1.0 TITLE PAGE

LIN-MD-67

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

STATISTICAL ANALYSIS PLAN - Clinical Study Report

Final: 11 May 2020

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3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BM	bowel movement
BSFS	Bristol Stool Form Scale
DSMB	Data Safety and Monitoring Board
eCRF	electronic case report form
eDiary	electronic diary
ECG	electrocardiogram, electrocardiographic
EOS	End-of-Study
EOT	End of treatment
FC	functional constipation
mITT	modified intent-to-treat
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 ($QTcF = QT/(RR)^{1/3}$)
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
WHO	World Health Organization

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 amended version of the protocol of Study LIN-MD-67 (version 1.0, May 2020). Specifications of tables, figures, and data listings are contained in a separate document.

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

Up to 30 participants, 2 to 5 years of age, will be sequentially enrolled in up to four cohorts in LIN-MD-67 study; eight participants per cohort for Cohorts 1 to 3 and six participants in the final cohort. For each cohort, participants will be randomly assigned to receive linaclotide or matching placebo as described below. Up to 40 sites from the United States and Canada are expected to participate in the study.

The study will consist of up to 4 cohorts, each of which will be 9 to 12 weeks in duration: 2 to 4-week Screening Period, a 2 to 3-week Preintervention Period, followed by a 4-week double-blind Study Intervention Period, and a 1-week Postintervention Period. The raw datasets of study LIN-MD-67 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.

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

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

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

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

Figure 4-1 Assignment of Participants to Dose Cohorts

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

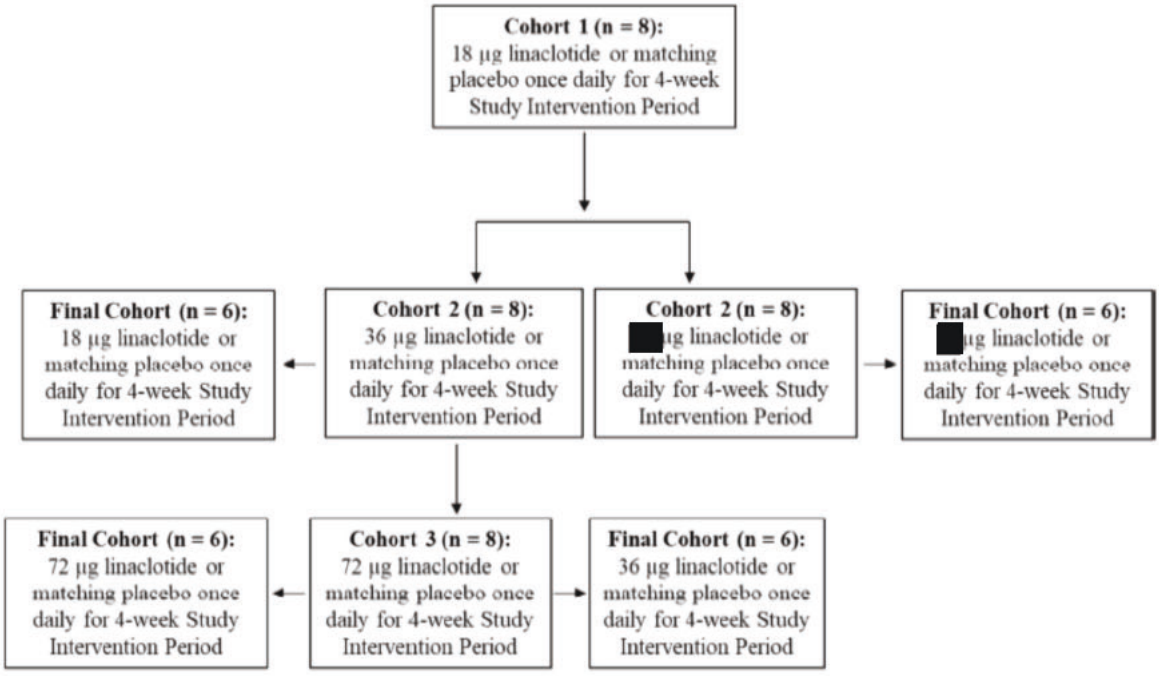
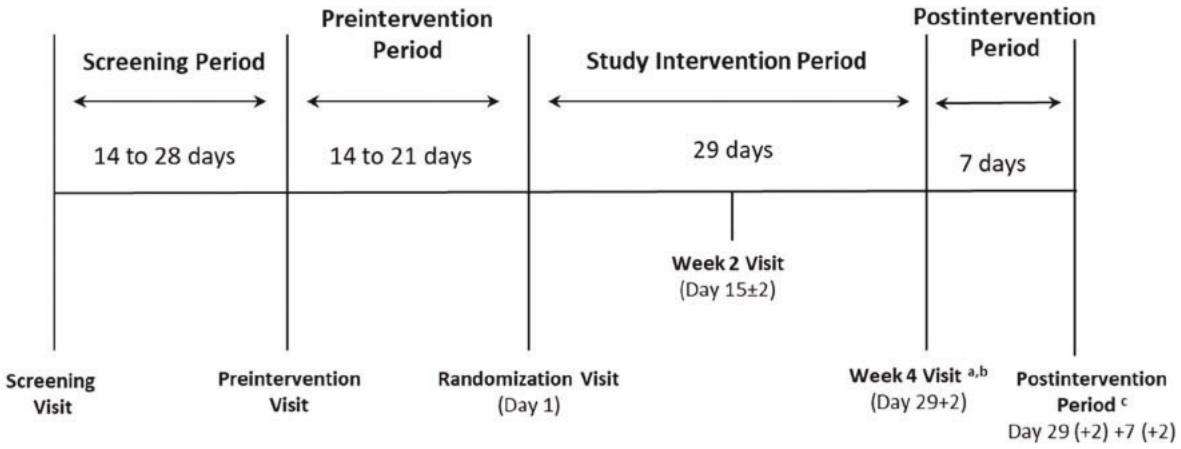


