1.0 TITLE PAGE

A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Safety and Efficacy Study of a Range of Linaclotide Doses Administered Orally to Children, Ages 7 to 17 Years, With Irritable Bowel Syndrome With Constipation (IBS-C) (ie, Fulfill Rome III Criteria for Child/Adolescent IBS and Fulfill Modified Rome III Criteria for Child/Adolescent Functional Constipation)

LIN-MD-63

STATISTICAL ANALYSIS PLAN

Final: 12 December 2016
Amendment #1: 16 Aug 2019

2.0 TABLE OF CONTENTS

2.1 LIST OF TABLES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
BM	bowel movement
CSBM	complete spontaneous bowel movement
eCRF	electronic case report form
[redacted]	[redacted]
eDiary	electronic diary
FC	functional constipation
IBS	irritable bowel syndrome
IBS-C	Irritable Bowel Syndrome with Constipation
ITT	intent to treat
IP	investigational product
OC	observed cases
p-BSFS	pediatric Bristol Stool Form Scale
PCS	potentially clinically significant
PID	patient identification
PMR	Post Marketing Request
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SBM	spontaneous bowel movement
SI	*Le Système International d'Unités* (International System of Units)
TEAE	treatment-emergent adverse event

4.0 INTRODUCTION

Amendment #1 is being made to the final statistical analysis plan (SAP) of study LIN-MD-63 dated 12 December, 2016. Based on [redacted] feedback to stop this trial [redacted], it was decided to terminate the study LIN-MD-63 early stopping the enrollment in this study. An abbreviated clinical study report (CSR) will be provided for this prematurely terminated study LIN-MD-63.

The actual sample size in this terminated study will be approximately 40% of the planned sample size; and the original planned inferential statistical analyses will lack meaningful interpretations. To limit the analyses for the abbreviated CSR, some changes are being made in the original SAP and also to the latest amended protocol (version 3 dated 16 May, 2017) specified analyses. The analyses of primary, secondary, and some additional efficacy parameters (as discussed in Section 10.4) will be provided using only descriptive summaries. Specifications of tables, figures, and data listings for this terminated trial are also being amended and will be contained in a separate document.

As per the original design, study LIN-MD-63 is a Phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group safety and efficacy study comparing 1 of 3 linaclotide doses (A, B, and C) or 290 ug (only patients 12 - 17 years of age) with placebo in pediatric patients, 7 to 17 years of age, with Irritable Bowel Syndrome with Constipation (IBS-C) (ie, Fulfill Rome III Criteria for Child/Adolescent IBS and Fulfill Modified Rome III Criteria for Child/Adolescent Functional Constipation).

The study would include a total of 6 visits and would be approximately 9 to 12 weeks in duration that includes 4 study periods as follows:

- Screening Period (14 to 28 days)
- Pretreatment Period (14 to 21 days)
- Double-blind Treatment Period (hereinafter referred to as Treatment Period) (at least 28 days [4 weeks] on treatment)
- Post-treatment Period (at least 7 days [1 week] after the Week 4 End-of-Treatment Visit)

According to the original study design, approximately 260 patients with IBS-C were planned to be randomized in this study. Randomization will be stratified by age group (7 - 11 years of age versus 12 - 17 years of age) with a minimum of 40% of patients within each age group. Patients 7 to 11 years of age will be randomized to linaclotide doses (A, B, or C) or placebo in a 1:1:1:1 allocation. Patients 12 to 17 years of age will be randomized to linaclotide doses (A, B, or C, or the approved adult dose, 290 ug) or placebo in a 1:1:1:1:1 allocation. However this study will be terminated early [redacted] before randomizing all planned randomized patients in this study.

Dosage will be determined by weight for patients 7 to 11 years of age (18 to <35 kg or >= 35 kg) as shown below in Table 4–1.

