Statistical Analysis Plan for Study M21-572

A Phase 3, Multicenter, Randomized, Double-blind, Parallel-group, Safety and Efficacy Study of Linaclotide Versus Placebo in Pediatric Subjects, Ages 2 to 5 Years, with Functional Constipation (FC) with a 24-week Open-label Treatment Extension

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Version 6.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for linaclotide (LINZESS) Study M21-572, A Phase 3, Multicenter, Randomized, Double-blind, Parallel-group, Safety and Efficacy Study of Linaclotide versus Placebo in Pediatric Subjects, Ages 2 to 5 Years, with Functional Constipation (FC) with a 24-week Open-label Treatment Extension.

Study M21-572 examines the efficacy and safety of linaclotide for 12 weeks (Part 1), and the long-term safety of linaclotide for 24 weeks (Part 2), in pediatric subjects with FC aged 2 to 5 years.

The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the statistical analyses for Study M21-572.

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

2.0 Study Objectives and Design

2.1 Study Objectives

The objective of this study is divided into two parts.

Part 1: To evaluate the safety and efficacy of 12 weeks of linaclotide therapy in comparison with placebo in pediatric subjects aged 2 to 5 years who meet modified Rome IV criteria for childhood FC.

Part 2: To assess the long-term safety of linaclotide administered to pediatric subjects with FC who have completed study intervention in Part 1 of this study or completed Study 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 subjects (age 2 to 5 years) with FC).

AbbVie is conducting this Phase 3 study in pursuit of an effective treatment of FC in subjects ages 2 to 5 years, for which there is currently no approved treatment. AbbVie's goal is to fulfill the associated Pediatric Research Equity Act postmarketing requirement (PMR) 2161-2 and provide efficacy and safety data on linaclotide in this pediatric population.

The clinical hypothesis of this study is divided into two parts.

Part 1: Once daily administration of linaclotide 72 µg for a 12-week study intervention period is safe and effective in pediatric subjects, 2 to 5 years of age, with FC.

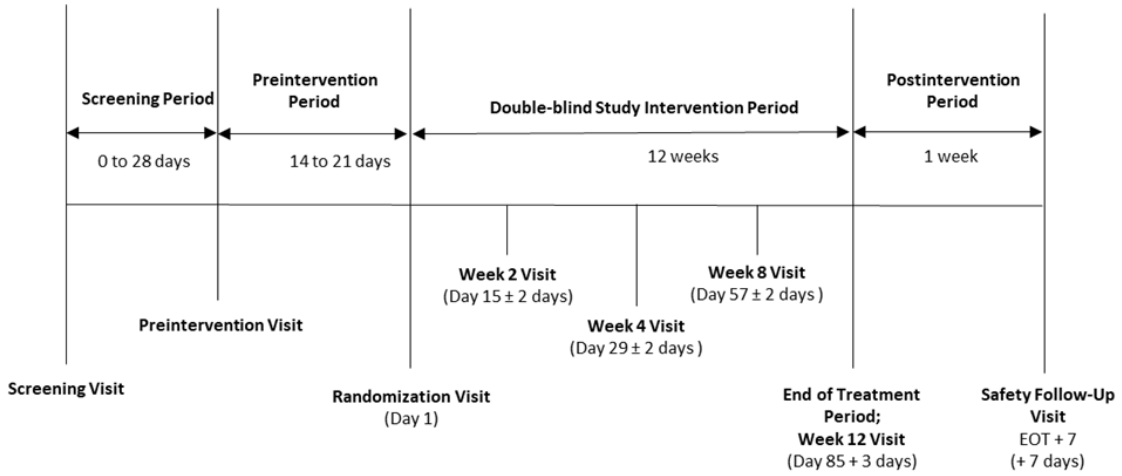
Part 2: Once daily administration of linaclotide 72 µg for a 24-week study intervention period is safe and well tolerated in pediatric subjects, 2 to 5 years of age, with FC.

2.2 Study Design Overview

Study M21-572 is a Phase 3, multicenter, 2-Part safety and efficacy study in pediatric subjects aged 2 to 5 years who meet modified Rome IV criteria for childhood FC.

Part 1 is a randomized, double-blind (DB), placebo-controlled, parallel-group, confirmatory safety and efficacy portion of the study comparing linaclotide 72 µg and placebo. Part 1 of the study includes a screening period, a preintervention period, a 12-week double-blind study intervention period, and 1-week postintervention period. The Part 1 schematic of the study is shown in Figure 1.

Figure 1. Part 1 Study Schematic



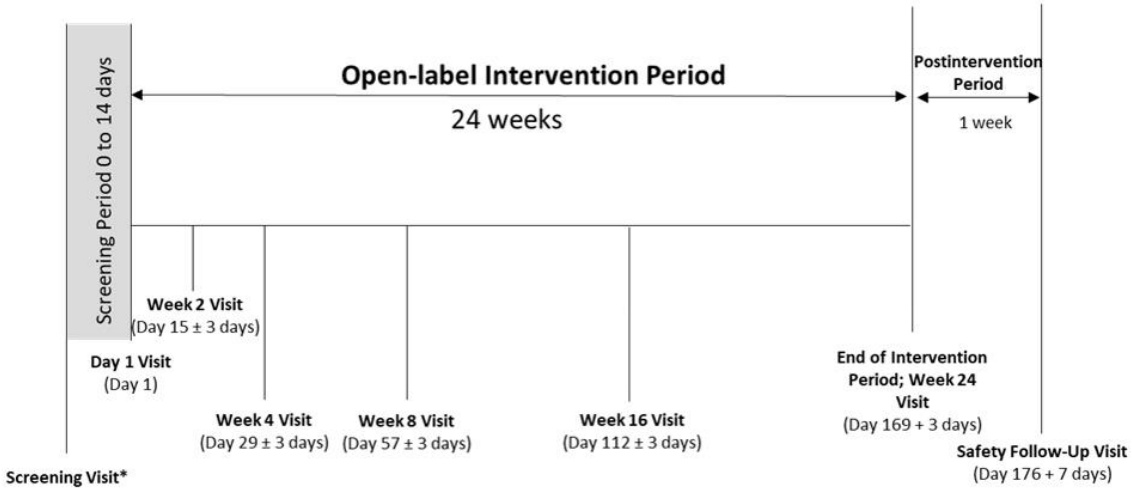
Note: Zero days for the screening period are for subjects who do not require the 1 or 14 day washout and can go directly into the preintervention period as long as they meet eligibility criteria. Minimum 14 days for the screening period is only applicable to subjects requiring a 14 day washout. See protocol for further information regarding the washout period. Laboratory results must be reviewed by the investigator before Randomization Visit (Day 1). The Safety Follow Up Visit is required only for those subjects who do not continue to Part 2 of the study.

