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Study ID: LIN-MD-62

Title: A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Safety and Efficacy Study of a Range of Linaclotide Doses Administered Orally to Children, Ages 6 to 17 Years, Who Fulfill Modified Rome III Criteria for Child/Adolescent Functional Constipation (FC)

Statistical Analysis Plan Amendment 2 Date: 28 June 2018

1 TITLE PAGE

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A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Safety and Efficacy Study of a Range of Linaclotide Doses Administered Orally to Children, Ages 6 to 17 Years, Who Fulfill Modified Rome III Criteria for Child/Adolescent Functional Constipation (FC)

LIN-MD-62

STATISTICAL ANALYSIS PLAN

Final: 23 May 2016
Amendment #1: 1 Nov 2017
Amendment #2: 28 June 2018

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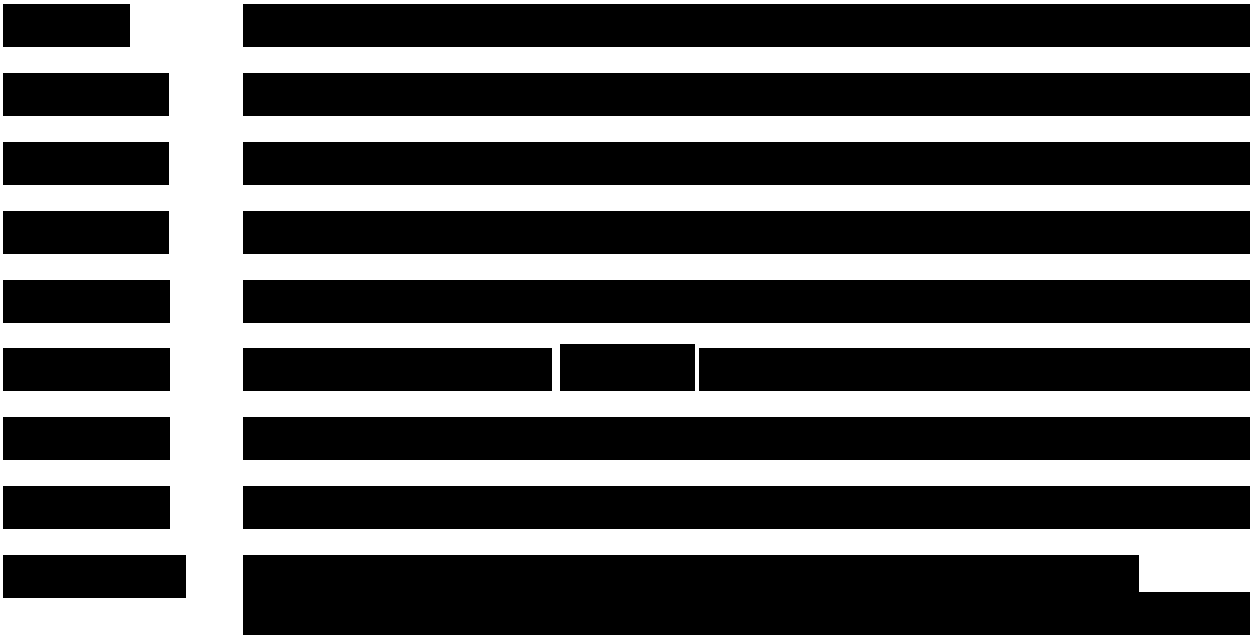
2.1 IN-TEXT TABLES



3 LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
BM	bowel movement
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CSBM	complete spontaneous bowel movement
eCRF	electronic case report form
[redacted]	[redacted]
eDiary	electronic diary
FC	functional constipation
ITT	intent to treat
IP	investigational product
[redacted]	[redacted]
LSMs	Least squares means
[redacted]	[redacted]
MAR	missing at random
MI	multiple imputation
MMRM	mixed-effects model for repeated measures
[redacted]	[redacted]
OC	observed cases
p-BSFS	pediatric Bristol Stool Form Scale
[redacted]	[redacted]
[redacted]	[redacted]
PID	patient identification
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SBM	spontaneous bowel movement
[redacted]	[redacted]
TEAE	treatment-emergent adverse event

4 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and/or specified in the final protocol of Study LIN-MD-62 (version dated 15 Apr, 2015) and the most recent amendment (version 1 dated 13 Aug, 2015). Specifications of tables, figures, and data listings are contained in a separate document.

