose day+1, Visit 7 date)+1
End of Double-Blind Intervention Period[b]	Final or Termination Visit during the double-blind Intervention Period	

a. Relative to the date of the first dose of double blind study intervention. Day 1 the date of the first dose of double blind study intervention. There is no Day 0 or Week 0.

b. Presented in analysis tables for safety parameters, including but not limited to electrocardiograms, clinical laboratory values, and vital signs.

Participants who rollover to the long-term safety study, LIN-MD-66, before the EOS visit (i.e. Visit 8, post-intervention visit) are not required to have this EOS visit or post-intervention visit.

If the assessment date (if the assessment date is unavailable, use visit date instead) is on or after the date of the first dose of study intervention, the study day is calculated by assessment date date of the first dose of study intervention + 1. If the assessment date is before the date of the first dose of study intervention, the study day is calculated by assessment date date of the first dose of study intervention. Therefore, a negative day indicates a day before the start of the study intervention.

If a participant has 2 or more visits within the same window, the last visit with a non-missing value will be used for analysis.

16.2 Visit Time Windows for Efficacy Analyses

Table 16-2 below presents the analysis weeks assigned for the efficacy analysis of the participant daily diary data related to BM and/or abdominal symptom characteristics. These analysis weeks

will be used in the calculations for all week-based endpoints (eg, SBM weekly frequency rate, etc.).

Table 16-2. Analysis Time Windows for Efficacy Analysis - Daily Questions

Period	Analysis Week	Begins[a]	Ends[a]
Preintervention (Baseline[b])	Week -2	Day -14	Day -8
	Week -1	Day -7	Day 1, time of randomization
Intervention	Week 1	Day 1, time after randomization	Day 7
	Week 2	Day 8	Day 14
	Week 3	Day 15	Day 21
	Week 4	Day 22	Day 28
	Week 5	Day 29	Day 35
	Week 6	Day 36	Day 42
	Week 7	Day 43	Day 49
	Week 8	Day 50	Day 56
	Week 9	Day 57	Day 63
	Week 10	Day 64	Day 70
	Week 11	Day 71	Day 77
	Week 12	Day 78	Day of last dose +1
Post-intervention	Post-intervention	Day of last dose + 1	Day of end of study visit

Note: On randomization day, if participant already completed morning diary, at the clinic visit, participants fill out a clinic diary and the assessments in the clinic diary will be part of the Preintervention Period. Morning diary assessments on randomization day will also be part of Preintervention Period. eDiary assessments in evening diary on the day of randomization will be part of the Intervention Period. eDiary assessments in morning diary at the day after the last dose day will be considered as assessments in the Intervention Period.

a. Relative to the date of randomization; Day 1 the day of randomization.

b. Baseline values for efficacy parameters will be derived from the daily morning and evening eDiaries and eCRF data collected in the Preintervention Period, specifically the period of time from 14 days before randomization up to the time of randomization.

For the Intervention Period, daily diary day is calculated as (diary date - date of randomization + 1). For the Preintervention Period, daily diary day is calculated as (diary date - date of randomization). However, the day of randomization is study Day 1 regardless. Participants will complete their diary entries twice per day for daily diary.

If a participant withdraws during the Intervention Period, the participant's morning diary assessments of daily eDiary on the day after last dose day will be captured as assessments in the Intervention Period. The impacted Intervention Period week shall be shortened to the end of the

withdrawn participant's Intervention Period and all subsequent Intervention Period weeks will be missing for that participant.

Table 16-3 below presents the weekly periods assigned for the efficacy analysis of the participant weekly diary data related to global severity items and global change items.

Table 16-3. Analysis Time Windows for Efficacy Analysis - Weekly Questions

Analysis Week	Begins[a]	Ends[a]
Week -2	Visit 2 day	Visit 2 day + 7
Week -1 (Baseline)	Visit 2 day + 8	Day 1
Week 1	Day 2	Day 8
Week 2	Day 9	Day 15
Week 3	Day 16	Day 22
Week 4	Day 23	Day 29
Week 5	Day 30	Day 36
Week 6	Day 37	Day 43
Week 7	Day 44	Day 50
Week 8	Day 51	Day 57
Week 9	Day 58	Day 64
Week 10	Day 65	Day 71
Week 11	Day 72	Day 78
Week 12	Day 79	last dose date +1
Post-intervention	Day of last dose date + 8	Day of end of study visit

a. Begin and end of each week from Week 1 onwards are relative to the date of the first dose of double blind study intervention. Day 1 the date of the first dose of double blind study intervention. There is no Day 0 or Week 0. End of Week 1 to Week 12 will be day of last dose + 1 or corresponding end day in table whichever comes earlier.

Participants who rollover to the long-term safety study, LIN-MD-66, before the EOS visit (i.e. Visit 8, post-intervention visit) are not required to have the EOS visit or post-intervention visit.

16.3 Derived Variables

16.3.1 Missing or Incomplete Morning/Evening eDiary Assessments

No imputation or derivation will be performed for missed morning/evening assessments unless otherwise specified.

16.3.2 Incomplete Morning/Evening eDiary Assessments

Missing responses in incomplete morning and/or evening assessments will not be imputed for most of the parameters, with the exception of rescue medication (RM) use and BM frequency.

If the answer to the RM use question is missing for any assessment (morning or evening), no RM usage will be considered during that diary period (morning or evening diary) in eDiary, with the exception that the missing RM will be considered "used" if the other available assessment during that diary period is "yes".

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

16.3.3 Incomplete Clinic Diary on Randomization Visit (If Present)

Missing responses in an incomplete clinic diary on randomization day will be handled in a similar way as mentioned for incomplete daily morning/evening assessments. Clinic diary on randomization day will be considered as part of morning diary on randomization day.

16.3.4 Stool Frequency

The derivation of SBM and CSBM frequencies require the collection of data on bowel movement frequency and rescue medication use. Participants will report their BM frequency (the number of BMs) and use of rescue medication by responding to the following:

Bowel Movement Frequency - Morning eDiary

For this parameter, participants will record their BM frequency by responding to the following in the morning eDiary:

- From bedtime last night until now, how many times did you poop (and poop came out)?
- Enter number of times.

Bowel Movement Frequency - Evening eDiary

For this parameter, participants will record their BM frequency by responding to the following in the evening eDiary:

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

Rescue Medication Use - Morning eDiary

For this parameter, participants will record whether they took rescue medication by responding to the following in the morning eDiary:

- From bedtime last night until now, did you take any medicine to help you poop, other than the study medicine?
  - Yes
  - No

Rescue Medication Use - Evening eDiary

For this parameter, participants will record whether they took rescue by responding to the following in the evening eDiary:

- From when you got up this morning until now, did you take any medicine to help you poop, other than the study medicine?
  - Yes
  - No

Spontaneous Bowel Movement (SBM)

An SBM is a BM that occurs in the absence of rescue medication (laxative, suppository, or enema) use on the calendar day of the BM or the calendar day before the BM.

Complete Spontaneous Bowel Movement (CSBM)/Incomplete Evacuation

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

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

Values of "No" correspond to a CSBM.

Stool Frequency Rates

The components for calculating a participant's stool frequency rates (SBM/CSBM weekly rates) for a given period are as follows:

- The number of BMs that occurred during that specific period
- The number of those BMs that were SBMs
- The number of those SBMs that were CSBMs
- The number of days during that specific period:
  - Randomization day with evening diary will be considered a half day for the double-blind Intervention Period.
  - Randomization day with morning and/or clinic diary will be considered a half day for the Preintervention Period.
  - The day after last dose will be considered a half day for the double-blind Intervention Period with morning diary and for the Postintervention Period with evening diary.

Duration of an Analysis Week

With respect to a participant's scheduled analysis weeks, the term duration is used. In regard to the duration of a week, it is expected that 1 or more of a participant's "weeks" may not be exactly 7 days in duration (eg, a participant may withdraw or discontinue early from the trial, may have half day data with diary entries, or may have missing diary day). Deviations from the 7 days norm are structural in nature; and, as such, the calculations of the weekly rates of SBMs or CSBMs will incorporate the actual days contributed within the time period (week or specific phase).

Weekly Stool Frequency Rate Calculations

The weekly frequency rate for SBMs (CSBMs) will be based on the total number of SBMs (CSBMs) occurring based on the diary entries during that time period, adjusting for differences in the length of the time period. Weekly stool frequency rates for each specific period will be calculated as follows:

- Weekly Frequency Rate (Specific Period)

$$\frac{\text{Total number of events (SBMs or CSBMs) during the specific period}}{\text{Number of days during the specific analysis period}} \text{ X } 7$$

16.3.5 Abdominal Pain

Abdominal pain scores will be collected twice daily in the eDiary (morning and evening).

Abdominal Pain - Daytime

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

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

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

- How much did your tummy hurt?
  1 a tiny bit
  2 a little
  3 some
  4 a lot

Abdominal Pain - Nighttime

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

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

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

- How much did your tummy hurt?
    1 a tiny bit
    2 a little
    3 some
    4 a lot

Abdominal Pain - Combination (Total 24-hour Period)

The Abdominal Pain Combination Score for a 24-hour period will be determined based on combined daytime symptoms of abdominal pain in evening eDiary assessments and nighttime symptoms of abdominal pain in morning eDiary assessments as follows:

- Combination score average of morning and evening assessments, if both morning and evening assessments are present
- Combination score morning or evening assessment, if either morning or evening assessment is present
- Combination score missing, if both morning and evening assessments are missing

The participant's abdominal pain score for a specific period based on evening assessments (daytime symptoms), morning assessments (nighttime symptoms), and combined morning and evening assessments will be derived as the mean of the non-missing abdominal pain scores within the corresponding diaries during the specific period. The abdominal pain scores of 0, 1, 2, 3, and 4 will be used to calculate the average, where '0' indicates no abdominal pain.

16.3.6 Stool Consistency

Participants will use the pediatric Bristol Stool Form Scale (p-BSFS), to rate their stool consistency for each BM:

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

Type 1 looks like small hard lumps or balls, like pebbles
Type 2 looks like fat sausage shape but lumpy and hard
Type 3 looks like a sausage but with cracks on it
Type 4 looks like a sausage or snake, smooth and soft
Type 5 looks like chicken nuggets, soft smooth blobs
Type 6 looks like oatmeal, fluffy mushy pieces
Type 7 looks like a milkshake, watery
99 - I don't know

"I don't know" is considered as a missing response. Stool consistency will be collected twice daily (morning and evening) in the eDiary and measured using the 7-point p-BSFS. Stool consistency (p-BSFS) score during a specific analysis period will be derived as mean of participant's non-missing, SBM-associated p-BSFS scores during that specific period.

16.3.7 Straining

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

- When you pooped, how hard did you push?
  - 0 not hard at all
  - 1 I pushed a tiny bit hard
  - 2 I pushed a little hard
  - 3 I pushed hard
  - 4 I pushed very hard

Straining will be collected twice daily (morning and evening) in the eDiary and measured using a 5-point scale. The participant's straining score in a specific analysis period will be the mean of participant's non-missing, SBM-associated straining scores during that specific period.

16.3.8 Abdominal Bloating

Abdominal bloating scores will be collected twice daily in the eDiary (morning and evening).

Abdominal Bloating - Daytime

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

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

If "yes" then participant answers the following question:

How big and full did your tummy FEEL?