Part 2 is an open-label (OL), long-term safety extension study with 24 weeks of linaclotide exposure that will enroll pediatric subjects with FC who completed study intervention in Part 1 of Study M21-572 or the Phase 2 Study LIN-MD-67. All subjects who were on 72 µg dose or placebo in Part 1 or are entering from Study LIN-MD-67 will be assigned to open label linaclotide 72 µg during the start of Part 2. Study LIN-MD-67 subjects who enroll into Part 2, as well as subjects who enroll > 28 days from the last dose of Part 1, will have a screening visit. Subjects completing Part 1 of this study can decide to enroll in Part 2 at the 12 Week Visit, in which case, the 12 Week Visit of Part 1 will also serve as the first visit of Part 2. The Part 2 schematic of the study is shown in Figure 2.

For subjects with poor tolerability, they can temporarily interrupt the study drug for up to 3 days and resume the same dose if tolerability improves. If not, subjects will discontinue

the investigational drug per the Discontinuation Criteria Section in Section 5.5 of the protocol.

Figure 2. Part 2 Study Schematic



* The Screening Visit is only for subjects rolling over from Study LIN MD 67 and subjects who enroll > 28 days from the last dose of Part 1.

2.3 Treatment Assignment and Blinding

In **Part 1**, subjects will be randomized in a 1:1 ratio to receive either linaclotide or placebo during the double-blind study intervention period. For **Part 2**, subjects will receive open-label linaclotide during the open-label extension period.

For Part 1, the randomization will be stratified by age group (2 to 3 years of age and 4 to 5 years of age).

All AbbVie personnel with direct oversight of the conduct and management of the trial (except for the AbbVie Drug Supply Management Team), the investigator, study site personnel, and the subject/parent/guardian/LAR (legally authorized representative) will remain blinded to each subject's double-blind treatment throughout the study. To maintain the blind, the linaclotide capsules and placebo capsules provided for the study will be

identical in appearance. The IWRS will provide access to unblinded subject treatment information in the case of a medical emergency.

2.4 Sample Size Determination

Part 1

The sample size for this study was based on the primary efficacy endpoint. Based on the Phase 2 Study (LIN-MD-67) and the data from the 6- to 11-year-old FC subjects in the Phase 3 Study LIN-MD-64, the expected treatment difference between the linaclotide group and the placebo group on the mean change from baseline in 12-week SBM frequency rate is assumed to be 1.4 SBMs/week with a common standard deviation (SD) of 2.5. Based on these assumptions, a sample size of 52 subjects in each treatment group will have 80% power to detect the 1.4 SBM treatment difference between the linaclotide group and the placebo group using a two-sample t-test at a two-sided 0.05 significant level. An additional 12 subjects are to be enrolled to allow for dropouts from the study, resulting in a total sample size of 116 subjects for the study.

Part 2

Subjects who completed Part 1 of Study M21-572 or the Phase 2 Study LIN-MD-67 are planned to be enrolled in this Part 2 long-term safety extension of Study M21-572. However, the actual number of subjects in this study will depend on the number of subjects who complete the lead-in studies and are eligible to be enrolled into this long-term safety extension after fulfilling the eligibility criteria.

3.0 Endpoints

3.1 Primary Endpoint

The primary efficacy endpoint is the change from baseline in 12-week spontaneous bowel movement (SBM) frequency rate (SBMs/week) observed by the primary caregiver during the double-blind study intervention period.

3.2 Secondary Endpoints

The secondary efficacy endpoints are:

- The change from baseline in 12-week stool consistency observed by the primary caregiver during the double-blind study intervention period
- The change from baseline in 12-week straining observed by the primary caregiver during the double-blind study intervention period
- The change from baseline in 12-week proportion of days with fecal incontinence observed by the primary caregiver during the double-blind study intervention period (for subjects who have acquired toileting skills during daytime and nighttime or acquired toileting skills during daytime only)

3.3 Additional Efficacy Endpoints

The additional efficacy endpoints for **Part 1** are:

- The achievement of no longer meeting modified Rome IV criteria for FC at the end of the 12-week double-blind study intervention period
- The global change in symptoms and the global severity of symptoms at each week during the study intervention period
- The use of rescue medication during the study intervention period
- The decrease in the use of rescue medication from baseline during the study intervention period
- The achievement of overall SBM response during the study intervention period (defined as a change from baseline of ≥ 2 SBMs/week during the study intervention period for SBMs observed by the primary caregiver and all SBMs reported)

The additional efficacy endpoints for **Part 2** are:

- The achievement of no longer meeting modified Rome IV criteria for FC at the end of the 24-week, long-term extension period

3.4 Safety Endpoint

The safety endpoints are adverse events (AEs) or safety findings by clinical laboratory assessments (clinical chemistry, complete blood count [CBC]), vital sign measurements (including postural vital signs), electrocardiograms (ECGs), physical examinations, height, and weight.

4.0 Analysis Populations

The following population sets will be used for the analyses.