Table 4–1. Double-blind Dosing Regimen

		4-Week Treatment Period			
Age Group	***Weight***	***Linaclotide Dose A***	***Linaclotide Dose B***	***Linaclotide Dose C***	***Approved Adult Dose***
Patients 7 -11 years[a]					
	18- < 35 kg	18 ug	36 ug	72 ug	—
		placebo	placebo	placebo	—
	≥ 35 kg	36 ug	72 ug	144 ug	—
		placebo	placebo	placebo	—
Patients 12 -17 years[b]					
		36 ug	72 ug	144 ug	290 ug[c]
		placebo	placebo	placebo	placebo

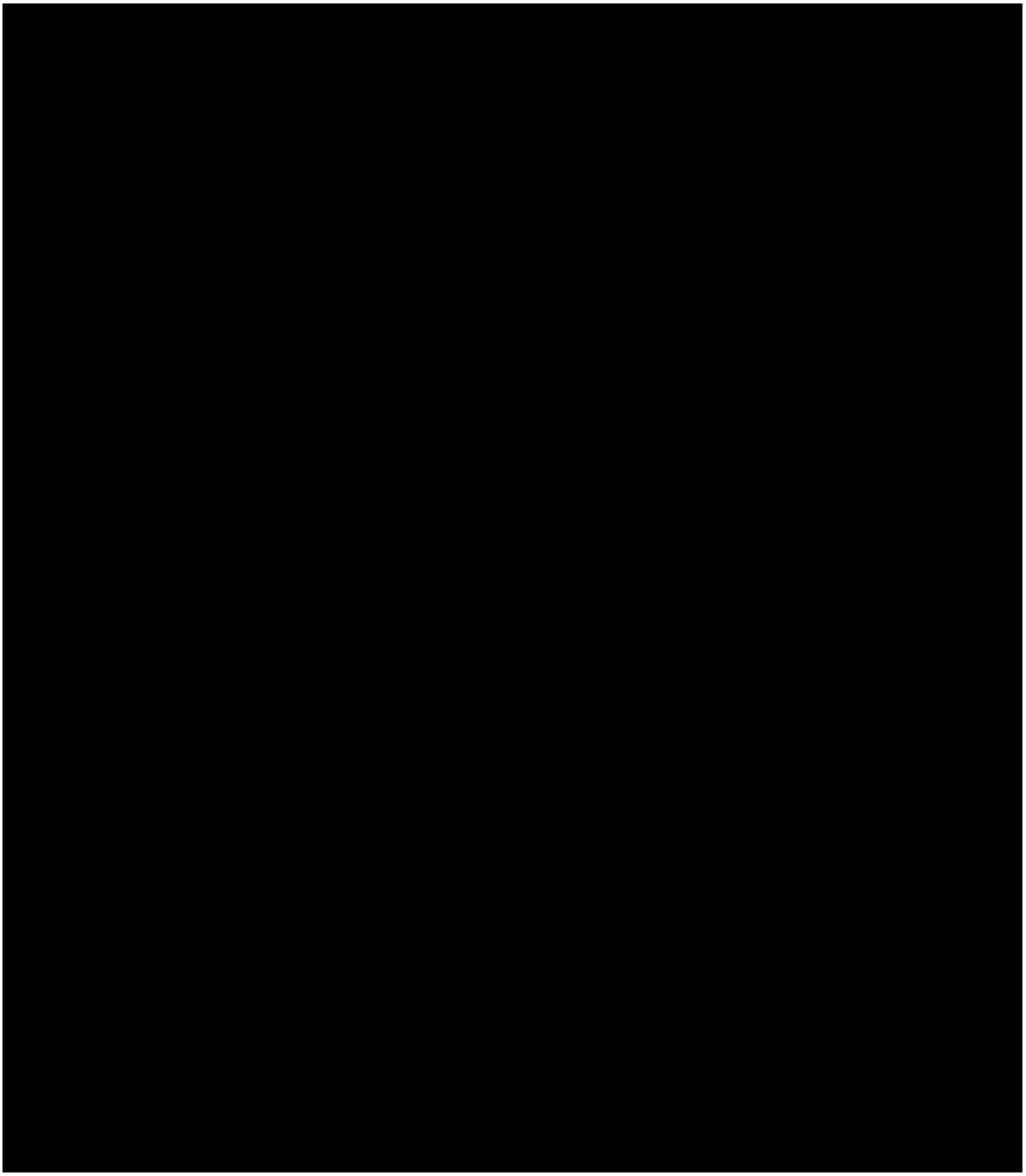
a Patients 7 to 11 years of age will receive linaclotide or placebo in a liquid oral solution or solid oral capsules.
b Patients 12 to 17 years of age will receive linaclotide or placebo in a solid oral capsule.
c Approved dose is for safety and exploratory efficacy only.