1 a tiny bit
2 a little
3 medium
4 very

Abdominal Bloating - Nighttime

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

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

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

- How big and full did your tummy FEEL?
  1 a tiny bit
  2 a little
  3 medium
  4 very

Abdominal Bloating - Combination (Total 24-hour Period)

The Abdominal Bloating Combination Score for a 24-hour period will be determined based on combined daytime symptoms of abdominal bloating in evening assessments and nighttime symptoms of abdominal bloating in morning assessments as follows:

- Combination score average of morning and evening assessments, if both morning and evening assessments are present
- Combination score morning or evening assessment, if either morning or evening assessment is present
- Combination score missing, if both morning and evening assessments are missing

The participant's abdominal bloating score for a specific period based on evening assessments (daytime symptoms), morning assessments (nighttime symptoms), and combined morning and evening assessments will be derived as the mean of the non-missing abdominal bloating scores

within the corresponding diaries during the specific period. The abdominal bloating scores of 0, 1, 2, 3, and 4 will be used to calculate the average, where '0' indicates no bloating.

16.3.9 Rome III Criteria

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

16.3.10 Participant-completed Global Items

Participant-completed global change and global severity items were developed by the sponsors. The participant-completed global items consist of 6 items, 3 assessing global change in the participant's symptoms and 3 assessing the global severity of the participant's symptoms. All 6 participant-completed global items have a 7-day recall period and will be completed weekly on the eDiary device. The global severity items will be completed beginning at the Preintervention Period through End-of-Study (EOS) and the global change items will be completed beginning at Randomization through EOS.

Participant-completed Global Change Items

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

- Compared to 7 days ago, my pooping problems today are:
  0 a lot better
  1 a little better
  2 the same
  3 a little worse
  4 a lot worse

- Compared to 7 days ago, my tummy problems today are:
  0 a lot better
  1 a little better
  2 the same
  3 a little worse
  4 a lot worse
- Compared to 7 days ago, my tummy pain today is:
  0 a lot better
  1 a little better
  2 the same
  3 a little worse
  4 a lot worse

Global Severity Items

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

- How bad have your pooping problems been over the past 7 days:
  0 I have not had pooping problems
  1 a little bad
  2 bad
  3 very bad
- How bad have your tummy problems been over the past 7 days:
  0 I have not had tummy problems
  1 a little bad
  2 bad
  3 very bad
- How bad has your tummy pain been over the past 7 days:
  0 I have not had tummy pain in the past 7 days
  1 a little bad
  2 bad
  3 very bad

16.3.11 Observer-completed Global Items

The observer-completed (parents/caregivers) 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 observer-completed global items will be completed weekly on the eDiary device. The global severity item will be completed beginning at the Preintervention Period through the EOS and the global change item will be completed beginning at Randomization through the EOS.

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

Observer-completed Global Change Item

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

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

Observer-completed Global Severity Item

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

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

16.4 Repeated or Unscheduled Assessments of Safety Parameters

If a participant has repeated assessments before the start of the first study intervention, the results from the final non-missing assessment made prior to the start of the study intervention will be used as baseline. If end-of-study assessments are repeated or if unscheduled visits occur, the last non-missing postbaseline assessment will be used as the end-of-study assessment for generating summary statistics. However, all postbaseline assessments will be used for PCS value determinations, and all assessments will be presented in the data listings.

16.5 Missing Date of the Last Dose of Study Intervention

When the date of the last dose of study intervention is missing for a participant in the Safety Population, all efforts should be made to obtain the date from the Investigator. If after all efforts are made it is still missing, the Visit 7 date (if available) -1 will be set as last dose date. In absence of the Visit 7 date, the double-blind disposition status date -1 will be set as last dose date.

16.6 Missing Severity Assessment for Adverse Events

If severity is missing for an AE that started before the date of the first dose of study intervention, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of study intervention, an intensity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

16.7 Missing Causal Relationship to Study Drug for Adverse Events

If the causal relationship to the study intervention is missing for an AE that started on or after the date of the first dose of study intervention, a causality of yes will be assigned. The imputed values for causal relationship to study intervention will be used for the incidence summary; the values will be shown as missing in the data listings.

16.8 Missing Date Information for Adverse Events

The following imputation rules only apply to cases in which the start date for AEs is incomplete (ie, partly missing).

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of study intervention, the month and day of the first dose of study intervention will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the first dose of study intervention, *December 31* will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the first dose of study intervention, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of study intervention, the day of the first dose of study intervention will be assigned to the missing day
- If either the year of the incomplete start date is before the year of the date of the first dose of study intervention or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of study intervention, the last day of the month will be assigned to the missing day
- If either the year of the incomplete start date is after the year of the date of the first dose of study intervention or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of study intervention, the first day of the month will be assigned to the missing day

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of study intervention, the date of the first dose of study intervention will be assigned to the missing start date
- If the stop date is before the date of the first dose of study intervention, the stop date will be assigned to the missing start date

16.9 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, including rescue medications, incomplete (ie, partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a participant, the start date will be imputed first.

16.9.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of study intervention, the month and day of the first dose of study intervention will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the first dose of study intervention, *December 31* will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the first dose of study intervention, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of study intervention, the day of the first dose of study intervention will be assigned to the missing day
- If either the year of the incomplete start date is before the year of the date of the first dose of study intervention or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of study intervention, the last day of the month will be assigned to the missing day.
- If either the year of the incomplete start date is after the year of the date of the first dose of study intervention or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of study intervention, the first day of the month will be assigned to the missing day

16.9.2 Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the date of the last dose of study intervention is missing, impute it as descripted in Section 16.5. If the imputed stop date is before the start date (imputed or nonimputed start date), the imputed stop date will be equal to the start date.

Missing month and day

- If the year of the incomplete stop date is the same as the year of the last dose of study intervention, the month and day of the last dose of study intervention will be assigned to the missing fields
- If the year of the incomplete stop date is before the year of the last dose of study intervention, *December 31* will be assigned to the missing fields
- If the year of the incomplete stop date is after the year of the last dose of study intervention, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dose of study intervention, the day of the last dose of study intervention will be assigned to the missing day
- If either the year of the incomplete stop date is before the year of the date of the last dose of study intervention or if both years are the same but the month of the incomplete stop date is before the month of the date of the last dose of study intervention, the last day of the month will be assigned to the missing day
- If either the year of the incomplete stop date is after the year of the date of the last dose of study intervention or if both years are the same but the month of the incomplete stop date is after the month of the date of the last dose of study intervention, the first day of the month will be assigned to the missing day

16.10 Character Values of Clinical Laboratory Parameters

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table because, for example, a character string is reported for a parameter of the numeric type, a

coded value must be appropriately determined for use in the statistical analyses. The actual values, however, as reported in the database will be presented in the data listings.

Table 16-4 shows examples of how some possible laboratory results should be coded for the analysis.

Table 16-4. Examples of Coding Special Character Values for Clinical Laboratory Parameters

Laboratory Test, SI Unit	Possible Laboratory Results	Coded Value for Analysis
CHEMISTRY		
ALT, U/L	< 5	5
AST, U/L	< 5	5
Bilirubin, total, µmol/L	< 2	2
URINALYSIS		
Glucose, mmol/L	= OR > 55, ≥ 55, > 0	Positive
	≤ 0, negative	Negative
pH	> 8.0, ≥ 8.0	8.0
	≥ 8.5	8.5
Protein	= OR > 3.0, ≥ 3.0, > 0	Positive
	≤ 0	Negative

ALT alanine aminotransferase; AST aspartate aminotransferase; SI Le Système International d'Unités (International System of Units).

17 Changes To Analyses Specified In Protocol

The following major changes were made in SAP Amendment #1 to the analyses specified in the protocol (version dated June-2020).

- The frequentist 95% exact binomial CI for the primary endpoint will be presented.
- A Bayesian 95% credible interval derived from a non-informative prior (a uniform prior) distribution will be provided.
- Added supplemental analyses for the primary endpoint to handle missing data for weekly SBM or AP scores.
- Participants from a non-compliant site will be excluded from the mITT population.

The following major changes have been made in this SAP Amendment #2:

- Section 6.3: Participants who were incorrectly randomized due to an implementation error for adding IBS-C participants in this study by the eDiary vendor will be excluded from the mITT population.
- Section 10.1.2: Added a supplemental analysis to compare the proportion of responders to 0.18 (the upper bound of the 95% CI of the adult placebo rate) based on a one-sample proportion exact test.
- Section 10.1.2: Removed “Exact binomial” from the sensitivity analysis of multiple imputation as the 95% CI will be based on the synthesized results from the 30 imputed datasets.
- Section 11.1: Modified TEAE definition to include any AE that occurs within 30 days (instead of 1 day) after the last dose of study intervention.

18 References

Carlin BP and Louis TA. Bayesian Methods for Data Analysis. 2009. Bayesian Design. Chapman and Hall/CRC.

19 Appendix 1: Simulation Codes for Bayesian Power Estimates By Sample Size and Effective Sample Size

The specifics of this approach are as follows:

1. Use the 6/12 weeks APS+2 responder rates from the treated adult subjects to form a prior distribution for the pediatric 6/12 weeks APS+2 responder rate. Since this responder rate is bounded between [0,1] the prior distribution of responder rate can be approximated by the Beta distribution. In this case,

   α (aggregate number of adult responders) and
   β (aggregate number of adult non-responders)
   $\theta \sim$ Beta(α, β) .....(1)

2. Suppose N subjects in LIN-MD-64 and for each θ Pr(Pediatric subject is a responder), and let X be the number of pediatric patients who are responders in LIN-MD-64 then:

   $X|\theta \sim Bi(N, \theta)$..... (2)

3. The posterior distribution is also a Beta distribution:

   $\theta |X \sim$ Beta(X + α, N X + β) .....(3)

4. Randomly select θ_j from the prior, and X_j from the binomial likelihood for j 1 to M simulated trials.

5. Tally the number of times the 2.5th percentile of the simulated posterior is greater than C, where C includes the Placebo responder rate observed in the Adult trials and upper bound of 95% CI of the Placebo responder rate in the Adult trials.

6. The proportion, tally/M, is the predictive probability (Bayesian Power) to exceed a rate of C with a trial of size N.

7. To investigate how sensitive the results are to the selection of the prior, we will down-weight the prior by multiplying α and β from our prior distribution by w, where ($0 \leq w \leq 1$). This will have the effect of allowing the prior to have the same center, but will have heavier tails or decreased confidence in the prior distribution. Down-weighting in this manner will allow each adult patient to be 'worth' the fraction w of a new pediatric patient. An alternative way of

expressing this 'worth' and describing the impact of the weights would be to describe an effective sample size. Effective Sample Size (ESS) is

calculated as $(\alpha + \beta)*w$ and is interpreted as the amount of new samples that the adult data will be equivalent to in an analysis.

8. A suitable sample size should have a sufficiently high Bayesian power across a range of weights for the prior distribution.

Here the priors are all of the "weighted" form, ie Beta((adult responder)*w,(adult non-responder)*w), $0 < w < 1$.

Keep seed as 99; w as 0.017 first and c as 0.16 and 0.18 to generate output as provided in Table 14-1 and Table 14-2.