Intent-to-Treat (ITT) Populations

The ITT population for the 12-week DB study intervention period (Part 1) (denoted by **ITT1**) includes all randomized subjects who received at least one dose of double-blinded study drug in Part 1. The ITT1 population will be used for all efficacy and baseline analyses for Part 1. For ITT1 population, subjects will be included in the analysis according to the treatment group that they are randomized to.

The ITT population for the 24-week OL treatment extension period (Part 2) (denoted by **ITT2**) includes all subjects who received at least one dose of linaclotide in Part 2.

Safety Populations

The safety population for Part 1 (denoted by **SA1**) includes all randomized subjects who received at least one dose of study drug in Part 1.

The safety population for Part 2 (denoted by **SA2**) includes all subjects who received at least one dose of linaclotide in Part 2.

For the safety populations, subjects are assigned to a treatment group based on the "as treated" treatment group, regardless of the treatment randomized. The "as treated" will be determined by the most frequent dose regimen received in the treatment period.

5.0 Subject Disposition

A summary of subject accountability by investigator will be provided where the number of subjects in each of the following categories will be tabulated for each treatment group for **Part 1** and **Part 2**:

- Subjects randomized (Part 1) or enrolled (Part 2) in the study;
- Subjects who took at least one dose of study treatment;
- Subjects who completed study treatment;
- Subjects who prematurely discontinued study treatment;
- Additional summary for **Part 2**
  - Subjects who received placebo in Part 1 or LIN-MD-67
  - Subjects who enrolled from study LIN-MD-67

The summary of subject accountability by investigator will also include the number of subjects screened and subjects who failed screening.

The number and percentage of subjects in the ITT population who prematurely discontinued study treatment will be summarized by reason for not completing study treatment overall and by treatment group.

6.0 Study Treatment Duration and Compliance

6.1 Study Treatment Duration

For the Safety Population, duration of treatment will be summarized for each treatment group, for **Part 1** and **Part 2**. Duration of treatment is defined for each subject as last dose date minus first dose date + 1. Duration of treatment will be summarized using the number of subjects treated, mean, standard deviation, median, minimum and maximum. In addition, the number and percentage of subjects in each treatment duration interval will be summarized:

- Part 1: ≤ 2 weeks, > 2 - ≤ 4 weeks, > 4 - ≤ 8 weeks, > 8 - ≤ 12 weeks, > 12 weeks
- Part 2: ≤ 4 weeks, > 4 - ≤ 8 weeks, > 8 - ≤ 12 weeks, > 12 - ≤ 18 weeks, > 18 - ≤ 24 weeks, > 24 weeks

Additionally, total continuous exposure with any linaclotide doses across Part 1 and Part 2 of the study will be summarized. Subjects who received linaclotide, completed Part 1, and enrolled in Part 2 within 28 days from last study intervention will be considered to have continuous exposure. The continuous exposure of linaclotide will be calculated as the sum of the exposure from Part 1 and Part 2. The number and percentage of subjects will be summarized.

- Part 1 and Part 2: ≥ 4 weeks, ≥ 12 weeks, ≥ 24 weeks, ≥ 36 weeks

6.2 Treatment Compliance

Treatment compliance will be summarized for the entire treatment period for the Safety Population in Part 1 and Part 2, separately. Treatment compliance is defined as the number of capsules actually taken by a subject divided by the number of capsules expected for the same period multiplied by 100. The number of capsules expected to be taken in a specific treatment period will be calculated by multiplying the number of days in that period by the number of capsules to be taken per day. Percent compliance will be summarized.

6.3 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 the primary caregivers on an electronic diary (eDiary). eDiary compliance will be assessed based on the number of days with fully completed eDiary assessments by the primary caregiver in a specific period. The eDiary can only be considered fully completed if the primary caregiver responded to every question in the eDiary. eDiary compliance will be

summarized for the preintervention period, and the double-blind intervention period, and for each week within each period based on the ITT Population.

Compliance for each subject/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 entry administered before the randomization time will be included in preintervention period.

7.0 Subject Characteristics

Categorical variables will be summarized with the number and percentage of subjects. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum and maximum).

7.1 Demographics and Baseline Characteristics

Demographics and baseline or disease characteristics will be summarized descriptively, overall and by treatment group for the ITT (ITT1 and ITT2) population. Unless otherwise specified, baseline is defined as the last non-missing value prior to the first administration of study treatment.

Continuous demographic variables include age, weight, and height.

Categorical demographic variables include:

- Sex
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race
- Age: 2-3, 4-5 years (inclusive)
- Region (Europe, North America, or Other)

Continuous disease characteristics variables include:

- spontaneous bowel movement (SBM) frequency rate (SBMs/week)
- stool consistency
- straining
- proportion of days with fecal incontinence

7.2 Medical History and Prior and Concomitant Medications

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. The number and percentage of subjects in each medical history category (by MedDRA system organ class (SOC) and preferred term) will be summarized overall and by treatment group. The SOC will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term).

Prior and concomitant medications will be summarized separately. The number and percentage of subjects taking prior and concomitant medications will be summarized by generic drug name based on the World Health Organization (WHO) Drug Dictionary. The actual version of the WHO Drug Dictionary will be noted in the statistical tables and clinical study report.

All medical history and concomitant medications summaries will be performed for the Safety Population (SA1 and SA2).

7.3 Protocol Deviations

For each of the following protocol deviation categories and across all categories, the number and percentage of randomized subjects with at least one protocol deviation will be summarized overall and by treatment group for the ITT Population (ITT1 and ITT2):

- Subject entered the study even though did not satisfy entry criteria;
- Subject developed withdrawal criteria during the study but was not withdrawn;
- Subject received wrong treatment or incorrect dose of study treatment;
- Subject took prohibited concomitant medication.

8.0 Handling of Potential Intercurrent Events for the Primary and Secondary Endpoints

Potential intercurrent events considered in this study include 1) the use of rescue medication; 2) premature discontinuation of study drug and; 3) study drug interruption. The primary endpoint (defined in Section 3.1) and the secondary endpoints (defined in Section 3.2) will be analyzed on the ITT population. Intercurrent events will be handled using the following methods for the efficacy analysis.