Study LIN-MD-62 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 145 ug (only patients 12 - 17 years of age) with placebo in pediatric patients, 6 to 17 years of age, with a diagnosis of functional constipation (FC) based on modified Rome III Child/Adolescent Criteria (ie, who fulfill modified Rome III criteria for child/adolescent FC).

The study will include a total of 6 visits and will 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)

Approximately 160 patients with FC are planned to be randomized in this study. Randomization will be stratified by age group (6 - 11 years of age versus 12 - 17 years of age) with a minimum of 40% of patients within each age group. Patients 6 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, 145 ug) or placebo in a 1:1:1:1:1 allocation.

Dosage will be determined by weight for patients 6 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

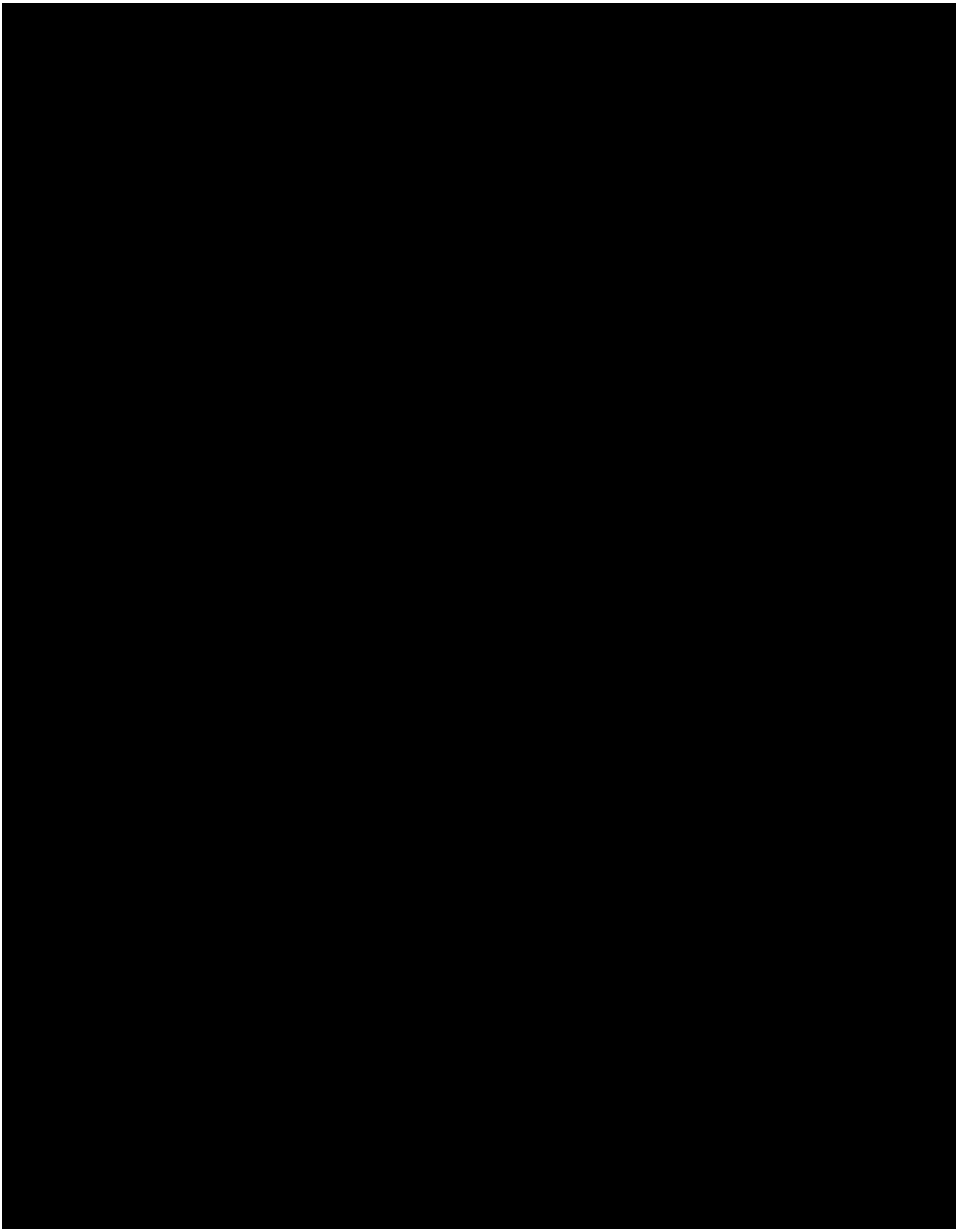
		4-Week Treatment Period			
Age Group	**Weight**	**Linaclotide Dose A**	**Linaclotide Dose B**	**Linaclotide Dose C**	**Approved Adult Dose**
Patients 6 -11 years[a]					
	18- < 35 kg	9 ug	18 ug	36 ug	—
		placebo	placebo	placebo	—
	≥ 35 kg	18 ug	36 ug	72 ug	—
		placebo	placebo	placebo	—
Patients 12 -17 years[b]					
		18 ug	36 ug	72 ug	145 ug[c]
		placebo	placebo	placebo	placebo