Figure 4-2 is the study schema for each cohort.

Figure 4-2 LIN-MD-67 Study Schema



Note: There is no Day 0.

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

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

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

The schedule of evaluations for Study LIN-MD-67 is presented in Table 4–1

Table 4–1 Schedule of Evaluations: Study LIN-MD-67

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

Schedule of Evaluations LIN-MD-67						
Study Periods (Duration)	**Screening (14-28 Days)**	**Preintervention (14-21 Days)**	**Study Intervention (29 Days)**			**Postintervention (7 Days)**
	Screening[a]	**Preintervention**	**Randomization[b]**	**Week 2**	**Week 4/EOT[c,d]**	**1 Week Postintervention Visit End of Study**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**
Study Day			**1**	**15 (± 2)**	**29 (+ 2)**	**Week 4/EOT + 7 (+2)**
IP and Rescue Medication Compliance and Accountability			X	X	X	X[q]

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

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

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

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

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

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

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

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

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

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

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

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

[m] Participants will arrive in a fasted state for this visit to receive their last dose of study intervention before or after assigned

PK sample is collected. PK samples should be collected at the same time as clinical labs. This visit should be scheduled at approximately same time as when participants take their daily dose.

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

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

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

[q] Protocol-permitted rescue medications only.

5.0 OBJECTIVES

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

6.0 PARTICIPANT POPULATIONS

6.1 SCREENED POPULATION

Screened population will consist of all participants who undergo 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 Randomized Population who receive at least 1 dose of double-blind study intervention and who had at least 1 postbaseline entry on bowel movement (BM) characteristic assessments that determine occurrences of spontaneous bowel movements (SBMs) (ie, BM frequency and rescue medication use). Participants will be summarized according to the randomized study intervention for all efficacy 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 receive for all safety analyses. If a participant received study intervention different from the randomized study intervention, actual study intervention received will be determined based on the study intervention received for majority of the double-blind Study Intervention Period. If there is a tie, higher dose will be considered for actual study intervention for that participant. Actual study intervention will be listed for the participants in the listing related to study intervention dosing information.

7.0 PARTICIPANT DISPOSITION

The disposition summaries will be provided by study intervention group for each cohort separately (as appropriate for double-blind Study Intervention Period and Postintervention Period). If any cohort has linaclotide dose similar to the other cohort, summary statistics will also be provided by combining the participants from similar dose cohorts. Summaries will also be provided for participants from all cohorts in the placebo group.

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 within the corresponding cohort; 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 the 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 within the corresponding cohort. The reasons for premature discontinuation from the study and from the corresponding period as recorded in the eCRF will be summarized (number and percentage) by study intervention group for the Randomized Population within each cohort. All participants who prematurely discontinue during the Study Intervention Period or Postintervention period will be listed by discontinuation reason for the Randomized Population for all the cohorts.