R-code for Bayesian power estimates:

```
set.seed(99)              #Seed for reproducibility
w <- c(.017)              #w are the weights, this program can only do one weight per
                          #run; run for other ws in Table 14-1 and Table 14-2
                          #(w  0.0135, 0.020, 0.027)
N <- seq(20,100,10)       #N are your sample sizes in this case from 20 to 100 by 10
C<- seq(0.16, 0.18,0.02)        #C is the cut point for determining success 0.16 is the
                                 #pooled placebo rate in adult; 0.18 95%UCL of placebo
                                 #rate in adult
Nrep <- 1000              #Nrep is the number of replicates
library(tidyr)
pct <- matrix(0,length(C),length(w)*length(N)+1);  pct[,1] <- C

#  The adult responder rate DATA:
no.resp <- 550; resp <- 340

#  NOW START MAIN SIMULATION LOOPS:
for(j in 1:length(w)){
  alpha <- resp*w[j]
  beta <- no.resp*w[j]
  cb.prior <- rbeta(Nrep,alpha,beta)
```

```
  for(k in 1:length(N)){
    cb.x <- rbinom(Nrep,N[k],cb.prior)
#  HERE IS THE CALCULATION OF THE 2.5TH PERCENTILE OF THE #POSTERIOR:
    cb.post <- rep(NA,Nrep)
    cb.post <- qbeta(0.025,cb.x + alpha,N[k] - cb.x + beta)


    cat(paste("\n N     ", N[k], "   w     ", w[j]))
    for(i in 1:length(C)){
      pct[i,1+(j-1)*length(N)+k] <- sum((cb.post > C[i])     T)/Nrep
      cat(paste("\n Percent of lower .025 points >",C[i]," is",
              round(pct[i,1+(j-1)*length(N)+k],3)))
    }

  }  # end of N[k] loop
}  # end of w[j] (prior) loop

#Data manipulations to create the dataframe
colnames(pct)<-c("Placebo",paste(N[1],"-",w[1]),paste(N[2],"-",w[1]),paste(N[3],"-
",w[1]),paste(N[4],"-",w[1]),

                 paste(N[5],"-",w[1]),paste(N[6],"-",w[1]),paste(N[7],"-",w[1]),paste(N[8],"-
",w[1]),paste(N[9],"-",w[1]))

rownames(pct)<-C
df<-as.data.frame(as.table(pct))
# tabulate<-filter(df, Var2 !   "Placebo")
tabulate<-dplyr::filter(df, Var2 !   "Placebo")
p<- tabulate %>% separate(Var2, c("SampleSize", "Weight"),sep  "-")
p$SampleSize<-as.factor(p$SampleSize)
p$SampleSize<- ordered(p$SampleSize, levels     c("20 ", "30 ", "40 ","50 ","60 ","70 ","80 ","90
","100 "))

p$Weight<-as.factor(p$Weight)
p<- tabulate %>% separate(Var2, c("SampleSize", "Weight"),sep  "-")
p$SampleSize<-as.factor(p$SampleSize)
p$Weight<-as.factor(p$Weight)
```

1.0 TITLE PAGE

LIN-MD-64

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

STATISTICAL ANALYSIS PLAN - Clinical Study Report

FOR FC PARTICIPANTS

Final: [redacted]

Amendment #1: [redacted]

2.0 TABLE OF CONTENTS

2.1 LIST OF TABLES

2.2 LIST OF FIGURES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BM	bowel movement
CMH	Cochran-Mantel-Haenszel
CP	conditional power
CSBM	complete spontaneous bowel movement
DSMB	Data Safety Monitoring Borad
eCRF	electronic case report form
eDiary	electronic diary
ECG	electrocardiogram, electrocardiographic
EMEA	Europe, the Middle East, and Africa
EOS	End- of- Study
EU	European Union
FC	functional constipation
IA	interim analysis
IBS-C	irritable bowel syndrome with constipation
LLN	lower limit of normal
LSM	least squares mean
MAR	missing at random
MCMC	Markov Chain Monte Carlo
mITT	modified intent-to-treat
MMRM	mixed-effects model for repeated measures
NMAR	not missing at random
OC	observed cases
p-BSFS	pediatric Bristol Stool Form Scale
PCS	potentially clinically significant
PID	participant identification
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
RM	rescue medication
SAE	serious adverse event
SAP	statistical analysis plan

SBM	spontaneous bowel movement
SD	standard deviation
SI	*Le Système International d'Unités* (International System of Units)
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal

4.0 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and/or specified in the final protocol of Study LIN-MD-64 (version dated Jun-2020) for functional constipation (FC) participants only. Specifications of tables, figures, and data listings for FC participants are contained in a separate document.

The statistical analyses of the efficacy and safety for irritable bowel syndrome with constipation (IBS-C) participants as specified in amended protocol of LIN-MD-64 (version dated Jun-2020) are documented in a separate statistical analysis plan.

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

A total of 326 participants with FC are targeted to be randomized in a 1:1 ratio to receive either linaclotide 72 µg (163 participants) or placebo (163 participants). The targeted FC participant population will include male and female participants. Randomization will be stratified by age group only (6 to 11 years of age versus 12 to 17 years of age) with a minimum of 40% of participants within each age group. The study aims to enroll approximately 1/3 of the participants in the European Union (EU). An optional interim analysis (IA) for futility in the FC population may be considered based on the enrollment of FC participants in this study (ie, if the rate of enrollment is below expectations). The details related to the planned sample size with the optional IA are provided in Section 13.0 and Section 14.0.

The study will include a total of 8 visits and will be up to 20 weeks in duration: a 2-to 4-week Screening Period, a 2- to 3-week Preintervention Period, followed by a 12-week double-blind Study Intervention Period and 1-week Postintervention Period. The raw datasets of study LIN-MD-64 capture Preintervention Period as Pretreatment Period, Study Intervention Period as Treatment Period, and Postintervention Period as Posttreatment Period. Participants will not receive study intervention (i.e. study treatment) during the Screening/Preintervention Period and the Postintervention Period.

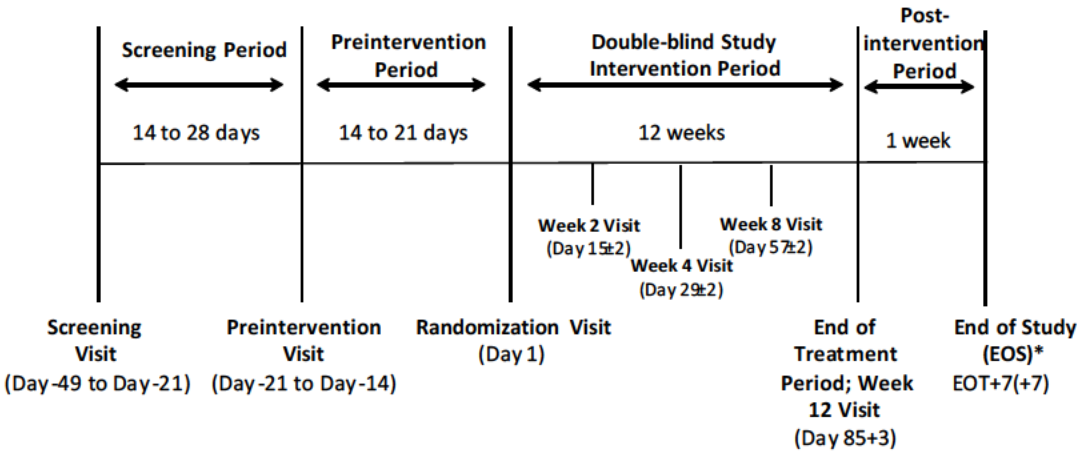
Participants who enter into the open-label long-term safety study, LIN-MD-66, before the End-of-Study (EOS) Visit are not required to have the EOS visit in LIN-MD-64.

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

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

Figure 4-1 is the schematic of the study design.

Figure 4-1 LIN-MD-64 Study Schema



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

The schedule of evaluations for Study LIN-MD-64 is presented in Table 4-1.

Table 4-1 Schedule of Evaluations: Study LIN-MD-64 (FC Participants)

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

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

a. Study procedures for screening in LIN-MD-66 can be combined with End of Treatment (EOT)/Week 12 Visit (Visit 7) for Study LIN-MD-64.
b Participants who rollover to the long-term safety study, LIN-MD-66, before the EOS Visit (Visit 8) are not required to have this visit.
c Participants must complete at least 12 weeks (84 days) of study intervention before arriving at the study site for the EOT/Week 12 Visit (Visit 7). All randomized participants who prematurely discontinue from the study intervention, regardless of cause, should complete assessments at this EOT/Week 12 Visit (Visit 7).
d. The parent/guardian/legally authorized representative must provide written informed consent and the participant must provide assent before the participant's enrollment in the study. If a parent or legal guardian is also the participant's caregiver, he or she will be asked to sign a combined parent and caregiver written informed consent. Caregivers other than parent or legal guardian must provide written informed consent.
e. Prior to dosing, the investigator or appropriate site staff member will assess if Rome IV criteria for Child/Adolescent FC (FC and IBS-C participants) or Rome IV criteria for Child/Adolescent IBS (IBS-C participants) was met and record the outcome in the eCRF. Eligibility for the study is not based on this assessment.
f. Eligibility report must be run prior to randomization.
g During the Screening Period, participants and their caregivers will receive information regarding lifestyle modifications (refer to Section 5.3 of the protocol. for details). There should be at least a 2-week interval between discussing the lifestyle modifications during the Screening Period and the participant's entry into the Preintervention Period.
h. Physical examinations will be performed by medically qualified site personnel and may be repeated at the investigator's discretion. If fecal impaction (as defined in footnote i) is documented during an optional repeat physical examination, the Study Physician must be notified.
i. Fecal impaction is defined as a hard mass in the lower abdomen identified on physical examination or a dilated rectum filled with a large amount of stool on rectal examination. If a rectal examination is performed, the medically qualified site personnel should assess for and document the presence of anal wink and normal anal tone.
j A fecal impaction assessment is only performed at the Preintervention Visit (Visit 2) if a fecal impaction was documented during the fecal impaction assessment at Screening (Visit 1). If there is no fecal impaction at the Preintervention Visit (Visit 2) (as defined in footnote i above), the participant may enter the Preintervention Period after adhering to any washout requirements. If fecal impaction is present upon re-examination, the participant will not be eligible for the study.
k. A fecal impaction assessment is performed at the Randomization Visit (Visit 3) after eDiary eligibility is confirmed and prior to randomization. If there is no fecal impaction at the Randomization Visit (Visit 3) (as defined in footnote i above), the participant is eligible for randomization. If fecal impaction is present upon examination, the participant will not be eligible for the study.
l Vital signs include temperature, respiratory rate, and weight. Postural vital signs (supine and standing) include pulse rate and systolic and diastolic blood pressure. At all visits, postural vital signs must be obtained after participants have been in a supine position for at least 2 to 3 minutes, followed by a standing position for at least 1 minute. Temperature may be recorded as oral, rectal or tympanic (ear). If possible, temperature should be obtained using the same method at each visit.
m. Clinical laboratory tests consist of clinical chemistry, hematology, and urinalysis. All laboratory tests requiring blood draws should be collected at the same time.
n. Serum pregnancy test will be obtained for female participants of childbearing potential.
o Urine pregnancy test will be obtained for female participants of childbearing potential. A negative urine pregnancy test is required prior to dosing at the Randomization Visit (Visit 3) and prior to study intervention dispensing at Week 4 (Visit 5) and Week 8 (Visit 6).
p A urine drug screen will be obtained at Screening (Visit 1) for all participants 12 to 17 years of age and only if deemed necessary by the investigator for participants 6 to 11 years of age. Urine drug screens may be repeated at the investigator's discretion at any time during the study.
q Protocol-permitted rescue medication will be dispensed in IWRS where applicable. Participants may choose a different protocol-permitted rescue medication at any subsequent visit, where available. Additional protocol-permitted rescue medications may be dispensed as needed at any subsequent visit, where available.
r At the Preintervention Visit (Visit 2), participants and parents/caregivers will be trained on the use of the eDiary device and instructed to complete both morning and evening assessments daily. At subsequent visits, study site staff will verify participant compliance with the eDiary device and remind participants to complete their morning and evening assessments daily. The global severity items will be completed beginning at the Preintervention Period through End-of-Study, and the global change items will be completed beginning at Randomization through End-of-Study.
s Study intervention will be administered at the study site during the Randomization Visit (Visit 3) after running the Eligibility report and confirming the participant has fasted for at least 2 hours. IWRS will be contacted to obtain the study intervention (bottle number) to be dispensed. Participants may eat 30 minutes after dosing (the requirement for study intervention to be administered 30 minutes prior to the meal will not apply for the first dose).
t. Protocol-permitted rescue medications only.
u Additional unscheduled visits may be allowed at the discretion of the investigator with approval from the sponsor.