[redacted]

Adverse events (AEs) will be monitored at every visit and vital signs will be collected at every visit starting from screening through end of study visit. Laboratory and electrocardiogram (ECG) measures will be collected at screening and at end of Treatment Period (Week 4/Visit 5).

The schedule of evaluations for Study LIN-MD-63 is presented in Table 4–2.

Table 4–2 **SCHEDULE OF EVALUATIONS: Study LIN-MD-63**



[redacted]

5.0 OBJECTIVES

The objective of this study is to evaluate the dose response, safety, and efficacy of 4 weeks of treatment with 1 of 3 linaclotide doses (A, B, or C) or 290 ug (as an exploratory objective in the adolescent patients 12 - 17 years of age using the approved adult dose) compared with placebo in pediatric patients 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.

6.0 PATIENT POPULATIONS

6.1 SCREENED POPULATION

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

6.2 RANDOMIZED POPULATION

The Randomized Population will consist of all patients in the Screened Population who are randomized to a treatment group in the study.

6.3 SAFETY POPULATION

The Safety Population will consist of all patients in the Randomized Population who took at least 1 dose of double-blind investigational product (IP).

All summaries in this population will be provided based on the treatment each patient was randomized to receive. Actual treatment received will be determined based on the study treatment received for majority of the DB treatment period. If there is a tie, higher dose will be considered for actual treatment for that patient. Actual treatment will be listed for the patients in the listing related to treatment dosing information.

6.4 INTENT-TO-TREAT POPULATION

The Intent-to-Treat (ITT) Population will consist of all patients in the Safety Population 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).

7.0 PATIENT DISPOSITION

The number and percentage of patients in 3 study populations (Randomized, Safety, and ITT) will be summarized overall, by treatment group, age group, and study center; the number of patients screened will be summarized overall only by age group and study center.

Screen-failure patients (ie, patients who are screened but do not enter into the Pretreatment Period), patients ineligible for randomization (ie, patients who enter into the Pretreatment Period but are not randomized at Visit 3, also labeled as pretreatment failures), and the associated reasons for failure as recorded in the electronic case report forms (eCRF) will be tabulated overall and also by age group for the all screened patients. The number and percentage of patients who complete the double-blind Treatment Period and Post-treatment Period and of patients who prematurely discontinue during the same period will be presented for each treatment group and pooled across treatment groups for the Randomized Population. The reasons for premature discontinuation from the double-blind study period or Post-treatment Period as recorded in the eCRF will be summarized (number and percentage) by treatment group for the Randomized Population. All patients who prematurely discontinue during the double-blind Treatment Period or Post-treatment Period will be listed by discontinuation reason for the Randomized Population.

[redacted]

Patients with any major protocol deviation, as well as each individual protocol deviation, will be listed by treatment group for the Randomized Population.

8.0 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 treatment group for the Safety and ITT Populations. Other baseline characteristics (including efficacy parameters related to bowel habits and symptoms as discussed in Section 10.0) will be summarized descriptively by treatment group for the ITT Population. Continuous variables will be summarized by number of patients and mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients. [redacted]

9.0 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

9.1 EXTENT OF EXPOSURE

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

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

9.2 MEASUREMENT OF TREATMENT COMPLIANCE

Dosing compliance for the double-blind Treatment Period is defined as the quantity of liquid solution or number of capsules actually taken by a patient during that period divided by the quantity/number of liquid solution/capsules prescribed for the Treatment Period multiplied by 100. [redacted]

[redacted]

9.3 EDIARY COMPLIANCE

Patients will complete the eDiary [redacted]
Patient'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 patient responded to each question in the corresponding eDiary.

[redacted]

[redacted]

[redacted]

[redacted]

10.0 EFFICACY ANALYSES

Efficacy analyses will be based on the ITT Population.