8.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

The demographic, baseline characteristics, medical and surgical histories, prior and concomitant medications, and significant protocol deviations will be summarized by study intervention group for each cohort separately. If any cohort has linaclotide dose similar to the other cohort, summary statistics will also be provided by combining the participants from similar dose cohorts. Summaries will also be provided for participants from all cohorts in the placebo group.

Demographic parameters (age; 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.

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 B2 Enhanced 201703 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 by study intervention group for the Randomized Population.

9.0 EXTENT OF EXPOSURE AND STUDY INTERVENTION COMPLIANCE

The summary statistics will be provided by study intervention group for each cohort separately. If any cohort has linaclotide dose similar to the other cohort, summary statistics will also be provided by combining the participants from similar dose cohorts. Summaries will also be provided for participants from all cohorts in the placebo group.

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.

Participant-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 capsule contents are to be sprinkled into 20 mL of bottled water, and 5 mL of this solution is dosed to the participant using as oral syringe as instructed in protocol Appendix 7 (Section 10.7 in protocol).

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

An observer-reported outcome (ObsRO) instrument assessing key signs and symptoms of FC for use in children (2 to 5 years of age) with FC was developed for completion by caregivers on the electronic diary (eDiary) daily. eDiary compliance will be assessed based on the number of days with fully completed daily eDiary assessments by the caregiver in a specific period. eDiary will be considered fully completed if the caregiver responded to each question in the daily 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:

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

On randomization day, the diary administered before the randomization time will be included in Preintervention 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. Caregiver-observed SBMs are defined as SBMs reported in the eDiary for which the caregiver identified being with the child for.

Baseline SBM weekly rates, stool consistency for caregiver-observed SBMs, and straining for caregiver-observed SBMs will be derived as discussed in Section 16.3 from 14 days prior to randomization and up to the time of randomization. A participant's baseline stool consistency and straining reported for caregiver-observed SBMs cannot be assessed if the participant does not have at least 1 caregiver-observed SBM during the Preintervention Period. For participants with no caregiver-observed SBMs reported in the eDiary during a study period, the consistency and straining assessments reported by caregiver will be considered missing for that study period in the analyses. Participants with missing baseline consistency and straining reported by the caregiver will be excluded from the respective consistency and straining change from baseline analyses.

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

An observed-cases approach to missing postbaseline data will be applied. Efficacy analyses will be performed via descriptive summary statistics in terms of mean, median, SD, standard error of mean, minimum, and maximum. No statistical testing will be performed to compare linaclotide dose with placebo. No multiplicity adjustment will be applied in this dose-ranging study.

10.1 KEY EFFICACY ENDPOINTS

There are 4 key efficacy endpoints in this study.

- **Change from Baseline in 4-Week Overall SBM Frequency Rate (SBMs/week) During the Study Intervention Period of Each Cohort**

The SBM rate per week during the Study Intervention Period will be derived based on the total number of SBMs reported by a caregiver as being directly observed by the caregiver during this period in the eDiary, as discussed in Section 16.3.4.

Descriptive statistics (mean, median, SD, standard error of mean, minimum, and maximum) will be provided by study intervention group for each cohort as main analysis approach. The sensitivity descriptive statistics will also be provided by first imputing the postbaseline missing daily data during Study Intervention Period with the worst response for caregiver-observed SBM (i.e. assuming 'Yes' response for missing rescue medication use).

Descriptive summary statistics similar to main analysis approach will be provided for change from baseline in 4-week overall SBM frequency rate including the SBMs not directly observed by the caregiver.

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

Stool consistency for caregiver-observed SBMs will be derived as discussed in Section 16.3.5. Descriptive statistics (mean, median, SD, standard error of mean, minimum, and maximum) will be provided by study intervention group for each cohort.

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

Straining for caregiver-observed SBMs will be derived as discussed in Section 16.3.6. The summary statistics for this key efficacy endpoint will be provided by study intervention group in the similar way as discussed for change from baseline in 4-week stool consistency reported by the caregiver during Study Intervention Period for each cohort.

- **Proportion of Days With Fecal Incontinence During Study Intervention Period (For Participants Who Have Acquired Toileting Skills During Daytime and Nighttime or Acquired Toileting Skills During Daytime Only) Within Each Cohort**

The presence of fecal incontinence in a day will be determined as discussed in Section 16.3.7. The proportion of days with fecal incontinence during the Study Intervention Period will be derived based on number of non-missing diary 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 within each cohort.