5.0 OBJECTIVES

For FC participant population, the objective of LIN-MD-64 is to evaluate the safety and efficacy of 12 weeks of linaclotide therapy in comparison with placebo in pediatric participants aged 6 to 17 years who fulfill modified Rome III Criteria for Child/Adolescent FC.

6.0 PARTICIPANT POPULATIONS

6.1 SCREENED POPULATION

Screened Population will consist of all participants who undergo the Screening Visit (Visit 1) and receive a participant identification (PID) number.

6.2 RANDOMIZED POPULATION

Randomized Population will consist of all participants in the Screened Population who are randomized to a study intervention group.

6.3 MODIFIED INTENT-TO-TREAT POPULATION

The Modified Intent-to-Treat (mITT) Population will consist of all participants in the Randomized Population who receive at least 1 dose of double-blind study intervention. Participants will be summarized according to the randomized study intervention for all efficacy analysis variables/endpoints.

6.4 SAFETY POPULATION

The Safety Population will consist of all participants in the Randomized Population who receive at least 1 dose of double-blind study intervention.

Participants will be summarized according to the study intervention they actually received for all safety analysis variables/endpoints. If a participant received study intervention other than randomized study intervention, actual study intervention received will be determined based on the study intervention received for the majority of the double-blind Study Intervention Period. If there is a tie, the higher dose will be considered the actual study intervention for that participant. The actual study intervention will be listed for the participants in the listing related to study intervention dosing information.

7.0 PARTICIPANT DISPOSITION

The number and percentage of participants in 3 study populations (Randomized, mITT, and Safety) will be summarized overall, by study intervention group, country, and study center; the number of participants screened will be summarized overall, only by country, and study center.

Screen-failure participants (ie, participants who are screened but do not enter into the Preintervention Period), participants ineligible for randomization (ie, participants who enter into the Preintervention Period but are not randomized at Visit 3, also labeled as preintervention failures), and the associated reasons for failure as recorded in the electronic case report forms (eCRF) will be tabulated overall for all screened participants.

The number and percentage of participants who complete the study, complete the double-blind Study Intervention Period, complete the Postintervention Period, prematurely discontinue the study, prematurely discontinue the double-blind Study Intervention Period, and prematurely discontinue the Postintervention Period will be presented for each study intervention group and pooled across study intervention groups for the Randomized Population. The reasons for premature discontinuation from the double-blind Study Intervention Period and the Postintervention Period as recorded in the eCRF will be summarized (number and percentage) by study intervention group for the Randomized Population. All participants who prematurely discontinue during the Study Intervention Period or Postintervention period will be listed by discontinuation reason for the Randomized Population.

Please note that a participant is considered to have completed the study if he/she has completed 12 weeks of double-blind study intervention, End-of-Treatment visit, and the EOS visit. Participants who rollover to the long-term safety study, LIN-MD-66, before the EOS Visit will be considered to have completed the study if he/she has completed 12 weeks of study intervention and the End-of-Treatment Visit.

8.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters (age; age group [6-11 and 12-17 years (inclusive)]; race; ethnicity; sex) and baseline characteristics (weight; height; and body mass index, calculated as weight [kg]/(height [m])^2) will be summarized descriptively by study intervention group for the mITT, and Safety Populations. The above demographics parameters will also be summarized by age group (6-11 and 12-17 years (inclusive)) within the Safety Population.

Other baseline characteristics (including efficacy parameters related to the bowel habits and symptoms as discussed in Section 10.0) will be summarized descriptively by study intervention group for the mITT Population.

Continuous variables will be summarized by number of participants, mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

Abnormalities in participants' medical and surgical histories will be coded using the Medical Dictionary for Regulatory Activities, version 23.0 or newer. The number and percentage of participants with abnormalities in medical and surgical histories in each system organ class and preferred term will be summarized by study intervention group for the Safety Population.

Prior medication is defined as any medication 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 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.

Both prior and concomitant medications will be coded by drug name and therapeutic class. The use of prior and concomitant medications will be summarized by the number and percentage of participants in each study intervention group for the Safety Population. If a participant took a specific medication multiple times or took multiple medications within a specific therapeutic class, that participant would be counted only once for the coded drug name or therapeutic class.

The World Health Organization (WHO) Drug Dictionary, version Global B3 March 2020 or newer, will be used to classify prior and concomitant medications by therapeutic class and drug name.

Unique participants reporting significant protocol deviations will be summarized in total and by study intervention group for the Randomized Population.

9.0 EXTENT OF EXPOSURE AND STUDY INTERVENTION COMPLIANCE

9.1 EXTENT OF EXPOSURE

Exposure to the study intervention for the Safety Population during the double-blind Study Intervention Period will be summarized for study intervention duration, calculated as the number of days from the date of the first dose of study intervention to the date of the last dose of study intervention, inclusive. Descriptive statistics (number of participants, mean, SD, median, minimum, and maximum) will be presented by study intervention group.

Patient-years, defined as exposure to the study intervention in years, will be summarized by study intervention for the Safety Population.

9.2 MEASUREMENT OF STUDY INTERVENTION COMPLIANCE

Dosing compliance for the double-blind Intervention Period is defined as number of capsules actually taken by a participant during that period divided by the number of capsules prescribed for that period multiplied by 100. This information will be obtained from the study intervention record of the participant's eCRF.

The number of capsules expected to be taken for the double-blind Intervention 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 intervention compliance will be presented by study intervention group between 2 consecutive visits, as well as for the whole double-blind Intervention Period for the Safety Population.

9.3 EDIARY COMPLIANCE

Participants will complete the electronic diary (eDiary) twice daily, once in the morning and once in the evening. Participant's eDiary compliance will be assessed based on the number of days with fully completed morning and evening assessments in a specific period. Morning or evening assessments will be considered fully completed if the participant responded to each question in the corresponding morning or evening eDiary. eDiary compliance will be summarized for the Preintervention Period, double-blind Intervention Period, Postintervention Period, and for each week within each period based on the mITT Population.

Compliance for each participant/interval will be calculated using the following formula:

$$\%Compliance = \frac{100 * \#\ of\ days\ with\ fully\ completed\ morning\ AND\ evening\ eDiary\ entries\ within\ the\ interval}{\#\ of\ expected\ days\ within\ the\ interval}$$

On randomization day, the morning diary and/or clinic diary will be included in Preintervention Period and the evening diary will be included in the double-blind Intervention Period. On the day after last dose date, the morning diary will be included in the double-blind Intervention Period and the evening diary will be included in the Postintervention Period.

10.0 EFFICACY ANALYSES

The efficacy analyses will be based on the mITT Population.

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

A SBM is a BM that occurs in the absence of laxative, suppository, or enema use on the calendar day of the BM or the calendar day before the BM. A complete spontaneous bowel movement (CSBM) is an SBM that is associated with a sense of complete evacuation.

The baseline SBM and CSBM weekly rates, stool consistency, straining, and abdominal symptoms (abdominal pain and bloating) will be derived as discussed in Section 16.3 from 14 days prior to randomization and up to randomization (as appropriate). A participant's baseline stool consistency and straining cannot be assessed if the participant does not have at least 1 SBM during the Preintervention Period. For participants who report no SBMs during a study period, the stool consistency and straining assessments will be considered missing for that study period in the analyses. Participants with missing baseline stool consistency and straining will be excluded from the respective stool consistency and straining analyses that involve change from baseline.

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

An observed-cases (OC) approach to missing postbaseline data will be applied. Sensitivity analyses to handle missing data are planned for only primary and secondary efficacy endpoints and details are provided in Sections 10.1.2 and 10.2.2 for primary and secondary endpoints respectively.

All statistical tests will be 2-sided at 5% level of significance. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

Multiplicity adjustment for the overall Type 1 error rate will be based on primary and secondary endpoints. The overall Type 1 family-wise error rate for testing the primary and secondary efficacy endpoints will be controlled at the 5% level of significance (2-sided) using a sequential testing procedure as stated in Table 10-1.

Table 10-1 Sequential Testing Procedure

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

Nominal p-values will be provided for the other efficacy endpoints as discussed in Section 10.3.

Depending on the enrollment status for FC participants in this study, an interim analysis (IA) for futility may be considered (details in Section 13.0). A futility check in this IA (when performed) will be performed based on the pre-selected non-binding futility boundary. Following a conservative approach, the final analysis will be performed at a slightly reduced alpha level of 0.049 (2-sided) in case this futility IA is conducted. The optional futility IA at 50% information is not planned to stop the study for efficacy.

10.1 PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint is the change from baseline in 12-week SBM frequency rate (SBMs/week) during the Study Intervention Period. The SBM frequency rate per week during the Study Intervention Period will be derived based on the total number of SBMs a participant reported during this period in the morning and evening assessments on the eDiary. The details of the derivation of this efficacy endpoint are provided in Section 16.3.4.

10.1.1 Main Analysis Approach

The statistical null hypothesis for the primary endpoint is as follows: linaclotide 72 ug is the same as placebo with respect to the primary efficacy analysis endpoint. This hypothesis will be tested using an analysis of covariance (ANCOVA) model with study intervention, age group (6-11 years of age and 12-17 years of age) as fixed factors and baseline value as a covariate. Least squares means (LSMs) for each study intervention group, difference in LSMs between linaclotide versus placebo, associated 2-sided 95% CI for these difference in LSMs, and the corresponding statistical test p-value will be reported.

Missing BM response and rescue medication response will be imputed as discussed in Section 16.3.2 unless mentioned specifically for sensitivity analyses.

10.1.2 Sensitivity Analysis

Three sensitivity analyses will be performed to assess the robustness of ANCOVA based on an OC approach.

Sensitivity Analysis 1: Under the Assumption of Missing at Random (MAR)

In this sensitivity analysis, participants need to complete all daily questions in both morning and evening diaries to have a complete diary day. If participant had either missing morning and/or evening diary on the same day, the diary day will be considered missing. If participant has less than 4 completed diary days (with both morning and evening diaries) in a postbaseline week during the Study Intervention Period, the corresponding postbaseline week value will be considered missing for that participant.

In this first sensitivity analysis to handle missing data in the nature of MAR, change from baseline in SBM frequency rate/week will be analyzed using a mixed effect model for repeated measures (MMRM) with study intervention, week, age group (6-11 years of age and 12-17 years of age), and study intervention-by-week interaction as fixed effects and baseline value as a covariate. All 12 weeks' data will be included in the MMRM model. The study intervention comparison between linaclotide group and placebo group for change from baseline in 12-week SBM frequency rate (SBM/week) during the Study Intervention Period will be estimated from the MMRM model. An unstructured covariance matrix will be used to model the covariance of within-participant results. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom (Kenward and Roger 1997).

Sensitivity Analysis 2: Under the Assumption of Not Missing at Random (NMAR)

In this sensitivity analysis, postbaseline week value will be left missing as discussed in first sensitivity analysis if participant has less than 4 completed diary days (with both morning and evening diaries) in a postbaseline week during the Study Intervention Period. In this second sensitivity analysis to handle missing data with NMAR, a missing postbaseline week during the Intervention Period will be imputed using the pattern-mixture model with control-based pattern imputation of Ratitch and O'Kelly (2011).

- Intermittent (non-monotone) missing data in both study intervention groups are imputed using the MCMC method under the MAR assumption.

- Remaining monotone missing data are imputed using a pattern-mixture model approach using a sequential regression imputation model estimated based on data from the placebo arm only.