Baseline values for efficacy parameters will be derived from the eDiary and eCRF data collected in the Pretreatment Period, specifically the period of time from 14 days before randomization up to the time of randomization. A spontaneous bowel movement (SBM) is a bowel movement (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 (daytime pain and daytime bloating) will be derived as discussed in Section 16.3. Baseline value for the patient-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 double-blind IP. The derivations of primary and secondary efficacy parameters are discussed in Section 16.3 unless otherwise mentioned in Section 10.0. [redacted]

A patient's baseline stool consistency and straining cannot be assessed if the patient does not have at least 1 SBM during the Pretreatment Period. For patients who report '0' SBMs during a study period, the consistency and straining assessments will be considered missing for that study period in the analyses. Patients with missing baseline consistency and straining will be excluded from the respective consistency and straining analyses that involve change from baseline.

An observed-cases (OC) approach to missing postbaseline data will be applied.

The overall analysis (incorporating both age groups) including placebo and linaclotide doses (A, B, and C) will be the analysis to evaluate the main objective of this study. [redacted] This study will be terminated early [redacted]. No statistical test will be performed. Only descriptive statistics will be provided by treatment group.

10.1 PRIMARY EFFICACY ANALYSIS

The primary efficacy parameter is the change from baseline in 4-week overall spontaneous bowel movement (SBM) frequency rate (SBMs/week) during the Treatment Period. The SBM rate per week during the Treatment Period will be derived based on the total number of SBMs a patient reported during this period in the morning and evening assessments on the eDiary. The details of the derivation of this efficacy parameter are provided in Section 16.3.4.

The primary efficacy parameter will be summarized descriptively overall and within each age group by treatment group. For the overall summary, linaclotide doses (A, B, and C), the adult approved dose (290 ug), and placebo will be included. [redacted]

10.2 KEY SECONDARY EFFICACY ANALYSIS

The key secondary efficacy parameter is the change from baseline in 4-week abdominal pain daytime symptoms based on evening assessment of abdominal pain symptoms. Abdominal pain scores will be collected twice daily in the eDiary: in the morning when a patient wakes up and in the evening at bedtime. Patients are asked to rate their abdominal pain from the time the patient wakes up until bedtime as part of the evening assessment, and a 5-point rating scale is derived from the patient's responses. The patient's 4-week abdominal pain daytime symptoms during the Treatment Period are defined as the average of the non-missing daily abdominal pain daytime symptoms reported in evening assessments in the eDiary during the 4-week Treatment Period. The details of the derivation of this efficacy parameter are provided in Section 16.3.8.

The change-from-baseline in 4-week abdominal pain daytime symptoms based on evening assessment will be summarized descriptively by treatment group overall and within each age group. For the overall summary, linaclotide doses (A, B, and C), the adult approved dose (290 ug), and placebo will be included. [redacted]

10.3 OTHER SECONDARY EFFICACY ANALYSES

The other secondary efficacy parameters are as follows:

- Change from baseline in 4-week stool consistency
- Change from baseline in 4-week of severity of straining

- Change from baseline in 4-week abdominal bloating daytime symptoms based on evening assessment

- Change from baseline in 4-week overall complete spontaneous bowel movement frequency rate (CSBM/week) during the Treatment Period

The derivation of each secondary efficacy parameter is discussed in Section 16.3.

The change-from-baseline other secondary efficacy parameters will be summarized descriptively by treatment group. For the overall summary, linaclotide doses (A, B, and C), the adult approved dose (290 ug), and placebo will be included. [redacted]

10.4 ADDITIONAL EFFICACY ANALYSES

[redacted]

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), and electrocardiographic (ECG) parameters. For each safety parameter of the clinical laboratory, vital signs, and ECG parameters, the last non-missing safety assessment before the first dose of IP will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by number of patients and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients. The safety summaries will be provided by treatment group. The summaries of the linaclotide approved adult dose (290 ug), will be included in the overall and within age group 12 to 17 years.

11.1 ADVERSE EVENTS

Adverse events will be coded by system organ class and preferred term using the *Medical Dictionary for Regulatory Activities,* version 18.0 or newer.