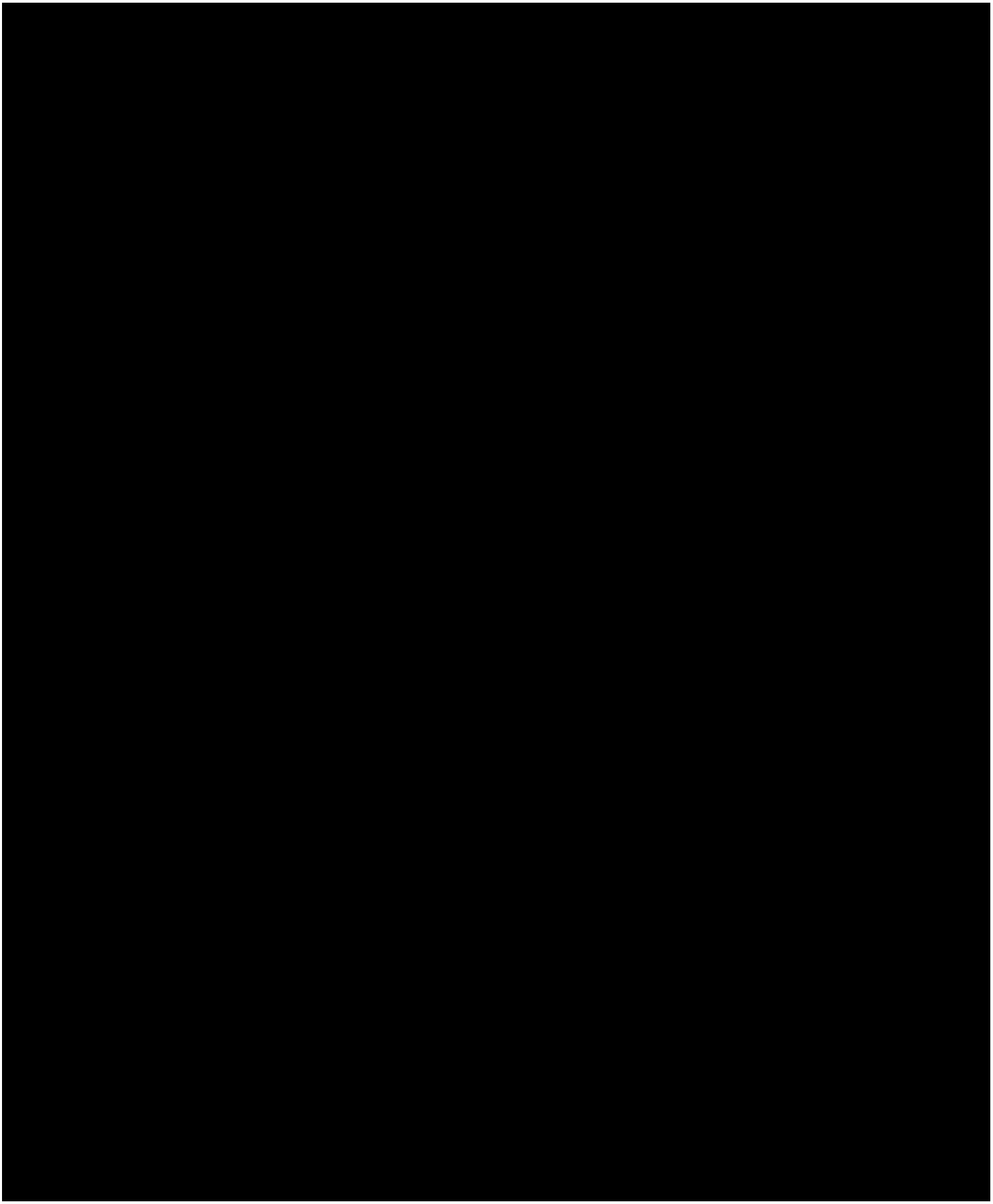
a Patients 6 to 11 years of age will receive linaclotide or placebo in a liquid oral solution.
b Patients 12 to 17 years of age will receive linaclotide or placebo in a solid oral capsule or a liquid oral solution.
c Approved dose is for safety and exploratory efficacy only.