Fifty imputed datasets will be generated. Based on each imputed dataset, change from baseline in SBM frequency rate/week will be analyzed using the MMRM model as discussed in the first sensitivity analysis. Model based estimates within each study intervention group and between study intervention comparison will be obtained for change from baseline in 12-week SBM frequency rate with each imputed dataset. The estimates will be combined using standard multiple imputation analysis techniques (via Proc MIANLYZE in SAS Version 9.4 or newer) to provide a single within group estimate, the single estimate of difference between linaclotide and placebo, associated 95% CI and p-value for linaclotide versus placebo comparison. Each imputed dataset will be provided in the listing.

Sensitivity Analysis 3: Imputing Missing Data With Worst Response

The third sensitivity analysis will be conducted imputing the postbaseline missing daily data during Intervention Period in the specific diary with the worst response for SBM (i.e. assuming '0' frequency for missing BM response and assuming 'Yes' response for missing rescue medication use). Based on this imputed data, the primary efficacy endpoint will be analyzed using the ANCOVA model in a similar way as discussed in the main analysis approach.

10.1.3 Exploratory Analysis

Study intervention-by-age group interaction will be investigated as an exploratory analysis using ANCOVA with study intervention, age group, study intervention-by-age group as fixed factors and baseline value as a covariate to assess whether the effects of study intervention on primary endpoint are consistent across age groups.

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

10.1.4 Estimand Framework

10.1.4.1 Main Analysis Approach

Population

The target population is participants with FC, ages 6-17 years old, satisfying the inclusion and exclusion criteria as specified in Sections 5.1 and 5.2 of the protocol, respectively. The analysis population is mITT as discussed in Section 6.3.

Variable

The variable is the change from baseline in the participant's 12-week SBM frequency rate (SBMs/week) during the Study Intervention Period as derived from the twice daily eDiary (morning and evening).

Accounting for Intercurrent Events

Intercurrent events and their handling rules are as follows:

- The BMs for the participants who took a laxative, enema, or suppository on the calendar day of the BM or the calendar day before the BM will not be considered as SBMs for the analysis.

- Participants who discontinue prematurely during but prior to the completion of the double-blind Study Intervention Period will have their eDiary data included up to the morning diary following the last dose date for primary endpoint. SBM frequency rate based on included eDiary data up to morning diary after last dose date will be considered equivalent to the 12-week SBM frequency rate.

- Participants with any intermediate missing diary data during the 12-week study intervention period will have their data included as observed. The SBM frequency rate (SBMs/week) will be calculated based on the available data (as discussed in Section 16.3.4) and this SBM frequency rate will be considered to be equivalent to the rate over the 12-week study intervention period.

Population-level Summary

The population-level summary for the primary endpoint is the difference in primary variable means between the linaclotide dose arm and placebo based on difference in LSMs from the ANCOVA model in main analysis approach (Section 10.1.1).

10.1.4.2 Sensitivity Analysis 1: Under the Assumption of MAR

Population and variable will be same as discussed for main analysis approach.

Accounting for Intercurrent Events

Intercurrent events and their handling rules are as follows:

- Presence of rescue medication will be handled in the same way as discussed for main analysis approach.

- For any postbaseline analysis week, if participant has less than 4 completed diary days (i.e. a completed diary day means completed both morning and evening diaries in a day) in an analysis week, participant's corresponding week's response will be considered missing.

Population-level Summary

The population-level summary for the primary endpoint is the difference in primary variable means between the linaclotide dose arm and placebo based on estimated difference between intervention groups during the 12-week study intervention period from the MMRM model as discussed in Section 10.1.2 for the first sensitivity analysis.

10.1.4.3 Sensitivity Analysis 2: Under the Assumption of NMAR

Population and variable will be same as discussed for main analysis approach.

Accounting for Intercurrent Events

Intercurrent events and their handling rules are as follows:

- Presence of rescue medication will be handled in the same way as discussed for main analysis approach.
- For any postbaseline analysis week, if participant has less than 4 completed diary days (i.e. completed both morning and evening diaries) in an analysis week, participant's corresponding week's analysis value will be considered missing and the postbaseline missing week during the intervention period will be imputed using the pattern mixture model with control-based pattern imputation.

Population-level Summary

The population-level summary for the primary endpoint is the difference in primary variable means between the linaclotide and placebo based on combined estimate using multiple imputation techniques, where each estimate for the difference between the linaclotide and placebo will be estimated from each imputed data using MMRM model as discussed in Section 10.1.2.

10.1.4.4 Sensitivity Analysis 3: Imputing Missing Data With Worst Response

Population and variable will be same as discussed for main analysis approach.

Accounting for Intercurrent Events

Intercurrent events and their handling rules are as follows:

- Presence of rescue medication will be handled in the same way as discussed for main analysis approach.
- If the response to the question of rescue medication usage is missing during postbaseline, any missing response during Study Intervention Period will be imputed with 'yes' response (i.e. participant took medicine to help poop, other than the study medicine during the specific diary period).
- Data for early discontinued participants will be handled in the same way as discussed for main analysis approach.

Population-level Summary

The population level summary will be handled in the same way using ANCOVA model as discussed for main analysis approach.

10.2 SECONDARY EFFICACY ENDPOINTS

There is only one secondary efficacy endpoint in this study, which is change from baseline in 12-week stool consistency during the Study Intervention Period. The details of the derivation of this efficacy endpoint are provided in Section 16.3.5.

10.2.1 Main Analysis Approach

The statistical null hypothesis for the secondary endpoint is as follows: linaclotide 72 ug is the same as placebo with respect to the secondary efficacy analysis endpoint. This hypothesis will be tested using the same ANCOVA model as for the primary endpoint in main analysis approach. LSMs for each study intervention group, difference in LSMs between linaclotide group versus placebo, associated 2-sided 95% CI for this difference in LSMs, and the corresponding statistical test p-value will be reported.

10.2.2 Sensitivity Analysis

The sensitivity analyses with MMRM (MAR) and worst response imputation with ANCOVA model as discussed for primary efficacy endpoint will also be performed for secondary efficacy endpoint. The worst response imputation of missing postbaseline stool consistency response during Study Intervention Period is discussed in Section 10.2.4 (at accounting for intercurrent events).

10.2.3 Exploratory Analysis

Study intervention-by-age group interaction will be investigated as an exploratory analysis using the ANCOVA with study intervention, age group, study intervention-by-age group as fixed factors and baseline value as a covariate to assess whether the effects of study intervention on secondary endpoint are consistent across age groups.

Cumulative distribution function plots will also be provided for the secondary efficacy endpoint by study intervention group.

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

10.2.4 Estimand Framework

Population

The population is similar to that for the primary endpoint. However, only participants with both baseline and at least one postbaseline stool consistency value from SBM during the Study Intervention Period will be included.

Variable

The variable is the change from baseline in the participant's 12-week stool consistency during the Study Intervention Period as derived from the twice daily eDiary (morning and evening).

Accounting for Intercurrent Events

Handling of intercurrent events will be similar to primary endpoint as discussed for the main analysis approach and first (MAR) sensitivity analysis.

In the second sensitivity analysis of imputing the missing data with worst response, missing postbaseline stool consistency value for SBM during Study Intervention Period will be imputed as Type 1 (looks like small hard lumps or balls, like pebbles).

Population Level Summary

Difference in means for secondary endpoint between linaclotide and placebo will be based on the following:

- Main Analysis Approach: Based on difference in LSMs from ANCOVA model
- Sensitivity Analysis 1 (MAR): Based on estimated difference from MMRM model in sensitivity analysis with MAR
- Sensitivity Analysis 2 (worst response imputation): Based on difference in LSMs from ANCOVA model

10.3 OTHER EFFICACY ENDPOINTS

The other efficacy endpoints are as follows:

- Overall SBM responders during the Study Intervention Period
- Weekly SBM + 2 responder during the Study Intervention Period
- Change from baseline in 12-week CSBM frequency rate (CSBMs/week) during the Study Intervention Period
- Change from baseline in 12-week abdominal pain (daytime, nighttime, and combined daytime and nighttime symptoms) during the Study Intervention Period
- Proportion of days with daytime fecal incontinence during the Study Intervention Period
- Change from baseline in 12-week straining during the Study Intervention Period
- Change from baseline in 12-week abdominal bloating (daytime, nighttime, and combined daytime and nighttime symptoms) during the Study Intervention Period
- Proportion of participants with an SBM within 24 hours after the first dose of study intervention
- Proportion of participants with an SBM within 48 hours after the first dose of study intervention

- Time to the first report of SBM after the first dose of study intervention
- Proportion of participants with an increase in rescue medicine or any other laxative, suppository, or enema use during 12-week Study Intervention Period
- Proportion of participants who report using rescue medicines or any other laxatives, suppositories, or enemas during 12-week Study Intervention Period
- Proportion of participants who no longer fulfill modified Rome III criteria for functional constipation at the end of the study intervention period
- Proportion of participants with each individual item score for the participant-completed global change items (pooping problems and tummy problems) at each week during Study Intervention Period
- Proportion of participants with each individual item score for the participant-completed global severity items (pooping problems and tummy problems) at each week during Study Intervention Period
- Change from baseline in participant-completed global severity items (pooping problems and tummy problems) at each week during Study Intervention Period
- Proportion of participants with each individual item score for the observer completed global change item and global severity item at each week during Study Intervention Period (collected for age group of 6-11 years only)

Overall SBM Responders During the Study Intervention Period

Overall SBM responders are defined as participants who have a change from baseline of ≥ 2 SBMs/week in the 12-week SBM frequency rate over the Intervention Period.

The above response threshold of at least 2-point change from baseline in 12-week SBM frequency rate (SBMs/week) to define the overall SBM responder may be revisited before unblinding based on the findings of blinded psychometric analysis to determine within participant clinically meaningful change. If this is the case, the revised response threshold will be documented in a SAP amendment.

To be qualified for an overall SBM responder, a participant must also meet the following conditions simultaneously:

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

The participant needs to fill out both morning and evening diary on the same day to have a completed diary day.

The proportion of responders in the linaclotide group will be compared with the proportion in the placebo group using a CMH test controlling for age group (6 - 11 years of age versus 12 - 17 years of age). Participants who are not assessable for the responder parameters due to missing information are considered non-responders. The number and percentage of responders for each study intervention group, the difference in responder rates between the linaclotide group and the placebo group, the corresponding 95% confidence interval, Mantel-Haenszel based odds ratio and corresponding 95% confidence interval, and the 2-sided p-value associated with the CMH tests will be presented.

Weekly SBM + 2 Responder During the Study Intervention Period

For any week in the study intervention period, a weekly SBM + 2 responder is a participant who has an SBM increase ≥ 2 in the SBM weekly rate from baseline for that week. For the analysis week, if a participant did not have at least 4 full days (with both completed morning and evening diaries) of diary entries, the participant will not be considered a weekly SBM + 2 responder for that corresponding week.

The threshold of at least 2 to define the weekly SBM responder may be revisited before unblinding based on the findings of blinded psychometric analysis to determine within participant clinical meaningful change. If this is the case, the revised response threshold will be documented in a SAP amendment.

This responder endpoint will be analyzed in a similar way as discussed for the Overall SBM Responders endpoint.

Change From Baseline in Other Efficacy Endpoints Related to Bowel Habits and Abdominal Symptoms

The derivations of 12-week CSBM frequency rate (CSBMs/week), abdominal pain (daytime, nighttime, and combined daytime and nighttime symptoms), straining, and abdominal bloating (daytime, nighttime, and combined daytime and nighttime symptoms) during the Study Intervention Period are discussed in details from Sections 16.3.4 to 16.3.8.

For change from baseline in 12-week CSBM frequency rate (CSBMs/week), 12-week abdominal pain (daytime, nighttime, and combined daytime and nighttime symptoms), 12-week straining, and 12-week abdominal bloating (daytime, nighttime, and combined daytime and nighttime symptoms), the linaclotide group will be compared to the placebo group using the same ANCOVA model as discussed for primary endpoint in main analysis approach (Section 10.1.1).