An AE will be considered a treatment-emergent adverse event (TEAE) if it was present after the first dose of IP or was present before the date of the first dose of IP and increased in severity after the first dose of IP. If more than 1 AE was reported before the first dose of IP and coded to the same preferred term, the AE with the greatest severity will be used for comparison with the AEs occurring during the Treatment Period. An AE that occurs more than 1 day after the date of the last dose of IP will not be considered as a TEAE.

The number and percentage of patients reporting TEAEs in each treatment group will be tabulated by descending percentage in any group, by system organ class and preferred term, and further categorized by severity. The incidence of treatment related TEAEs will be summarized by treatment group, preferred term. If more than 1 AE is coded to the same preferred term for the same patient, the patient 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 incidence of common ($\geq$ 5% of patients in any treatment group) TEAEs will be summarized by preferred term, and treatment group.

The overall summary of AEs will also be provided by treatment group. The overall summary of AEs and incidences of patients reporting TEAEs in each treatment group will also be provided within each age group.

A serious adverse event (SAE) that occurred between the date of the first dose of IP and 30 days after the date of the last dose of IP, inclusive, will be considered an on-therapy SAE. The number and percentage of patients who have on-therapy SAEs will be summarized by preferred term and treatment group.

The number and percentage of patients in the Safety Population who have AEs leading to premature discontinuation of the IP will be summarized by preferred term and treatment.

[redacted]

[redacted] AEs during the Post-treatment Period will also be included in the listings.

11.2 CLINICAL LABORATORY PARAMETERS

Clinical laboratory test values (in SI units) 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 patients who have PCS postbaseline clinical laboratory values will be tabulated by treatment group for the double-blind Treatment Period. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 postbaseline assessment for the corresponding period. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS postbaseline value for the corresponding period. A supportive tabular display of patients with PCS postbaseline values will be provided, including the PID number, baseline and all postbaseline (including non-PCS) values. In this listing, any patient with PCS value (if any) during the Post-treatment Period and all AEs that occurred in patients with PCS postbaseline laboratory values will also be included.

Table 11.2–1 Criteria for Potentially Clinically Significant Laboratory Results

[redacted]

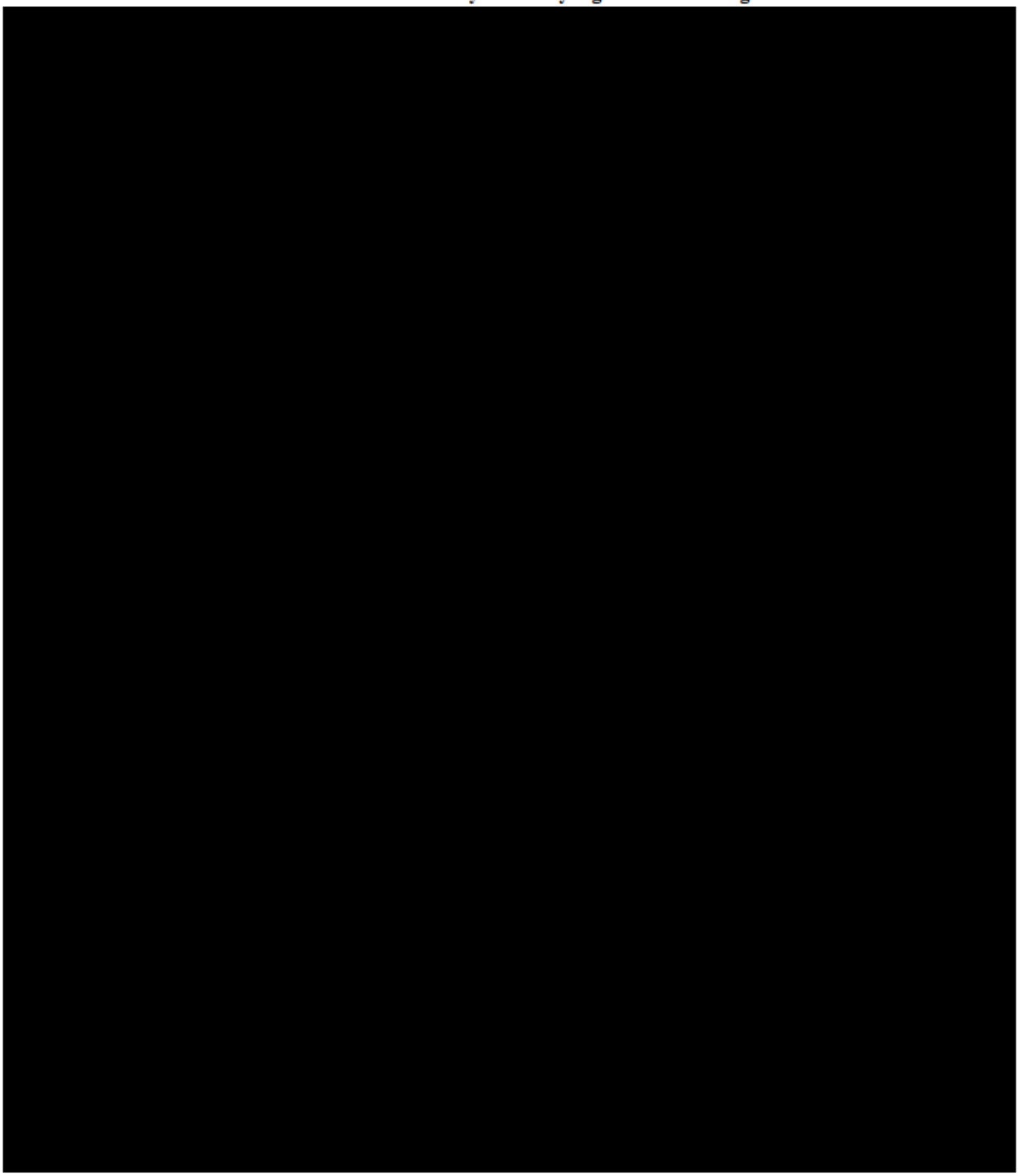
[redacted]