Patients will complete the electronic diary (eDiary) twice daily (morning and evening) throughout the Pretreatment Period, Treatment Period, and Post-treatment Period and must complete at least 4 weeks of treatment before arriving at the study site for the Week 4 Visit (Visit 5). Patients will not receive investigational product (IP) during the Post-treatment Period, but will continue to complete the eDiary twice daily throughout the Post-treatment Period.

[redacted]

Adverse events (AEs) will be monitored at every visit [redacted]





5 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 145 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 6 to 17 years of age who fulfill modified Rome III criteria for child/adolescent FC.

6 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. If patient received treatment other than randomized treatment, actual treatment received will be determined based on the study treatment received for majority of the

double-blind 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 and additional summary of treatment emergent adverse events (TEAEs) will be provided if there is a difference between planned randomized treatment and actual treatment for more than one patient.

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 PATIENT DISPOSITION

The number and percentage of patients in 3 study populations (Randomized, Safety, and ITT) will be summarized overall, by treatment group, [redacted], and study center; [redacted]

[redacted]. 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. [redacted]

[redacted]

8 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters (age; age group [6-11 and 12-17 years (inclusive)]; race; ethnicity; sex) and baseline characteristics (weight; height; and body mass index, calculated as weight [kg]/(height [m])^2) will be summarized descriptively by treatment group for the Safety and ITT Populations. [redacted] 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]

[redacted]

[redacted]

10 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 (pain and bloating) will be derived as discussed in Section 16.3. [redacted] The derivation of each efficacy parameter is discussed in Section 16.3 unless otherwise mentioned in Section 10.

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. [redacted]

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] All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance. All confidence intervals (CIs) will be 2-sided 95% CI, unless stated otherwise. No multiplicity adjustment will be applied in this dose-ranging study. Nominal p-values will be provided for the efficacy parameters as a measure of strength of association between the endpoint and the treatment effect.