In the analysis of any key efficacy endpoint, if any cohort has linaclotide dose similar to the other cohort, descriptive summary statistics will also be provided by combining the participants from the similar dose cohorts. In addition, the summary statistics will also be provided for placebo group by combining placebo participants from all cohorts.

Cumulative distribution function plots will be provided for the key efficacy endpoints related to change from baseline by study intervention group. Weekly descriptive summary of the change from baseline key efficacy endpoints will be provided by study intervention group.

10.2 OTHER EFFICACY ENDPOINTS

The other efficacy endpoints are discussed below:

- Proportion of participants with each individual item score for the global change in child's constipation and the global severity of child's constipation at each week during the double-blind Study Intervention Period.

The details of these global items are discussed in Section 16.3.8. Counts and percentages will be provided by study intervention group for each category of global change in child's constipation [redacted] and global severity of child's constipation [redacted] at each week during the Study Intervention Period for each cohort.

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

Modified Rome III criteria will be assessed by the investigator at the Screening Visit (Visit 1) and at the end of the study intervention period at the EOT Visit (Visit 5). A participant will be considered as fulfilling modified Rome III criteria if a "yes" response is recorded to the overall question of whether the participant meets modified Rome III criteria for functional constipation. For the EOT assessment, these criteria will be assessed over the 4-week double-blind study intervention period. In the event a participant discontinues the study prematurely, these criteria will be assessed over the duration of time the participant received double-blind study intervention. Counts and percentages will be provided by study intervention group for participants no longer fulfilling modified ROME III criteria at the end of the study intervention period for each cohort.

If any cohort has linaclotide dose similar to the other cohort, summaries for other efficacy endpoints will also be provided combining the participants from similar dose cohorts. The summary statistics will also be provided for placebo group combining placebo participants from all cohorts.

10.3 SUBGROUP ANALYSIS FOR EFFICACY ENDPOINTS

No subgroup analysis is planned for this study.

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, and weight. For each safety parameter of the clinical laboratory, vital signs, 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 for each cohort separately. If any cohort has a similar linaclotide dose with another cohort, the safety summaries will also be provided combining participants from the similar dose cohorts. Summaries will also be provided for participants from all cohorts in the placebo 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 1 day 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 serious adverse event (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.

For the all screened participants, separate tabular displays 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 within the corresponding cohort for the following laboratory parameters:

Hematology: Absolute and differential white blood cell 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

If any cohort has a similar linaclotide dose with another cohort, the safety summaries will also be provided combining participants from the similar dose cohorts. Summaries will also be provided for participants from all cohorts in the placebo group.

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 11.2–1. 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 within the corresponding cohort. 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 within the corresponding cohort. 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 for all the cohorts. 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 within the corresponding cohort for the following categories: low, normal, and high, which are provided by lab vendor.

The PCS summaries for laboratory parameters and shift table from baseline to the end of double-blind Intervention Period will also be provided combining participants from the similar linaclotide dose cohorts (if any) and combining participants from all cohorts in the placebo group.

Table 11.2–1 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 (ALP)	U/L	—	≥1.2 x ULN
Aspartate aminotransferase (AST)	U/L	—	≥ 3 × ULN
Bicarbonate	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Bilirubin, total (TBL)	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 vital signs (ie, temperature, body weight, respiratory rate, supine pulse rate, supine systolic and diastolic blood pressure) and changes from baseline values at each assessment time point will be presented by study intervention group within the corresponding cohort.

Vital sign values will be considered PCS if they meet both the observed-value criteria and the change-from-baseline criteria listed in Table 11.3–1. The number and percentage of participants with PCS postbaseline values will be tabulated by study intervention group within the corresponding cohort 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 for the corresponding cohort. 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.

If any cohort has a similar linaclotide dose with another cohort, the above discussed vital signs summaries will also be provided combining participants from the similar dose cohorts. Summaries will also be provided for participants from all cohorts in the placebo group.