11.3 VITAL SIGNS

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 patients with PCS postbaseline values will be tabulated by treatment group. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS postbaseline value. A supportive tabular display of patients with PCS postbaseline values will be provided, including the PID number, baseline and all postbaseline (including non-PCS) values.

A tabular display showing all AEs that occurred in patients who had PCS postbaseline vital sign values will also be included in this listing.

Table 11.3–1 **Criteria for Potentially Clinically Significant Vital Signs**



[redacted]

13.0 INTERIM ANALYSIS

No interim analysis is planned for this study.

14.0 DETERMINATION OF SAMPLE SIZE

As per the original plan, the planned sample size is designed for the overall analysis of placebo and linaclotide dose groups (A, B, and C), with 58 patients per treatment group (232 patients in total for the overall analysis). With the inclusion of additional 23 to 31 patients 12 to 17 years of age for the linaclotide approved adult dose, 290 ug, the planned sample size for the study is approximately 260 patients. [redacted]

This study is to be terminated [redacted] The actual sample size will be approximately around 40% of the sample size as planned above.

15.0 STATISTICAL SOFTWARE

Statistical analyses will be performed using [redacted]

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 treatment days (window) during which an actual visit may occur.

Table 16.1–1. Visit Time Windows for Safety Analyses

[redacted]

16.2 VISIT TIME WINDOWS FOR EFFICACY ANALYSES

Table 16.2–1 below presents the analysis weeks assigned for the efficacy analysis of the patient 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 16.2–1. Analysis Time Windows for Efficacy Analysis - Daily Questions

[redacted]

Table 16.2–2. Analysis Time Windows for Efficacy Analysis - Weekly Questions

[redacted]

[redacted]

[redacted]

[redacted]

16.3.3 Incomplete Clinic Diary on Randomization Visit (If Present)

[redacted]

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/Incomplete Evacuation
A complete spontaneous bowel movement (CSBM) is an SBM that is associated with a sense of complete evacuation.

Stool Frequency Rates
The components for calculating a patient'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:

[redacted]

Duration of an Analysis Week
With respect to a patient'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 patient's "weeks" may not be exactly 7 days in duration [redacted] 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) =

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

16.3.5 Stool Consistency

Patients will use the pediatric Bristol Stool Form Scale (p-BSFS) 7-point ordinal scale to rate their stool consistency:

"Use the card ***provided*** to 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 [redacted] and measured using the 7-point p-BSFS.