8.1 Use of Rescue Medication

The BMs for the subjects who took a laxative, enema, or suppository on the calendar day of the BM or the calendar day before the BM will not be considered as SBMs for the analysis. This is a Composite Strategy since the occurrence of the intercurrent event is taken to be a component of the SBM definition (defined in Section 9.1).

8.2 Premature Discontinuation of Study Drug

Subjects who discontinue prematurely during but prior to the completion of the double-blind study intervention period will have their eDiary data included up to the last dose date for the primary endpoint. This is a While-On-Treatment Strategy for analysis using ANCOVA model and a Hypothetical Strategy for analysis using mixed effect model

for repeated measures (MMRM).

8.3 Study Drug Interruption Due to Poor Tolerability

Subjects who have study drug interruption due to poor tolerability (identified based on action taken with "drug interrupted" on Adverse Events eCRF) will have their eDiary data included as observed (AO) (i.e., regardless of interruption of study drug). This is a Treatment-Policy Strategy given the data collected for the endpoint are used regardless of whether the intercurrent event occurs.

9.0 Efficacy Analyses

9.1 General Considerations

All efficacy analyses will be conducted on the ITT 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 and 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. Primary caregiver-observed SBMs are defined as SBMs reported in the eDiary for which the primary caregiver identified being with the child for. All reported SBMs are defined as the total number of SBMs reported in the eDiary, including those SBMs not directly observed by the primary caregiver.

Baseline SBM weekly rates, stool consistency for primary caregiver-observed SBMs, and straining for primary caregiver-observed SBMs will be derived as discussed in Appendix B from 14 days prior to randomization and up to the time of randomization. A subject's baseline stool consistency and straining reported for primary caregiver-observed SBMs cannot be assessed if the subject does not have at least 1 primary caregiver-observed SBM during the preintervention period. For subjects with no primary caregiver-observed SBMs reported in the eDiary during a study period, the consistency

and straining assessments reported by primary caregiver will be considered missing for that study period in the analyses. Subjects with missing baseline consistency and straining reported by the primary 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.

Post-baseline SBM weekly rates, stool consistency for primary caregiver-observed SBMs, and straining for primary caregiver-observed SBMs will be derived as discussed in Appendix B for each analysis period, including weekly and study intervention period.

The overall type I error rate of the primary and secondary endpoints will be controlled using the fixed sequence multiple testing procedure (Section 13.0). All statistical tests will be carried out at a 2-sided 5% significance level. Statistical inferences along with the corresponding 2-sided 95% confidence intervals will be provided, unless stated otherwise.

9.2 Handling of Missing Data

Sensitivity analyses to handle missing data are planned for only the primary and secondary efficacy endpoints.

9.2.1 Missing at Random (MAR)

To handle missing data in the nature of MAR, change from baseline in SBM frequency rate/week will be analyzed using a mixed effect model for repeated measures (MMRM) with study intervention, week, age group (2 to 3 years of age and 4 to 5 years of age), and study intervention-by-week interaction as fixed effects and baseline value as a covariate. All 12-week data will be included in the MMRM model. In this analysis, if a subject has less than 4 completed daily diary days in a postbaseline week during the study intervention period, the corresponding postbaseline week value will be considered missing for that subject. The study intervention comparison between linaclotide group and placebo group for overall change from baseline in SBM frequency rate (SBMs/week) over the

12-week study intervention period will be estimated from the MMRM model. An unstructured covariance matrix will be used to model the covariance of within-subject-results. If unstructured covariance matrix does not converge, a compound symmetry covariance structure may be used instead. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.[1] Missing values will not be explicitly imputed.

9.2.2 Missing Not at Random (MNAR)

To handle missing data with MNAR, a missing postbaseline week during the intervention period will be imputed using the pattern mixture model with control-based pattern imputation of Ratitch and O'Kelly.[2] Assuming missing values following a premature discontinuation will follow the outcome from the placebo arm. In this analysis, if a subject has less than 4 completed daily diary days in a postbaseline week during the study intervention period, the corresponding postbaseline week value will be considered missing for that subject.

- Intermittent (non-monotone) missing data in both treatment groups are imputed using the MCMC method assuming the MAR.
- Remaining monotone missing data are imputed using a pattern-mixture model approach using a sequential regression imputation model estimated based on data from the placebo arm only.
- The following covariates will be included in the imputation model: age group (2 to 3 years of age and 4 to 5 years of age) and baseline value.
- The following covariates will be included in the analysis model: study intervention, week, age group (2 to 3 years of age and 4 to 5 years of age), and study intervention-by-week interaction as fixed factors and baseline value as a covariate.

Thirty imputed datasets will be generated. Based on each imputed dataset, change from baseline in SBM frequency rate/week will be analyzed using the MMRM model as discussed in the first sensitivity analysis (Section 9.2.1). Model-based estimates within each treatment group and between treatment comparisons will be obtained for the change

from baseline in 12-week SBM frequency rate with each imputed dataset using MMRM. The estimates will be combined using standard multiple imputation analysis techniques (via PROC MIANLYZE in SAS Version 9.4 or newer) to provide a single within-group estimate, the single estimate of the difference between linaclotide and placebo, associated 95% CI and p-value for linaclotide versus placebo comparison.

9.2.3 Tipping Point Analysis

Two stages of tipping point analysis will be conducted as a sensitivity analysis: stage one is to impute missing data using multiple imputation (MI) under missing at random (MAR) assumption, and stage two relies on the assumption of missing not at random (MNAR) to adjust the multiple imputed values by a pre-specified set of shift parameters for each treatment group independently. The tipping points are outcomes where the significance of the treatment effect is reversed.