Cumulative distribution function plots will also be provided for the change from baseline other efficacy endpoints by study intervention group.

By-week summary of the other efficacy endpoints will be provided by study intervention group.

Proportion of Days with Daytime Fecal Incontinence During the Study Intervention Period

Fecal incontinence will be collected daily in the evening eDiary. Participants are asked a question (as discussed in Section 16.3.9) regarding episodes of fecal incontinence in the evening diary. A "yes" response to that question will be counted as presence of daytime fecal incontinence in the corresponding day. The proportion of days with daytime fecal incontinence during the Study Intervention Period will be derived based on number of non-missing reported days with fecal incontinence responses during the Study Intervention Period in the denominator.

Descriptive statistics (mean, median, SD, standard error of mean, minimum, and maximum) by study intervention group will be provided.

Proportion of Participants with an SBM within 24 Hours of First Dose of Study Intervention

A participant is a 24-hour responder if the participant has at least 1 SBM within 24 hours of first dosing of study intervention. Any SBM reported in the evening diary on randomization day and in the morning diary at the day after first dose date (i.e., Day 2) will be considered a SBM within 24 hours. The proportion of responders will be analyzed in a similar way as discussed earlier for SBM responder endpoints.

Proportion of Participants with an SBM within 48 hours of First Dose of Study Intervention

A participant is a 48-hour responder if the participant has at least 1 SBM within 48 hours of first dosing of study intervention. Any SBM reported from the evening diary on randomization day to the morning diary on the second day after first dose date (i.e., Day 3) will be considered a SBM within 48 hours. The proportion of responders will be analyzed in a similar way as discussed earlier for SBM responder endpoints.

Time to First Report of SBM After the First Dose of Study Intervention

Time to first report of SBM after the first dose of study intervention (i.e. time to diary reporting with first SBM) is defined as the number of hours elapsed from the first dose of study intervention taken to the diary reporting time with the first SBM. Reporting may not occur in real time; first eDiary reporting will be approximately within 12 hours after the first dose with all subsequent reports occurring in 12-hour spans twice daily (morning and evening) Participants who do not achieve an SBM during the Intervention Period will be considered censored, with the censoring time defined as number of hours elapsing from the first dose of study intervention taken to 11:59 AM (morning diary end period) on the day after last dose date.

Proportion of Participants With an Increase in Rescue Medicine or Any Other Laxatives, Suppositories, or Enema Use During 12-week Study Intervention Period

The proportion of participants who have an increase from baseline in the percentage of days using rescue medicine or any other laxatives, suppositories, or enemas in the linaclotide dose group during the 12-week Intervention Period will be compared to the proportion in the placebo group using a CMH test controlling for age group. The number and percentage of responders for each study intervention group, the difference in responder rates between the linaclotide group and the placebo group, the corresponding 95% confidence interval, Mantel-Haenszel -based odds ratio and corresponding 95% confidence interval, and the 2-sided p-value associated with the CMH tests will be presented.

Proportion of Participants Who Report Using Rescue Medicines or Any Other Laxative, Suppositories, or Enema During 12-week Study Intervention Period

The proportion of participants who report using rescue medicines or any other laxative, suppositories, or enemas during the Study Intervention Period in the linaclotide group will be compared with the proportion in the placebo group using a CMH test controlling for age group. The similar analyses as discussed for the proportion of participants with an increase in rescue medicine or any other laxatives, suppositories, or enema use will be provided by study intervention group.

Participant-Completed Global Change Items and Global Severity Items at Each Week During Study Intervention Period

The details of participant-completed global change item scores and global severity item scores are discussed in Section 16.3.10. For each of the participant-completed global change items (pooping problems and tummy problems) and global severity items (pooping problems and tummy problems), study intervention comparison (linaclotide versus placebo) will be performed using a CMH test, controlling for age group at each week after randomization during the Study Intervention Period. Counts and percentages for each category within each individual item will be provided by study intervention group.

Change from baseline in the participant-completed global severity items (pooping problems and tummy problems) at each post baseline week during the Study Intervention Period will also be analyzed using the same ANCOVA model as discussed for primary endpoint in main analysis approach (Section 10.1.1).

Observer-Completed Global Change Item and Global Severity Item at Each Week During Study Intervention Period

The observer-completed global change item and global severity item will be assessed on a weekly basis in the eDiary, for the 6 - 11 years of age group only as discussed in Section 16.3.11. Summary statistics of observer-completed global items will be provided by study intervention group in the 6 - 11 years of age group at each week during the Study Intervention Period. Counts and percentages for each category of global change item and global severity item will be provided by study intervention group.

Proportion of Participants Who No Longer Fulfill Modified Rome III Criteria for FC at the End of the Study Intervention Period

The details of the derivation of this endpoint are discussed in Section 16.3.12. The proportion of participants who no longer fulfill modified Rome III criteria for FC at the end of the study intervention period will be presented by study intervention group.

10.4 SUBGROUP ANALYSIS FOR EFFICACY ENDPOINTS

Primary and secondary efficacy endpoints will be analyzed in a similar way as discussed for main analysis approach (except age not included as factor in the model for age subgroup analyses) for the following subgroups (within each subgroup category) based on the mITT Population if sample size allows.

- Age group (6-11 years group, 12-17 years group)
- Region (North American, EU, and Other),
- Race (white, non-white),
- Gender (male, female)

Due to the reduction in the number of participants included in analyses of subgroups, p-values will not be reported in the presentations of results obtained in subgroup analyses. Subgroups will be interpreted with caution due to limited sample size within each subgroup category.

11.0 SAFETY ANALYSES

The safety analysis will be performed using the Safety Population. The safety parameters will include adverse events (AEs) and clinical laboratory parameters, vital sign (including postural), electrocardiographic (ECG) parameters, height, and weight. For each safety parameter of the clinical laboratory, vital signs, height, weight, and ECG parameters, the last non-missing safety assessment before the first dose of study intervention will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by number of participants and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants. The safety summaries will be provided by study intervention group.

11.1 ADVERSE EVENTS

Adverse events will be coded by system organ class and preferred term using the *Medical Dictionary for Regulatory Activities,* version 23.0 or newer.

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; 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 30 days after the last dose of study intervention 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 SAE criterion.

The number and percentage of participants reporting TEAEs in each study intervention group will be tabulated by descending percentage in any group, by system organ class and preferred term, and further categorized by severity and causal relationship to the study intervention. 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 greatest severity and strictest causality for the summarization by severity and causal relationship. The above summaries of TEAEs, further categorized by severity and causal relationship will also be provided within each age group. If there are 5 or less participants with severe or related TEAEs in any study intervention group, the corresponding age group summaries for TEAEs by severity or causal relationship will not be provided.

The incidence of common (≥ 5% of participants in any study intervention group) TEAEs will be summarized by system organ class, preferred term, and study intervention group.

Summary tables will be provided for participants with TESAEs, AEs of special interest, and participants with TEAEs leading to premature discontinuation of study intervention.

For the Safety Population, separate listings will be presented for participants who died, participants with SAEs, participants with AEs leading to premature discontinuation, and participants with AEs of special interest. AEs during the Postintervention Period will also be included in the listings. Listing of all AEs will also be presented.

11.2 CLINICAL LABORATORY PARAMETERS

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 laboratory parameters:

Hematology:	Absolute and differential white blood cell count, erythrocyte count, hemoglobin, hematocrit, platelet count, red blood cell count, and red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration)
Chemistry:	Sodium, potassium, calcium, chloride, bicarbonate, magnesium, phosphate, glucose, blood urea nitrogen, creatinine, total protein, alkaline phosphatase (ALP), albumin, total bilirubin (TBL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol
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 11-1. The number and percentage of participants who have PCS postbaseline clinical laboratory values will be tabulated by study intervention for the double-blind Intervention Period. The percentages will be calculated relative to the number of participants with available non-PCS baseline values and at least 1 postbaseline assessment for the double-blind Intervention Period. The numerator will be the total number of participants with available non-PCS baseline values and at least 1 PCS postbaseline value for the double-blind Intervention Period. A supportive tabular display of participants with PCS postbaseline values will be provided, including the PID number, baseline and all postbaseline (including non-PCS) values. In this listing, any participant with PCS value (if any) during the Post-intervention period will also be included.

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 double-blind 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.

Table 11-1 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- 17 (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
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
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.

11.3 VITAL SIGNS

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

Vital sign values will be considered PCS if they meet both the observed-value criteria and the change-from-baseline criteria listed in Table 11-2. The number and percentage of participants with PCS postbaseline values will be tabulated by study intervention group for the double-blind Intervention Period and Postintervention Period separately. The percentages will be calculated relative to the number of participants with available non-PCS baseline values and at least 1 postbaseline assessment in the specific period. The numerator will be the total number of

participants with available non-PCS baseline values and at least 1 PCS postbaseline value during the specific period. A supportive tabular display of participants with PCS postbaseline values will be provided, including the PID number, baseline and all postbaseline (including non-PCS) values.

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

Table 11-2 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 systolic blood pressure from supine to standing at observed time point is at least 10 mmHg greater than the decrease in systolic blood pressure 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 diastolic blood pressure from supine to standing at observed time point is at least 10 mmHg greater than the decrease in diastolic blood pressure 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]
Systolic Blood Pressure, mm Hg (Supine)	High	Age 6-11 (inclusive): ≥ 140 Age 12-17 (inclusive): ≥ 155	Increase of ≥ 20
	Low	Age 6-11 (inclusive): ≤ 80 Age 12-17 (inclusive): ≤ 90	Decrease of ≥ 20
Diastolic Blood Pressure, mm Hg (Supine)	High	Age 6-11 (inclusive): ≥ 95 Age 12-17(inclusive): ≥ 105	Increase of ≥ 15
	Low	Age 6-11 (inclusive): ≤40 Age 12-17 (inclusive): ≤ 45	Decrease of ≥ 15
Pulse Rate, bpm (Supine)	High	Age 6-11 (inclusive): ≥ 140 Age 12-17 (inclusive): ≥ 120	Increase of ≥ 15
	Low	Age 6-11 (inclusive): ≤ 50 Age 12-17 (inclusive): ≤ 40	Decrease of ≥ 15
Weight, kg	High	—	Increase of ≥ 5%
	Low	—	Decrease of ≥ 5%

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

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

* Change from supine value = standing value – supine value

11.4 ELECTROCARDIOGRAM

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

Electrocardiographic parameter values are considered PCS if they meet or exceed the higher-limit PCS criteria listed in Table 11-3. The number and percentage of participants with PCS postbaseline ECG values will be tabulated by study intervention group for the double-blind invention period. The percentages will be calculated relative to the number of participants with available non-PCS baseline values and at least 1 postbaseline assessment for the double-blind Intervention Period. The numerator is the total number of participants with available non-PCS baseline values and at least 1 PCS postbaseline value for the double-blind Intervention Period. A supportive tabular display of participants with PCS postbaseline values will be provided, including the PID number, baseline, all postbaseline (including non-PCS) values, and change from baseline. In this listing, any participant with PCS value (if any) during Postintervention Period will also be included.

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 double-blind 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.

Table 11-3 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 (16-17 (inclusive) years)
PR interval	msec	PR > 225 msec (6-7 (inclusive) years) PR > 250 msec (8-17 (inclusive) years)
QTc(F)	msec	>480

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

11.5 OTHER SAFETY PARAMETERS

11.5.1 Potential Hy's Law

Potential Hy's Law criteria within a 24-hour window is defined by a post baseline elevation of ALT or AST ≥ 3x ULN, along with TBL ≥ 2x ULN and a non-elevated ALP < 2x 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 drug to within 30 days after the last dose of study intervention will be summarized. Supportive tabular displays will also be provided.