[redacted]

10.1 Primary Efficacy Parameter

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.

For the primary efficacy parameter, comparison between each linaclotide dose (A, B, and C) and placebo will be performed using an analysis of covariance (ANCOVA) model with treatment and age group (6 - 11 years of age and 12 - 17 years of age) as factors and baseline value as a covariate. Least squares means (LSMs) for each treatment group, differences in LSMs between each linaclotide treatment group versus placebo, associated 2-sided 95% CIs for these differences in LSMs, and the corresponding statistical test p-values will be reported. [redacted].

[redacted]

[redacted]

[redacted]

[redacted]

10.2 Secondary Efficacy Parameters

The secondary efficacy parameters are as follows:

- Change from baseline in 4-week abdominal pain daytime symptoms based on evening assessment
- 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
- Change from baseline in 4-week fecal incontinence daytime symptoms based on evening assessment

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

For each change-from-baseline secondary efficacy parameter (except fecal incontinence), each linaclotide dose group (A, B, and C) will be compared with the placebo group using an ANCOVA model with treatment (linaclotide doses A, B, and C, and placebo) and age group (6 - 11 years of age and 12 - 17 years of age) as factors and baseline value as a covariate. LSMs for each treatment group, differences in LSMs between each linaclotide treatment group versus placebo, associated 2-sided 95% CIs for these differences in LSMs, and the corresponding statistical test p-values will be reported. [redacted]

[redacted]

Change from baseline in 4-week fecal incontinence daytime symptoms based on evening assessment will be summarized descriptively by treatment group (linaclotide doses A, B, C, and placebo). Fecal incontinence measurement will be available only for those patients who were randomized following the implementation of fecal incontinence assessment in the protocol (amendment #3).

[redacted]

In addition, the 4-week stool consistency and severity of straining scores will be derived following the approach used in adult studies as discussed in Section 16.3 (Sections 16.3.5 and 16.3.6, respectively). Change from baseline in 4-week stool consistency and severity of straining scores derived based on adult derivation will also be analyzed following the same approach as discussed above for overall ITT Population.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

11 SAFETY ANALYSES

The safety analysis will be performed using the Safety Population. [redacted]

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.