Table 11.3–1 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 2-5 (inclusive): ≥ 125	Increase of ≥ 20
	Low	Age 2-5 (inclusive): ≤ 70	Decrease of ≥ 20
Diastolic Blood Pressure, mm Hg (Supine)	High	Age 2-5 (inclusive): ≥ 85	Increase of ≥ 15
	Low	Age 2-5 (inclusive): ≤35	Decrease of ≥ 15
Pulse Rate, bpm (Supine)	High	Age 2-3, boy (inclusive): ≥ 165 Age 4-5, boy (inclusive): ≥ 133 Age 2-3, girl (inclusive): ≥188 Age 4-5, girl (inclusive): ≥134	Increase of ≥ 15
	Low	Age 2-3, boy (inclusive): ≤87 Age 4-5, boy (inclusive): ≤63 Age 2-3, girl (inclusive): ≤85 Age 4-5, girl (inclusive): ≤68	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 within each cohort. 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 11.4–1. The number and percentage of participants with PCS postbaseline ECG values will be tabulated by study intervention group for the double-blind invention period within the corresponding cohort. 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 within the corresponding cohort. 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 of the corresponding cohort. 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 within each cohort 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.

If any cohort has a similar linaclotide dose with another cohort, the ECG summaries discussed above will also be provided combining participants from the similar dose cohorts and summaries will also be provided for participants from all cohorts in the placebo group.

Table 11.4–1 Criteria for Potentially Clinically Significant Electrocardiograms

Parameter	Unit	Higher Limit
QRS interval	msec	QRS >= 115 msec (2-5 (inclusive) years)
PR interval	msec	PR > 225 msec (2-5 (inclusive) years)
QTc(F)	msec	>480

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

11.5 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 $\geq$ 3x ULN, along with TBL $\geq$ 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

There is no planned interim analysis of efficacy in this study.

13.1 DATA SAFETY MONITORING BOARD

An independent DSMB will review unblinded interim safety data at defined intervals throughout the study. After at least 6 participants in Cohorts 1 to 3 complete at least 2 weeks of double-blind study intervention, the independent DSMB will review unblinded interim safety data Based on this review, the DSMB will recommend whether the subsequent planned dose level should be tested. Further details of the DSMB (composition, policy, and procedures) are specified in a separate DSMB Charter.

14.0 DETERMINATION OF SAMPLE SIZE

Up to 30 participants, 2 to 5 years of age, will be sequentially enrolled into LIN-MD-67; 8 participants each into Cohorts 1 to 3 will be randomly assigned with 3:1 allocation ratio either to linaclotide dose or matching placebo and 6 additional participants in the final cohort will be randomly assigned with 5:1 allocation ratio either to linaclotide dose or matching placebo. Participants will be randomly assigned to receive linaclotide or matching placebo as described in Section 4.0.

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

15.0 STATISTICAL SOFTWARE

Statistical analyses will be performed using version 9.3 (or newer) of SAS on a Linux operating system.

16.0 DATA HANDLING CONVENTIONS

16.1 VISIT TIME WINDOWS FOR SAFETY ANALYSES

Table 16.1–1 presents the visits assigned for safety analyses and the corresponding range of study intervention days (window) during which an actual visit may occur.

Table 16.1–1 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 [Day 22, max (last dose day+1, Visit 5 date)]
Postintervention Visit	Day 36	Days >= max (last dose day+1, Visit 5 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.

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 16.2–1 below presents the analysis weeks assigned for the efficacy analysis of the participant daily diary data related to BM 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 16.2–1 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

Period	Analysis Week	Begins[a]	Ends[a]
	Week 4	Day 22	Day of last dose
Postinterevention	Post-treatment	Day of last dose + 1	Day of end of study visit

Note: On randomization day, any eDiary assessment prior to randomization time will be part of the Preintervention Period and any eDiary assessment after randomization time will be part of double-blind study 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 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. Caregivers will complete the diary entries once per day for daily diary.

If a participant withdraws during the Intervention Period, the participant's Intervention Period for daily diary responses shall end at the day of the last dose. 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 16.2–2 below presents the weekly periods assigned for the efficacy analysis of the weekly diary data related to global severity of symptoms and global change in symptoms.

Table 16.2–2 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	last dose date +1
Postintervention	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 4 will be day of last dose + 1 or corresponding end day in table whichever comes earlier.

Global severity of child's constipation will be collected starting from Preintervention Visit (Visit 2) and global change in child's constipation will be collected starting one week after Randomization visit.

16.3 DERIVED VARIABLES

16.3.1 Missed eDiary Assessments

No imputation or derivation will be performed for missed eDiary assessments unless otherwise specified.

16.3.2 Incomplete eDiary Assessments

Missing responses in incomplete eDiary 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 in eDiary, no RM usage will be considered during that diary period in eDiary.

If the answer to the question related to BM frequency is missing in any daily eDiary, BM frequency will be considered as zero for that diary period in the eDiary.