12.0 HEALTH OUTCOMES ANALYSES

Not applicable.

13.0 INTERIM ANALYSIS

An IA to assess futility of linaclotide using the primary endpoint at 50% information may be considered based on the enrollment of FC participants in this study (ie, if the rate of enrollment is below expectations). The IA for FC participants will provide unblinded analysis of the primary efficacy endpoint for FC to assess futility of linaclotide for FC with approximately 50% of FC participants who completed the 12-week double-blind intervention period or have discontinued prematurely from the 12-week double-blind intervention period (Table 13-1). In the event this interim futility analysis occurs, the Data Safety Monitoring Board (DSMB) (responsible for safety monitoring) will review the unblinded IA results and make recommendations regarding the continuation of the study. To maintain the scientific reliability of the final results and prevent potential bias into the conduct of the study and analysis, individuals involved in the IA will not be involved in any operational aspects of the study. The unblinded IA using the primary endpoint to assess futility will be performed by an independent statistician (not involved with study team). Since there will be no plan to stop the trial for efficacy in this futility IA with nonbinding futility boundary, no alpha will be spent for the interim look. However, following a conservative approach, the final analysis for FC will still be conducted at an alpha level of 0.049 (2-sided) in case this futility IA is conducted.

Table 13-1 Summary of Interim Analysis Strategy for FC Participants

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

Note: Assumed standard deviation and treatment difference as in Table 14-1.

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

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

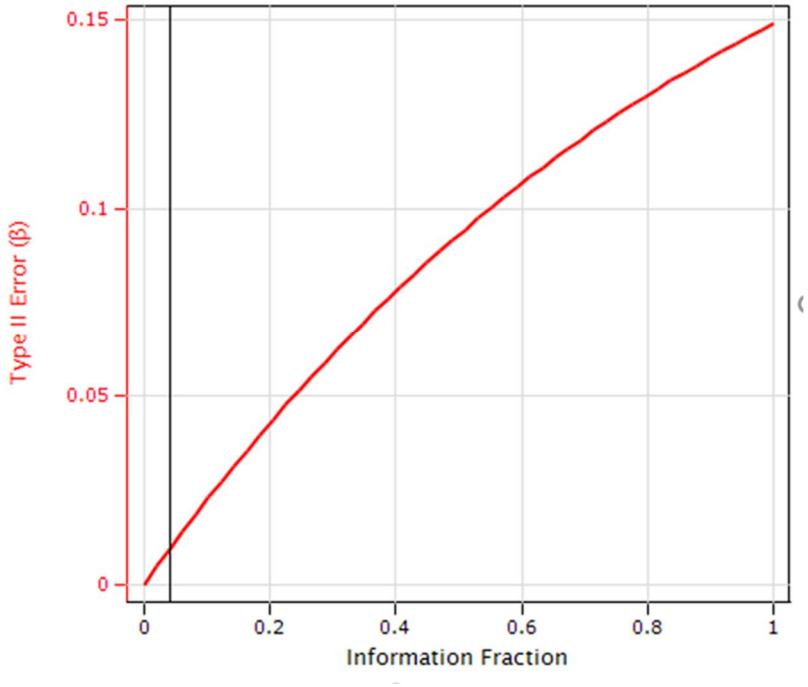
Conditional power will be calculated based on the formula of Chen et al (Chen 2004) which is given by:

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

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

Figure 13-1 plots the cumulative amounts of Type II error spent for different proportions of planned sample size.

Figure 13-1 Plot of Type II Error Spending Function[a]



[a] Plot was generated using East Version 6.4.

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

Scenarios of the IA at different information fractions with the corresponding conditional powers at current trend, treatment differences, amount of β spent, and the overall powers of the final analysis (if the study continues after IA) at total planned sample size of 378 are provided in Table 13-2 below.

Table 13-2 Different Interim Analysis Scenarios

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

Note: Assumed standard deviation and treatment difference as in Table 14-1.

East Version 6.4 was used.

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

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

14.0 DETERMINATION OF SAMPLE SIZE

The sample size of this study was determined based on the primary efficacy endpoint. A total of 326 participants are targeted to be randomized to this study in a 1:1 allocation ratio to receive either linaclotide 72 µg (163 participants) or placebo (163 participants) for 12-weeks of double-blind Study Intervention Period. The assumptions and power estimate for this planned sample size are summarized in Table 14-1.

Table 14-1 Sample Size Assumptions for the Primary Efficacy Endpoint

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

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

Depending on the enrollment status (i.e if enrollment is very slow) for FC participants in this study, an IA for futility may be considered. Assuming that this optional futility IA is performed at 50% of information based on using the primary efficacy endpoint for FC participants, a total sample size of 378 FC participants (189 participants in each study intervention group) will need to be randomized to ensure 85% power for the final analysis at a slightly reduced significance level of 4.9% (following a conservative approach, Section 10.0) to demonstrate that linaclotide is superior to placebo (based on the same assumptions as presented in Table 14-1). The optional IA for futility in FC participants is discussed in Section 13.0.

15.0 STATISTICAL SOFTWARE

Statistical analyses will be performed using version 9.4 (or newer) of SAS on a Linux operating system.

16.0 DATA HANDLING CONVENTIONS

16.1 VISIT TIME WINDOWS FOR SAFETY ANALYSES

Table 16-1 presents the visits assigned for safety analyses and the corresponding range of study intervention days (window) during which an actual visit may occur.

Table 16-1 Visit Time Windows

Derived Visit	*Scheduled Visit Day*[a]	*Window*
Baseline	Day 1	Days ≤ 1
Week 2 Visit	Day 15	Days [2, 21]
Week 4 Visit	Day 29	Days [22, 42]
Week 8 Visit	Day 57	Days [43, 70]
Week 12 Visit	Day 85	Days [Day 71, max (last dose day+1, Visit 7 date)]
Post-intervention Visit	Day 92	Days >= max (last dose day+1, Visit 7 date)+1
End of Double-Blind Intervention Period[b]	Final or Termination Visit during the double-blind Intervention Period	

a Relative to the date of the first dose of double-blind study intervention. Day 1 = the date of the first dose of double-blind study intervention. There is no Day 0 or Week 0.

b Presented in analysis tables for safety parameters, including but not limited to electrocardiograms, clinical laboratory values, and vital signs.

Participants who rollover to the long-term safety study, LIN-MD-66, before the EOS visit (i.e. Visit 8, post-intervention visit) are not required to have this EOS visit or post-intervention visit.

If the assessment date (if the assessment date is unavailable, use visit date instead) is on or after the date of the first dose of study intervention, the study day is calculated by assessment date – date of the first dose of study intervention + 1. If the assessment date is before the date of the first dose of study intervention, the study day is calculated by assessment date – date of the first dose of study intervention. Therefore, a negative day indicates a day before the start of the study intervention.

If a participant has 2 or more visits within the same window, the last visit with a non-missing value will be used for analysis.

16.2 VISIT TIME WINDOWS FOR EFFICACY ANALYSES

Table 16-2 below presents the analysis weeks assigned for the efficacy analysis of the participant daily diary data related to BM and/or abdominal symptom characteristics. These analysis weeks will be used in the calculations for all week-based endpoints (eg, SBM weekly frequency rate, stool consistency weekly scores, etc.).

Table 16-2 Analysis Time Windows for Efficacy Analysis - Daily Questions

Period	Analysis Week	Begins[a]	Ends[a]
Preintervention (Baseline[b])	Week -2	Day -14	Day -8
	Week -1	Day -7	Day 1, time of randomization
Intervention	Week 1	Day 1, time after randomization	Day 7
	Week 2	Day 8	Day 14
	Week 3	Day 15	Day 21
	Week 4	Day 22	Day 28
	Week 5	Day 29	Day 35
	Week 6	Day 36	Day 42
	Week 7	Day 43	Day 49
	Week 8	Day 50	Day 56
	Week 9	Day 57	Day 63
	Week 10	Day 64	Day 70
	Week 11	Day 71	Day 77
	Week 12	Day 78	Day of last dose +1
Post-intervention	Post-intervention	Day of last dose + 1	Day of end of study visit

Note: On randomization day, if participant already completed morning diary, at the clinic visit, participants fill out a clinic diary and the assessments in the clinic diary will be part of the Preintervention Period. Morning diary assessments on randomization day will also be part of Preintervention Period. eDiary assessments in evening diary on the day of randomization will be part of the Intervention Period. eDiary assessments in morning diary at the day after the last dose day will be considered as assessments in the Intervention Period.

a Relative to the date of randomization; Day 1 = the day of randomization.

b Baseline values for efficacy parameters will be derived from the daily morning and evening eDiaries and eCRF data collected in the Preintervention Period, specifically the period of time from 14 days before randomization up to the time of randomization.

For the Intervention Period, daily diary day is calculated as (diary date - date of randomization + 1). For the Preintervention Period, daily diary day is calculated as (diary date - date of randomization). However, the day of randomization is study Day 1 regardless. Participants will complete their diary entries twice per day for daily diary.

If a participant withdraws during the Intervention Period, the participant's morning diary assessments of daily eDiary on the day after last dose day will be captured as assessments in the Intervention Period. The impacted Intervention Period week shall be shortened to the end of the withdrawn participant's Intervention Period and all subsequent Intervention Period weeks will be missing for that participant.

Table 16-3 below presents the weekly periods assigned for the efficacy analysis of the participant weekly diary data related to global severity items and global change items.

Table 16-3 Analysis Time Windows for Efficacy Analysis - Weekly Questions

Analysis Week	Begins[a]	Ends[a]
Week -2	Visit 2 day	Visit 2 day + 7
Week -1 (Baseline)	Visit 2 day + 8	Day 1
Week 1	Day 2	Day 8
Week 2	Day 9	Day 15
Week 3	Day 16	Day 22
Week 4	Day 23	Day 29
Week 5	Day 30	Day 36
Week 6	Day 37	Day 43
Week 7	Day 44	Day 50
Week 8	Day 51	Day 57
Week 9	Day 58	Day 64
Week 10	Day 65	Day 71
Week 11	Day 72	Day 78
Week 12	Day 79	last dose date +1
Post-intervention	Day of last dose date + 8	Day of end of study visit

a Begin and end of each week from Week 1 onwards are relative to the date of the first dose of double-blind study intervention. Day 1 = the date of the first dose of double-blind study intervention. There is no Day 0 or Week 0. End of Week 1 to Week 12 will be day of last dose + 1 or corresponding end day in table whichever comes earlier.

Participants who rollover to the long-term safety study, LIN-MD-66, before the EOS visit (i.e. Visit 8, post-intervention visit) are not required to have the EOS visit or post-intervention visit.

16.3 DERIVED VARIABLES

16.3.1 Missed Morning/Evening eDiary Assessments

No imputation or derivation will be performed for missed morning/evening assessments unless otherwise specified.

16.3.2 Incomplete Morning/Evening eDiary Assessments

Missing responses in incomplete morning and/or evening assessments will not be imputed for most of the parameters, with the exception of rescue medication (RM) use and BM frequency.

If the answer to the RM use question is missing for any assessment (morning or evening), no RM usage will be considered during that diary period (morning or evening diary) in eDiary, with the exception that the missing RM will be considered "used" if the other available assessment during that diary period is "yes".

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

16.3.3 Incomplete Clinic Diary on Randomization Visit (If Present)

Missing responses in an incomplete clinic diary on randomization day will be handled in a similar way as mentioned for incomplete daily morning/evening assessments. Clinic diary on randomization day will be considered as part of morning diary on randomization day.

16.3.4 Stool frequency

Spontaneous Bowel Movement (SBM)

A SBM is a BM that occurs in the absence of laxative, suppository, or enema use on the calendar day of the BM or the calendar day before the BM.