The steps for conducting a two-dimensional tipping point analysis using PROC MI for the primary efficacy endpoints are described below:

- Step 1: In each treatment group, missing data with non-monotone patterns will be imputed via MI under MAR assumption using observed data and PROC MI to create 30 datasets with only a monotone missing pattern.
- Step 2: Pre-specify the set of shift parameters K1 for the linaclotide group and K2 for the placebo group (refer to the table below). For given constants, k1 belongs to K1 and k2 belongs to K2, adjust the imputed values by k1 and k2 for each group respectively using the MNAR statement with the MONOTONE option in PROC MI.
- Step 3: For each pair of pre-specified shift parameters (k1, k2), the mixed model used for the primary efficacy analysis will be applied for each of the 30 complete datasets.
- Step 4: Integrate the analysis results across 30 datasets by Rubin's rule using PROC MIANALYZE.

If one pair of shift parameters is found to reverse the study conclusion, i.e., p-value larger than 0.05, then the shift parameters are identified as the tipping point. The analysis results for a grid of shift parameter combinations will be provided in tabular format.

Pre-defined Shifts Parameters	
Linaclotide: specified K1	Placebo: specified K2
-1	1
-2	2
-3	3

Note: Assume the bigger the value the better the drug effect, the K1 and K2 will need to be adjusted based on the real data at the end of the study.

9.2.4 Imputing Missing Data with Worst Response

To impute missing data with the worst response, the process is conducted by imputing the post-baseline missing daily data during study intervention period in the specific diary with the worst response for SBM (a missing BM is assumed to be "0" and a missing rescue medication response is assumed to be "YES"). Based on this imputed data, the primary efficacy endpoint will be analyzed using the MMRM model under MAR.

9.3 Primary Efficacy Endpoint and Analyses

9.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in 12-week overall SBM frequency rate (SBMs/week) observed by the primary caregiver during the double-blind study intervention period. The SBM frequency rate per week during the study intervention period will be derived based on the number of SBMs observed by the primary caregiver during this period in the daily assessments on the eDiary. The details of the derivation of this efficacy endpoint are provided in Appendix B.

9.3.2 Main Analysis of Primary Efficacy Endpoint

The statistical null hypothesis for the primary endpoint is as follows: linaclotide 72 µg is the same as placebo with respect to the primary efficacy endpoint. This hypothesis will be

tested under the assumption of Missing Not at Random (MNAR) for missing data as specified in Section 9.2.2. This analysis will be based on ITT1 population.

The attributes of the estimand corresponding to the primary efficacy objective are summarized in Table 1.

Table 1. Summary of the Estimand Attributes Corresponding to the Primary Efficacy Objective

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Primary	linaclotide and placebo (see Section 3.1)	Change from baseline in 12-week SBM frequency rate (SBMs/week) observed by the primary caregiver during the study intervention period	ITT1	IE1: use of any rescue therapy for the treatment of FC IE2: premature discontinuation of study drug IE3: study drug interruption due to poor tolerability All data occurred on the day of or the day after IE1 will not be used. All data after IE2 will not be used. All data during and after IE3 will be used. See Section 8.0.	Mean change from baseline in 12-week SBM frequency rate (SBMs/week) during the study intervention period in linaclotide and placebo

9.3.3 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint

The following sensitivity analyses on handling the missing data will be performed to assess the robustness of the primary efficacy analysis under the assumption of MNAR:

- Sensitivity Analysis 1: MMRM Under the Assumption of MAR; missing values are not explicitly imputed (see Section 9.2.1 for details).

- Sensitivity Analysis 2: An analysis of covariance (ANCOVA) model with study intervention, age group (2 to 3 years of age and 4 to 5 years of age) as fixed factors and baseline value as a covariate.
- Sensitivity Analysis 3: Tipping Point Analysis (see Section 9.2.3 for details).
- Sensitivity Analysis 4: Imputing Missing Data with Worst Response (see Section 9.2.4 for details).
- Sensitivity Analysis 5: SBM frequency rate (SBMs/week) is calculated based on the average SBM among non-missing diaries using MMRM model under MAR:

$$\text{SBM Frequency Rate} = \frac{\text{Number of SBMs observed by the primary caregiver during the week}}{\text{Number of nonmissing diaries during the week}} \times 7.$$

As a supplementary analysis of the primary endpoint, the change from baseline in 12-week SBM frequency rate (SBMs/week) including all SBMs reported during the study intervention period will be summarized. Another supplemental analysis excluding subjects with baseline SBM frequency rate ≥ 3 SBMs/week from the primary efficacy endpoint will be conducted. The supplementary analyses will be conducted using the same main analysis as the primary endpoint.

9.4 Secondary Efficacy Endpoints and Analyses

9.4.1 Secondary Efficacy Endpoints

There are three secondary efficacy endpoints in this study which are:

- The change from Baseline in 12-week stool consistency observed by the primary caregiver during the double-blind study intervention period
- The change from Baseline in 12-week straining observed by the primary caregiver during the double-blind study intervention period
- The change from baseline in 12-week proportion of days with fecal incontinence observed by the primary caregiver during the double-blind study

intervention period (for subjects who have acquired toileting skills during daytime and nighttime or acquired toileting skills during daytime only)

9.4.2 Main Analyses of Secondary Efficacy Endpoints

The statistical null hypothesis for the secondary endpoints is as follows: linaclotide 72 µg is the same as placebo with respect to the secondary efficacy endpoints. This hypothesis will be tested under the assumption of MNAR for missing data as specified in Section 9.2.2. This analysis will be based on ITT1 population.

The attributes of the estimands corresponding to the secondary efficacy objectives are summarized in Table 2.