16.3.3 Incomplete Clinic Diary on Randomization Visit

Missing responses in an incomplete clinic diary on randomization day will be handled in a similar way as mentioned for incomplete daily eDiary assessments.

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.

Stool Frequency Rates

The components for calculating a participant's stool frequency rates (SBM 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 days during that specific period:
- Randomization day will be considered as a half day for the double-blind Intervention Period and Preintervention Period.

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 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 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 will be based on the total number of SBMs reported by a caregiver as being directly observed by the caregiver 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:

$$\text{Weekly Frequency Rate (Specific Period)} = \frac{\text{Total number of SBMs reported by a caregiver as being directly observed during the specific time period}}{\text{Number of days during the specific analysis period}} \times 7$$

The weekly frequency rate for SBMs will also be derived based on the total number of SBMs occurring based on the diary entries during that time period (including SBMs not directly observed by the caregiver), adjusting for differences in the length of the time period.

Weekly Frequency Rate (Specific Period) including SBMs not directly observed by caregiver =

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

16.3.5 Stool Consistency

The caregiver will be asked to rate the child's observed stool consistency for each BM the caregiver was present for using the Bristol Stool Form Scale (BSFS), a 7-point ordinal scale:

"Choose the option that is most like the Xth (eg, 1st, 2nd, 3rd, ...) bowel movement you were with the child for"

Type 1: Separate hard lumps, like nuts (hard to pass)
Type 2: Sausage-shaped, but lumpy
Type 3: Like a sausage but with cracks on its surface
Type 4: Like a sausage or snake, smooth and soft
Type 5: Soft blobs with clear cut edges (easy to pass)
Type 6: Fluffy pieces with ragged edges, a mushy stool
Type 7: Watery, no solid pieces. Entirely liquid
99 - I don't know

A participant's stool consistency score for the Study Intervention Period will be the average of the non-missing BSFS scores for the caregiver-observed SBMs during that specific period.

16.3.6 Straining

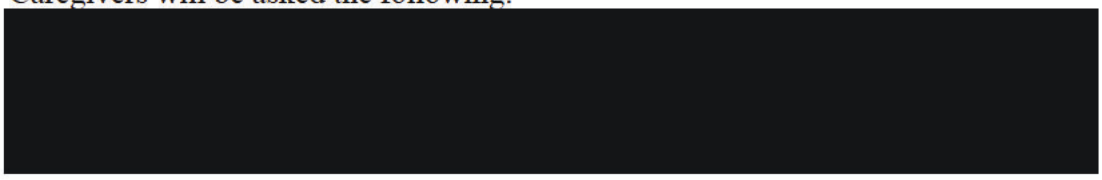
If the caregiver was present for the BM, the caregiver will be asked to rate the amount of straining observed when the child passed the BM using the following two 3-point rating scales. The caregiver will be asked to assess the degree of straining for every BM for which he/she was present by responding to the following two questions in the daily eDiary:

The participant's daily straining score for each caregiver-observed BM will be derived based on the average of non-missing responses of the two straining questions. The participant's straining score will be the average of the non-missing daily average straining scores for the caregiver-observed SBMs during the specific period.

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

Caregivers of children who have acquired toileting skills for BMs will be asked about their child's fecal incontinence episodes. Toileting skills will be assessed as part of the first daily diary and responses will be carried through to the completion of the study.

Caregivers will be asked the following:



Caregivers who choose the first response option for toilet training status [redacted] at the start of the study will be presented with the following question assessing daily fecal incontinence throughout the course of the study:

[redacted]

If the caregiver replies "Yes" to the question above, they will be presented with the following question:

[redacted]

Caregivers who choose the second option for toilet training status [redacted] at the start of the study will be presented with the following question assessing daily fecal incontinence throughout the course of the study:

[redacted]

Any "yes" response for the question related to the [redacted] will be counted as presence of fecal incontinence in the corresponding day.

16.3.8 Global Items

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

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

[redacted]

Global Severity Item
The global severity item assesses the severity of the child's constipation 1 item) as follows:

[redacted]

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 as appropriate unless specified. 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 5 date (if available) will be set as last dose date. In absence of the Visit 5 date, the double-blind disposition status date 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.

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

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 16.4. 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 interventiont, 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 16.10–1 shows examples of how some possible laboratory results should be coded for the analysis.

Table 16.10–1 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 changes to analyses specified in the amended protocol (version 1.0, May 2020).

18.0 REFERENCES

None