Complete Spontaneous Bowel Movement (CSBM)/Incomplete Evacuation

A CSBM is an SBM that is associated with a sense of complete evacuation.

Stool Frequency Rates

The components for calculating a participant's stool frequency rates (SBM/CSBM weekly rates) for a given period are as follows:

- The number of BMs that occurred during that specific period
- The number of those BMs that were SBMs
- The number of those SBMs that were CSBMs
- The number of days during that specific period:
    - Randomization day with evening diary will be considered a half day for the double-blind Intervention Period.
    - Randomization day with morning and/or clinic diary will be considered -a half day for the Preintervention Period.
    - The day after last dose will be considered a half day for the double-blind Intervention Period with morning diary and for the Postintervention Period with evening diary.

Duration of an Analysis Week

With respect to a participant's scheduled analysis weeks, the term duration is used. In regard to the duration of a week, it is expected that 1 or more of a participant's "weeks" may not be exactly 7 days in duration (eg, a participant may withdraw or discontinue early from the trial, may have half day data with diary entries, or may have missing diary day). Deviations from the 7 days norm are structural in nature; and, as such, the calculations of the weekly rates of SBMs or CSBMs will incorporate the actual days contributed within the time period (week or specific phase).

Weekly Stool Frequency Rate Calculations

The weekly frequency rate for SBMs (CSBMs) will be based on the total number of SBMs (CSBMs) occurring based on the diary entries during that time period, adjusting for differences in the length of the time period. Weekly stool frequency rates for each specific period will be calculated as follows:

- Weekly Frequency Rate (Specific Period) =

$$\frac{\text{Total number of events (SBMs or CSBMs) during the specific period}}{\text{Number of days during the specific analysis period}} \text{ X } 7$$

16.3.5 Stool Consistency

Participants will use the pediatric Bristol Stool Form Scale (p-BSFS), to rate their stool consistency for each BM:

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

Type 1 = looks like small hard lumps or balls, like pebbles
Type 2 = looks like fat sausage shape but lumpy and hard
Type 3 = looks like a sausage but with cracks on it
Type 4 = looks like a sausage or snake, smooth and soft
Type 5 = looks like chicken nuggets, soft smooth blobs
Type 6 = looks like oatmeal, fluffy mushy pieces
Type 7 = looks like a milkshake, watery
99 - I don't know

Stool consistency will be collected twice daily (morning and evening) in the eDiary and measured using the 7-point p-BSFS. Stool consistency (p-BSFS) score during a specific analysis period will be derived as mean of participant's non-missing, SBM-associated p-BSFS scores during that specific period.

16.3.6 Straining

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

- When you pooped, how hard did you push?

  0 = not hard at all
  1 = I pushed a tiny bit hard
  2 = I pushed a little hard
  3 = I pushed hard
  4 = I pushed very hard

Straining will be collected twice daily (morning and evening) in the eDiary and measured using a 5-point scale. The participant's straining score in a specific analysis period will be the mean of participant's non-missing, SBM-associated straining scores during that specific period.

16.3.7 Abdominal Bloating

Abdominal bloating scores will be collected twice daily in the eDiary (morning and evening).

Abdominal Bloating - Daytime

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

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

If "yes" then participant answers the following question:

- How big and full did your tummy FEEL?

    1 = a tiny bit
    2 = a little
    3 = medium
    4 = very

Abdominal Bloating - Nighttime

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

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

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

- How big and full did your tummy FEEL?

    1 = a tiny bit
    2 = a little
    3 = medium
    4 = very

Abdominal Bloating - Combination (Total 24-hour Period)

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

The participant's abdominal bloating score for a specific period based on evening assessments (daytime symptoms), morning assessments (nighttime symptoms), and combined morning and evening assessments will be derived as the mean of the non-missing abdominal bloating scores within the corresponding diaries during the specific period. The abdominal bloating scores of 0, 1, 2, 3, and 4 will be used to calculate the average, where '0' indicates no bloating.

16.3.8 Abdominal Pain

Abdominal pain scores will be collected twice daily in the eDiary (morning and evening).

Abdominal Pain - Daytime

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

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

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

- How much did your tummy hurt?

  1 = a tiny bit
  2 = a little
  3 = some
  4 = a lot

Abdominal Pain - Nighttime

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

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

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

- How much did your tummy hurt?

  1 = a tiny bit
  2 = a little
  3 = some
  4 = a lot

Abdominal Pain - Combination (Total 24-hour Period)

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

The participant's abdominal pain score for a specific period based on evening assessments (daytime symptoms), morning assessments (nighttime symptoms), and combined morning and evening assessments will be derived as the mean of the non-missing abdominal pain scores within the corresponding diaries during the specific period. The abdominal pain scores of 0, 1, 2, 3, and 4 will be used to calculate the average, where '0' indicates no abdominal pain.

16.3.9 Fecal Incontinence - Daytime

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

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

16.3.10 Participant-completed Global Items

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

Participant-completed Global Change Items

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

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

    0 = a lot better
    1 = a little better
    2 = the same
    3 = a little worse
    4 = a lot worse

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

    0 = a lot better
    1 = a little better
    2 = the same
    3 = a little worse
    4 = a lot worse

Global Severity Items

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

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

  0 = I have not had pooping problems
  1 = a little bad
  2 = bad
  3 = very bad

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

  0 = I have not had tummy problems
  1 = a little bad
  2 = bad
  3 = very bad

16.3.11 Observer-completed Global Items

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

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

Observer-completed Global Change Item

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

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

Observer-completed Global Severity Item

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

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

16.3.12 Modified Rome III Criteria

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

16.4 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If a participant has repeated assessments before the start of the first study intervention, the results from the final non-missing assessment made prior to the start of the study intervention will be used as baseline. If end-of-study assessments are repeated or if unscheduled visits occur, the last non-missing postbaseline assessment will be used as the end-of-study assessment for generating summary statistics. However, all postbaseline assessments will be used for PCS value determinations, and all assessments will be presented in the data listings.

16.5 MISSING DATE OF THE LAST DOSE OF STUDY INTERVENTION

When the date of the last dose of study intervention is missing for a participant in the Safety Population, all efforts should be made to obtain the date from the Investigator. If after all efforts are made it is still missing, the Visit 7 date (if available) -1 will be set as last dose date. In absence of the Visit 7 date, the double-blind disposition status date -1 will be set as last dose date.

16.6 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE that started before the date of the first dose of study intervention, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of study intervention, an intensity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

16.7 MISSING CAUSAL RELATIONSHIP TO STUDY DRUG FOR ADVERSE EVENTS

If the causal relationship to the study intervention is missing for an AE that started on or after the date of the first dose of study intervention, a causality of yes will be assigned. The imputed values for causal relationship to study intervention will be used for the incidence summary; the values will be shown as missing in the data listings.

16.8 MISSING DATE INFORMATION FOR ADVERSE EVENTS

The following imputation rules only apply to cases in which the start date for AEs is incomplete (ie, partly missing).

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of study intervention, the month and day of the first dose of study intervention will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the first dose of study intervention, *December 31* will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the first dose of study intervention, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of study intervention, the day of the first dose of study intervention will be assigned to the missing day
- If either the year of the incomplete start date is before the year of the date of the first dose of study intervention or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of study intervention, the last day of the month will be assigned to the missing day

- If either the year of the incomplete start date is after the year of the date of the first dose of study intervention or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of study intervention, the first day of the month will be assigned to the missing day

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of study intervention, the date of the first dose of study intervention will be assigned to the missing start date

- If the stop date is before the date of the first dose of study intervention, the stop date will be assigned to the missing start date

16.9 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

For prior or concomitant medications, including rescue medications, incomplete (ie, partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a participant, the start date will be imputed first.

16.9.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of study intervention, the month and day of the first dose of study intervention will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of study intervention, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of study intervention, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of study intervention, the day of the first dose of study intervention will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the first dose of study intervention or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of study intervention, the last day of the month will be assigned to the missing day.

- If either the year of the incomplete start date is after the year of the date of the first dose of study intervention or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of study intervention, the first day of the month will be assigned to the missing day

16.9.2 Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the date of the last dose of study intervention is missing, impute it as descripted in Section 16.5. If the imputed stop date is before the start date (imputed or nonimputed start date), the imputed stop date will be equal to the start date.

Missing month and day

- If the year of the incomplete stop date is the same as the year of the last dose of study intervention, the month and day of the last dose of study intervention will be assigned to the missing fields

- If the year of the incomplete stop date is before the year of the last dose of study intervention, *December 31* will be assigned to the missing fields

- If the year of the incomplete stop date is after the year of the last dose of study intervention, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dose of study intervention, the day of the last dose of study intervention will be assigned to the missing day

- If either the year of the incomplete stop date is before the year of the date of the last dose of study intervention or if both years are the same but the month of the incomplete stop date is before the month of the date of the last dose of study intervention, the last day of the month will be assigned to the missing day

- If either the year of the incomplete stop date is after the year of the date of the last dose of study intervention or if both years are the same but the month of the incomplete stop date is after the month of the date of the last dose of study intervention, the first day of the month will be assigned to the missing day

16.10 CHARACTER VALUES OF CLINICAL LABORATORY PARAMETERS

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table because, for example, a character string is reported for a parameter of the numeric type, a coded value must be appropriately determined for use in the statistical analyses. The actual values, however, as reported in the database will be presented in the data listings.

Table 16-4 shows examples of how some possible laboratory results should be coded for the analysis.

Table 16-4 Examples of Coding Special Character Values for Clinical Laboratory Parameters

Laboratory Test, SI Unit	Possible Laboratory Results	Coded Value for Analysis
CHEMISTRY		
ALT, U/L	< 5	5
AST, U/L	< 5	5
Bilirubin, total, µmol/L	< 2	2
URINALYSIS		
Glucose, mmol/L	= OR > 55, ≥ 55, > 0	Positive
	≤ 0, negative	Negative
pH	> 8.0, ≥ 8.0	8.0
	≥ 8.5	8.5
Protein	= OR > 3.0, ≥ 3.0, > 0	Positive
	≤ 0	Negative

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SI = Le Système International d'Unités (International System of Units).

17.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

There are no major changes to analyses specified in the amended protocol #1 (version dated June-2020).

The following other efficacy endpoint is added in Section 10.3 of the SAP.

- Change from baseline in participant-completed global severity items (pooping problems and tummy problems) at each week during Study Intervention Period

18.0 HISTORY OF CHANGES

Following changes have been made in this SAP Amendment:

- Section 6.3: Updated mITT population to include all participants in the Randomized Population who receive at least 1 dose of double-blind study intervention.
- Section 7.0: Removed the reasons for premature discontinuation from the study in participant disposition as there is no corresponding eCRF.
- Section 11.1: Modified TEAE definition to include any AE that occurs within 30 days (instead of 1 day) after the last dose of study intervention.
- Section 16.3.2: Modified the imputation rule for missing rescue medication (RM) use question. Missing RM usage will be considered as "used" for morning or evening diary if the other available assessment during that period indicated RM was taken.

19.0 REFERENCES

Chen YH, DeMets DL, and Lan KK. Increasing the sample size when the unblinded interim result is promising. Stat Med. 2004;23(7):1023-1038.

Hwang IK, Shih WJ, and De Cani JS. Group sequential designs using a family of type 1 error probability spending functions. Stat Med. 1990;9(12):1439-1445.

Kenward, M.G., Roger, J.H. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 1997; 53:983-97.

Ratitch B, and O'Kelly M. Implementation of Pattern-Mixture Models Using Standard

SAS/STAT Procedures. *In Proceedings of PharmaSUG 2011 (Pharmaceutical Industry SAS Users Group)*. Paper SP04. Nashville.