Table 2. Summary of the Estimand Attributes Corresponding to the Secondary Efficacy Objectives

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Secondary	linaclotide and placebo (see Section 3.2)	Change from Baseline in 12-week stool consistency observed by the primary caregiver during the study intervention period	ITT1	IE1: use of any rescue therapy for the treatment of FC IE2: premature discontinuation of study drug IE3: study drug interruption due to poor tolerability All data occurred on the day of or the day after IE1 will not be used. All data after IE2 will not be used. All data during and after IE3 will be used. See Section 8.0	Mean change from Baseline in 12-week stool consistency observed by the primary caregiver during the study intervention period in linaclotide and placebo

Estimand Label	Attributes of the Estimand				
	Treatment	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Secondary	linaclotide and placebo (see Section 3.2)	Change from Baseline in 12-week straining observed by the primary caregiver during the study intervention period	ITT1	IE1: use of any rescue therapy for the treatment of FC IE2: premature discontinuation of study drug IE3: study drug interruption due to poor tolerability All data occurred on the day of or the day after IE1 will not be used. All data after IE2 will not be used. All data during and after IE3 will be used. See Section 8.0	Mean change from Baseline in 12-week straining observed by the primary caregiver during the study intervention period in linaclotide and placebo
Secondary	linaclotide and placebo (see Section 3.2)	Change from baseline in 12-week proportion of days with fecal incontinence observed by the primary caregiver during the study intervention period	ITT1 among subjects who have acquired toileting skills during daytime and nighttime or acquired toileting skills during daytime only	IE1: use of any rescue therapy for the treatment of FC IE2: premature discontinuation of study drug IE3: study drug interruption due to poor tolerability All data occurred on the day of or the day after IE1 will not be used. All data after IE2 will not be used. All data during and after IE3 will be used. See Section 8.0	Mean change from Baseline in 12-week proportion of days with fecal incontinence observed by the primary caregiver during the study intervention period in linaclotide and placebo (for subjects who have acquired toileting skills during daytime and nighttime or acquired toileting skills during daytime only)

9.4.3 Sensitivity and Supplementary Analyses for Secondary Efficacy Endpoints

The following sensitivity analyses will be performed for the first two secondary efficacy endpoints (stool consistency and straining):

- Sensitivity Analysis 1: MMRM Under the Assumption of MAR; missing values are not explicitly imputed (see Section 9.2.1 for details).
- Sensitivity Analysis 2: ANCOVA model with study intervention, age group (2 to 3 years of age and 4 to 5 years of age) as fixed factors and baseline value as a covariate. This analysis will be based on all available data and ITT1 population.
- Sensitivity Analysis 3: Impute missing data (responses with "I don't know") with worst response, missing postbaseline stool consistency and straining value for primary caregiver-observed SBMs during the study intervention period will be imputed as Type 1 (Separate hard lumps, like nut) and "Yes, a lot," respectively.
- Sensitivity Analysis 4: A subject needs to have at least 4 non-missing daily scores (consider responses of "I don't know" as missing) in the corresponding week to be counted as having a non-missing score for that week.
- Sensitivity Analysis 5: A subjects' missing baseline consistency and straining scores, due to the absence of any SBM during the baseline period, are assigned the worst possible scores at baseline (i.e., Bristol Stool Form Scale Type 1 for consistency and straining score 2).

Sensitivity analyses 3, 4, and 5 will be performed using MMRM model under MAR.

The following sensitivity analyses will be performed for the third secondary efficacy endpoint (fecal incontinence):

- Sensitivity Analysis 1: ANCOVA model with study intervention, age group (2 to 3 years of age and 4 to 5 years of age) as fixed factors and baseline value as a covariate.

- Sensitivity Analysis 2: a subject needs to have at least 4 non-missing daily scores (consider responses of "I don't know" as missing) in the corresponding week to be counted as having a non-missing score for that week. This sensitivity analyses will be performed using MMRM model under MAR.

9.4.4 Supportive Secondary Efficacy Endpoints and Analyses

There are no supportive secondary efficacy endpoints.

9.5 Additional Efficacy Endpoints and Analyses

Additional efficacy endpoints are defined in Section 3.3.

The AO approach will be used for missing data handling in the analyses of categorical efficacy endpoints. Descriptive statistics will be provided for categorical efficacy endpoints for each treatment group. Continuous endpoints will be analyzed using the same MMRM model under MAR.

9.6 Efficacy Subgroup Analyses

The following subgroup analyses will be conducted for the primary and secondary efficacy endpoints. Descriptive statistics (number, mean, median, standard deviation, minimum and maximum for continuous data) will be provided.

- Sex (male, female)
- Age (2 to 3 and 4 to 5 years)
- Race (White, Not White)

10.0 Safety Analyses

10.1 General Considerations

Safety analyses will be performed on the safety populations in the 12-week DB period (Part 1, SA1 population) and the 24-week OL treatment extension period (Part 2, SA2 population).

The Baseline for safety analysis will be treatment dependent. For SA1 population, laboratory and vital signs measurements, the Baseline value is defined as the last available measurement before the first study drug administration for each subject. For SA2 population, the Baseline value is defined below:

- If subjects enroll into Part 2 within 28 days of the last dose date of Part 1, the baseline of Part 1 will be used as the baseline value in Part 2.
- If subjects enroll into Part 2 after 28 days of the last dose date of the lead-in study (Part 1 or LIN-MD-67), the last non-missing assessment made before the first dose of the study intervention in this study will be used as the baseline value in Part 2.

10.2 Adverse Events

Adverse events (AEs) will be summarized and presented using primary MedDRA System Organ Classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study report. Specific AEs will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same AE occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

10.2.1 Treatment-Emergent Adverse Events

The Treatment-Emergent Adverse Events (TEAEs) for SA1 and SA2 populations are defined as follows.

Part 1 (SA1 population): TEAEs for Part 1 are defined as events that begin either on or after the first dose of the study drug in Part 1 and whichever are earlier of the following:

- the first dose of study drug in Part 2
- 30 days after the last dose administration of the study drug in Part 1

Part 2 (SA2 population): TEAEs for Part 2 are defined as events that begin either on or after the first dose of OL linaclotide study drug in Part 2 and within 30 days after the last dose administration of the study drug.