Stool consistency (p-BSFS) scores during an analysis period will be derived to be consistent with derivation in adult studies as mean of patient's non-missing, SBM-associated p-BSFS scores during the analysis period.

16.3.6 Severity of Straining

Degree of straining will be assessed via patient's responses to the following:

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 [redacted] and measured using a 5-point scale.

Straining scores during an analysis period will be derived to be consistent with derivation in adult studies as mean of patient's non-missing, SBM-associated straining scores during the analysis period.

16.3.7 Abdominal Bloating

Abdominal bloating will be collected [redacted] via patient's responses to the following questions.

Patient will record their assessment of abdominal bloating by responding to the following in the evening diary:

From when you got up this morning until now, did your tummy FEEL big and full?
1 = yes
0 = no
98 = I don't know what you mean

99 = I don't remember

If "yes" then patient answers the following question using 4-point scale:

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

[redacted]

The patient's abdominal bloating daytime symptoms during the analysis period are defined as the average of the non-missing daily abdominal bloating daytime symptoms reported in evening assessments in the eDiary during the analysis period based on the scores of 0, 1, 2, 3, and 4. For the daytime baseline symptoms, 14 days prior to the randomization will be considered.

16.3.8 Abdominal Pain

Abdominal pain scores will be collected [redacted] ia patient's responses to the following questions.

Patient will record their assessment of abdominal pain by responding to the following [redacted]:

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

If "yes", then patient answers the following question using a 4-point scale:

- How much did your tummy hurt?

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

[redacted]

To calculate patient's 4-week abdominal pain score, responses "no" will be coded as '0'. The patient's 4-week abdominal pain daytime symptoms during the specific period are defined as the average of the non-missing daily abdominal pain daytime symptoms reported in evening assessments in the eDiary during specific period based on scores of 0, 1, 2, 3, and 4. For the daytime baseline symptoms, 14 days prior to the randomization will be considered.

[redacted]

[redacted]

16.5 MISSING DATE OF THE LAST DOSE OF STUDY TREATMENT

When the date of the last dose of study treatment is missing for a patient in the Safety Population, all efforts should be made to obtain the date from the Investigator. [redacted]

[redacted]

[redacted]

16.9 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

[redacted]

16.9.1 Incomplete Start Date

[redacted]

[redacted]

16.9.2 Incomplete Stop Date

[redacted]

17.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

Based on [redacted] feedback [redacted] to stop this phase 2 study, it was decided to terminate the study stopping the enrollment in the study LIN-MD-63 early than planned, before the target number of patients have been enrolled and an abbreviated CSR will be planned. To limit the analyses in the abbreviated CSR, not all analyses planned in original SAP (dated 12 December, 2016) and the latest amended protocol (version 3 dated 16 May, 2017) will be performed.

No statistical testing will be performed for efficacy parameters and only descriptive statistics will be provided for primary, secondary, and additional efficacy parameters of global items. No sensitivity and exploratory analyses will be conducted for efficacy parameters. Though the summary of linaclotide approved adult dose 290 ug will be provided to support exploratory objective. Only key safety summaries will be provided as discussed in Section 11.0. Summary statistics by age group will be provided only for key efficacy and safety parameters.

Following changes have been made in this SAP amendment.

- Section 6.3 and Section 11.1: Additional summary of TEAEs will not be provided based on actual treatment in presence of difference between planned treatment and actual treatment for more than one patient.
- Section 8.0: Summaries for prior and concomitant medication, medical histories, and formulation of IP will not be provided. Demographics and baseline characteristics will not be summarized by age group within ITT Population.
- [redacted]
- Section 10.0: The key changes in efficacy analyses are listed below.
  - No exploratory analysis [redacted] nd sensitivity analysis will be conducted for primary and secondary efficacy parameters. [redacted]
  - No testing will be performed for efficacy parameters. No model-based estimates, 95% confidence intervals will be provided. Only descriptive summary statistics will be provided.

[redacted]

- Section 11.0: The key changes in safety analyses are listed below.
  - [redacted]
- [redacted]
- Section 16.3: This section has been updated to discuss only the derivation of primary and secondary efficacy parameters, [redacted]

18.0 REFERENCES

None