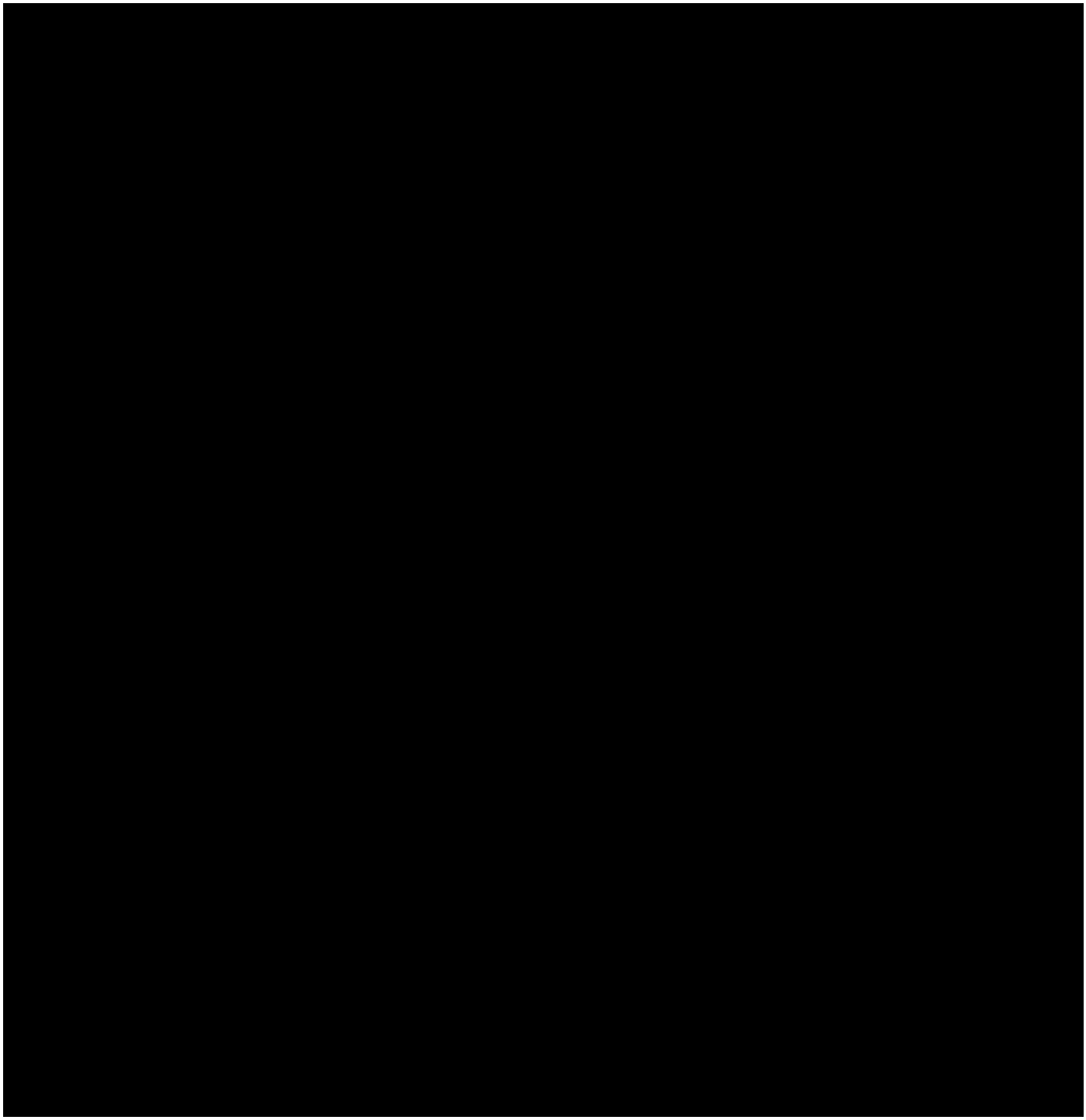
The number and percentage of patients reporting TEAEs in each treatment group will be tabulated [redacted], by system organ class and preferred term, [redacted]

The incidence of common (≥ 5% of patients in any treatment group) TEAEs will be summarized by system organ class, preferred term, and treatment group. [redacted]