Events where the onset date is the same as the study treatment start date are assumed to be treatment-emergent. All TEAEs will be summarized overall, as well as by primary MedDRA SOC and Preferred Term. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

If an incomplete onset date was collected for an AE, the event will be assumed to be treatment-emergent unless there is other evidence that confirms that the event was not treatment-emergent (e.g., the event end date was prior to the study drug start date).

The number and percentage of subjects experiencing TEAEs will be summarized by treatment group if applicable.

10.2.2 Adverse Event Overview

An overview of AEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any TEAE
- Any TEAE related to study treatment according to the investigator

- Any severe TEAE
- Any serious TEAE
- Any TEAE leading to discontinuation of study treatment
- Any TEAE leading to interruption of study treatment
- Any TEAE leading to death
- TEAEs of Special Interest
- All deaths
    - Deaths occurring ≤ 30 days after last dose of study treatment
    - Deaths occurring > 30 days after last dose of study treatment

In addition, an overview of AEs per 100 patient-years of study exposure will be presented for the AE categories defined above. The number of TEAEs reported, the total number of years of study drug exposure, and the TEAE rate per 100 patient-years will be presented.

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

TEAEs will be summarized by SOC and PT; by maximum relationship to study treatment as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and SOC and PT; by maximum severity and SOC and PT; and by subject number and SOC and PT. Specific AEs will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same AE occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

In addition, TEAEs will be summarized by PT and sorted by decreasing frequency for the linaclotide treatment group.

10.2.4 Treatment-Emergent Adverse Events per Patient-Years of Exposure

Exposure-adjusted event rate (EAER) per 100 patient-years will be provided, where EAERs will be reported as events per 100 patient-years and are defined as the number of TEAEs divided by the total exposure in 100 patient-years:

100 * (Number of TEAEs) / (Total Patient-Years)

where total patient-years is defined as the sum of the study drug exposure of all subjects, normalized by 365.25, and rounded to 1 decimal place. Note that one event per preferred term per day per subject will be counted in the calculation of the number of AEs (i.e., a preferred term will not be counted twice on the same day for the same subject).

The EAER summary will be provided for each AE category in the AE overview summary (defined in Section 10.2.2) and for the TEAE summary by SOC and PT.

10.2.5 Deaths, Serious Adverse Events, and Adverse Events Leading to Study Treatment Discontinuation

SAEs (including deaths) and AEs leading to study drug discontinuation will be summarized by SOC and PT and additional listing formats will be provided.

10.2.6 Treatment Emergent Adverse Events of Special Interest

The treatment emergent adverse events of special interest (AESIs) including significant volume depletion and/or significant electrolyte abnormalities andor ECG abnormalities that are considered by the investigator or sponsor to be related to diarrhea will be monitored throughout this study.

The number and percentage of subjects with AESIs during the study will be tabulated by preferred term. AESIs will also be provided in a listing.

10.2.7 Diarrhea Treatment Emergent Adverse Events

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

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

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

Additional summaries for other TEAEs from patients with diarrhea will be summarized.

10.3 Analysis of Laboratory Data

Data collected from central and local laboratories, including additional laboratory testing due to an SAE, will be used in all analyses, except for Baseline where SAE-related

laboratory assessments on or before the first dose of study drug will be excluded. The clinical laboratory tests defined in the protocol operations manual (e.g., hematology, clinical chemistry, urinalysis) will be summarized.

Each laboratory variable will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from baseline to each applicable postbaseline visit will be summarized for selected laboratory variables, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error, and 95% confidence interval will be presented for the mean change from baseline within each treatment group.

Changes in laboratory parameters will be tabulated using shift tables categorized as low, normal, or high based on the normal ranges of the laboratory used for each sample. A shift table from baseline to minimum and maximum value (based on normal range) will be created. A similar shift table will be provided to summarize shifts from baseline to the final postbaseline value.

Laboratory abnormalities meeting CTC criteria grade 3 and 4, with a grade worsening compared to baseline, will be summarized. Toxicity grading scale is based on National Cancer Institute Common Toxicity Criteria (NCI CTC) AE version 4.03. The number and percentage of subjects who have a laboratory value meeting the criteria will be summarized by treatment group. Listings will be provided to summarize subject-level laboratory data for subjects meeting the criteria.

Laboratory abnormalities will be evaluated based on Potentially Clinically Important (PCI) criteria (Appendix C). For each laboratory PCI criterion, the number and percentage of subjects who have a laboratory value meeting the criteria will be summarized by treatment group. Listings will be provided to summarize subject-level laboratory data for subjects meeting PCI criteria. The percentages will be calculated relative to the number of subjects with available non-PCI baseline values and at least 1 postbaseline assessment for the assessment period. The numerator will be the total number of subjects with available

non-PCI baseline values and at least 1 PCI postbaseline assessment for the assessment Period. A supportive tabular display of subjects with PCI postbaseline values will be provided.

Potential Hy's Law

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

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

Assessment of Liver Enzyme and Bilirubin Elevations

The liver-specific laboratory tests include the serum glutamic pyruvic transaminase (SGPT/ALT), serum glutamic-oxaloacetic transaminase (SGOT/AST), alkaline phosphatase (ALP), and total bilirubin (TBL). The frequencies and percentages of subjects with post baseline liver specific function test values that meet the following criteria of potential clinical interest will be summarized by treatment group:

- ALT ≥ 3 × ULN
- ALT ≥ 5 × ULN
- ALT ≥ 10 × ULN
- ALT ≥ 20 × ULN
- AST ≥ 3 × ULN
- AST ≥ 5 × ULN
- AST ≥ 10 × ULN
- AST ≥ 20 × ULN
- TBL ≥ 2 × ULN
- ALP ≥ 1.5 × ULN

- ALT or AST ≥ 3 × ULN
- ALT and/or AST ≥ 3 × ULN and TBL ≥ 1.5 × ULN
- ALT and/or AST ≥ 3 × ULN and TBL ≥ 2 × ULN
- ALT or AST ≥ 5 × ULN for more than 2 weeks
- ALT or AST ≥ 8 × ULN

where ULN is the upper normal limit. The maximum ratio relative to the ULN will be used to determine if subjects meet any of the criteria listed above.