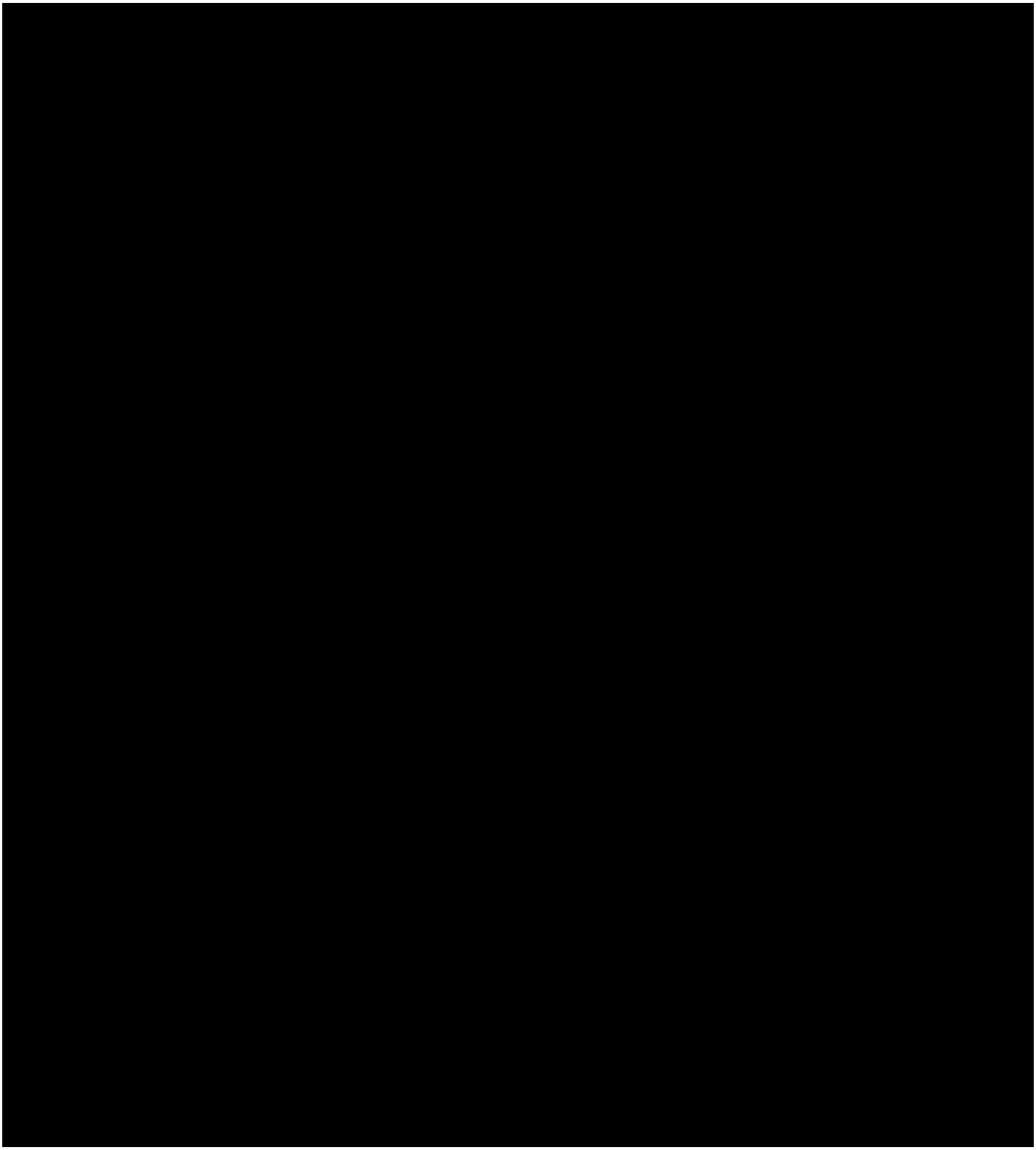
The overall summary of AEs will also be provided by treatment group.

[redacted]

[redacted]



[redacted]



[redacted]

[redacted]

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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

13 INTERIM ANALYSIS

No interim analysis is planned for this study.

[redacted]

[redacted]

[redacted]

15 STATISTICAL SOFTWARE

Statistical analyses will be performed using version [redacted]

16 DATA HANDLING CONVENTIONS

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]

[redacted]

[redacted]

[redacted]

[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.

[redacted]

In the evening diary, if patients responded “yes” for RM use question but missed to report the timing of RM use or replied ‘I don’t know” for the timing of RM use, the missing or “I don’t know” response will be coded as “Yes” for all the periods in the evening diary. [redacted]

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:
- Randomization day with evening diary will be considered as a half day for the double-blind Treatment Period.
- Randomization day with morning and/or clinic diary will be considered as a half day for the Pretreatment Period.
- The day after last dose will be considered as a half day for the double-blind Treatment Period and for the Post-treatment Period.

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 (eg, a patient may withdraw or discontinue early from the trial, may have half day data with diary entries, or may have missing diary day). Deviations from the 7 days norm are structural in nature; and, as such, the calculations of the weekly rates of SBMs or CSBMs will incorporate the actual days contributed within the time period (week or specific phase).

Weekly Stool Frequency Rate Calculations

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

- Weekly Frequency Rate (Specific Period) =

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

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 twice daily in the eDiary, in the morning when a patient wakes up and in the evening at bedtime, and measured using the 7-point p-BSFS. The patient's p-BSFS score in the specific period will be the observed weighted average of the daily p-BSFS scores [redacted] and the denominator in the observed weighted average will be the sum of the weights during this period. The daily p-BSFS score will be the average of nonmissing morning and/or evening assessments of the p-BSFS score from the SBMs reported by the patient on that specific day during that corresponding period.

[redacted]

[redacted]

In addition, stool consistency (p-BSFS) scores during an analysis period will also 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 twice daily in the eDiary, in the morning when a patient wakes up and in the evening at bedtime, and measured using a 5-point scale. The patient's straining score in the specific analysis period will be the observed weighted average of daily straining score [redacted] and the denominator in the observed weighted average will be the sum of the weights during this period. The daily score will be the average of the nonmissing morning and/or evening assessments of the straining score from the SBMs reported by the patient on that specific day during the analysis period.

[redacted]

In addition, straining scores during an analysis period will also 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 twice daily in the eDiary, in the morning when a patient wakes up and in the evening at bedtime 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/[redacted] symptoms during the analysis period are defined as the average of the nonmissing daily abdominal bloating daytime[redacted] symptoms reported in evening[redacted] assessments in the eDiary during the analysis period based on the scores of 0, 1, 2, 3, and 4.

[redacted]

[redacted]

16.3.8 Abdominal Pain

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 via patient's responses to the following questions.

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

From when you got up this morning until now, did your tummy hurt at all?

- Yes
- 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 [redacted] symptoms during the specific period are defined as the average of the nonmissing daily abdominal pain daytime [redacted] symptoms reported in evening/[redacted] assessments in the eDiary during specific period based on scores of 0, 1, 2, 3, and 4.

[redacted]

[redacted]

16.3.9 Fecal Incontinence

Fecal incontinence will be collected once daily in evening diary for those patients who will be randomized after the implementation of Amendment #3 (version 3.0 dated 16 May 2017) of the protocol.

Patients will be asked to record their episodes of fecal incontinence by responding to the following evening assessments.

- From when you got up this morning until now, did you have a pooping accident

(even a little)?

o Yes

o No

From when you got up this morning until now, did you have any poop marks or

stains on your underwear?

o Yes

o No

o I don’t know

If patients answered “Yes” for any of the above questions, patients will be considered to have fecal incontinence. In any analysis period, Fecal incontinence daytime symptoms, based on the evening assessment, will be calculated as the average of nonmissing patient scores reported in the evening diary during the analysis period.

[redacted]

[redacted]

3 [redacted]

[redacted]

[redacted]

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[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]

[redacted]).

17 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

[redacted]

18 HISTORY OF CHANGES

Following changes have been made in this SAP Amendment:

[redacted]

[redacted].

[redacted]

[redacted]

Following changes have been made in SAP Amendment #1 to be consistent with amended protocol (version 3.0) dated 16 May 2017.

[redacted]

- Section 10.2: Addition of a new secondary efficacy parameter of change from baseline in 4-week fecal incontinence daytime symptoms based on evening assessment and shifting the change from baseline in 4-week abdominal pain daytime symptoms based on evening assessment to secondary efficacy parameter from additional efficacy parameter.

Other changes are the followings:

[redacted]

- [redacted]

- [redacted].

- [redacted]

- Section 18.0 has been added to document the history of changes in this amendment. Following section numbers have been updated as a result.

19 REFERENCES

Carpenter, J.R., Kenward, M.G. Missing data in randomized controlled trials- a practical guide; 2007. p 119-138; Free Downloadable at registered users area www.missingdata.org.uk.

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