A listing of potentially clinically significant liver function laboratory values will be provided. The listing will include all subjects who meet any of the following 4 criteria:

- ALT ≥ 3 × ULN, or
- AST ≥ 3 × ULN, or
- ALP ≥ 1.5 × ULN, or
- TBL ≥ 1.5 × ULN.

10.4 Analysis of Vital Signs

Descriptive statistics for vital signs (i.e., temperature, body weight, height, 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 treatment group.

Vital sign values will be considered PCI if they meet both the observed-value criteria and the change-from-baseline criteria listed in Table C-4. The number and percentage of subjects with PCI postbaseline values will be tabulated by treatment group for the double-blind intervention period separately. The percentages will be calculated relative to the number of subjects with available non-PCI baseline values and at least 1 postbaseline assessment in the specific period. The numerator will be the total number of subjects with available non-PCI baseline values and at least 1 PCI postbaseline value during the specific period for the corresponding cohort. A supportive tabular display of subjects with PCI

postbaseline values will be provided, including the PID number, baseline and all postbaseline (including non-PCI) values.

10.5 Other Safety Analyses

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 treatment group within each cohort. The QTc will be calculated using both the Bazett and Fridericia corrections.

Electrocardiographic parameter values are considered PCI if they meet or exceed the higher-limit PCI criteria listed in Table C-5. The number and percentage of subjects with PCI postbaseline ECG values will be tabulated by treatment group for the double-blind invention period. The percentages will be calculated relative to the number of subjects with available non-PCI 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 subjects with available non-PCI baseline values and at least 1 PCI postbaseline value for the double-blind intervention period of the corresponding cohort. A supportive tabular display of subjects with PCI postbaseline values will be provided, including the PID number, baseline, all postbaseline (including non-PCI) values, and change from baseline. In this listing, any subject with PCI value (if any) during postintervention period will also be included.

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

A shift table from baseline to the end of double-blind intervention period in the central reader's overall interpretation of the ECG will be presented by treatment group within each cohort for the following categories: normal and abnormal.

10.6 Safety Subgroup Analyses

Subgroup analyses for age group (2 to 3 years of age and 4 to 5 years of age) will be performed for the summaries of TEAEs.

11.0 Other Analyses

Not applicable.

12.0 Interim Analyses

Interim analysis(es), which includes both safety and efficacy analyses, will be conducted and unblinded to the Sponsor after all subjects have completed or prematurely discontinued during Part 1. The analysis of efficacy for Part 1 will be considered final. Available Part 2 data will be analyzed if needed.

A final analysis will be completed after all subjects have completed both parts of the study.

12.1 Data Monitoring Committee

An external data monitoring committee (DMC) composed of persons independent of AbbVie and with relevant expertise in their field will review unblinded safety data from the ongoing study. The primary responsibility of the DMC will be to protect the safety of the subjects participating in this study.

A separate DMC charter describes the roles and responsibilities of the DMC members, frequency of data reviews, relevant data to be assessed, and general operations.

13.0 Overall Type I Error Control

The overall type I error rate of the primary and secondary endpoints will be controlled using the fixed sequence multiple testing procedure. Specifically, the testing will utilize the endpoint sequence of the primary and secondary endpoints in the order as specified in Section 3.1 and Section 3.2 at the α level of 0.05 (two-sided).

No multiplicity adjustment will be applied to the additional efficacy endpoints listed in Section 3.3. The analysis for additional efficacy endpoints will be performed at the nominal α level of 0.05 (two-sided).

14.0 Version History

Table 3. SAP Version History Summary

Version	Date	Summary
1.0	23 November 2022	Initial version
2.0	14 September 2023	• [redacted]

Version	Date	Summary
3.0	29 January 2024	[redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] or the secondary efficacy endpoint (Section 9.4.3)
4.0	06 November 2024	• [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]

Version	Date	Summary
5.0	04 March 2025	[redacted]
6.0	02 April 2025	[redacted]

15.0 References

1. Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics. 1997;53(3):983-97.
2. Ratitch B, O'Kelly M. Implementation of Pattern-Mixture Models Using Standard SAS/STAT Procedures. Paper presented at: In Proceedings of PharmaSUG (Pharmaceutical Industry. SAS Users Group); 2011; Nashville, TN. Paper SP04. Available from: https://www.pharmasug.org/proceedings/2011/SP/PharmaSUG-2011-SP04.pdf.

Appendix A. List of SAP Signatories

Name	Title	Role/Functional Area
[redacted]		Author
		Clinical Statistics
		Statistical Programming
		Medical/Scientific Monitor

Appendix B. Variable Derivation

Missed eDiary Assessments

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

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.

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.

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 subject'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 subject'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 subject's "weeks" may not be exactly 7 days in duration (e.g., a subject 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 primary 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:

Weekly Frequency Rate (Specific Period)

$$\frac{\text{Total number of SBMs reported by a caregiver during the specific period}}{\text{Number of days during the specific period}} * 7$$

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

Stool Consistency

The primary 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 bowel movement #X you were with the child for"

Type 1: Separate hard lumps, like nuts

Type 2: Sausage-shaped but lumpy

Type 3: Like a sausage, but with cracks on the surface

Type 4: Like a sausage or snake, smooth and soft

Type 5: Soft blobs with clear cut edges

Type 6: Fluffy pieces with ragged edges, a mushy stool

Type 7: Watery, no solid pieces.

I don't know.

"I don't know" is considered as a missing BSFS score. A subject's stool consistency score for the study intervention period will be the average of the non-missing BSFS scores for the primary caregiver-observed SBMs during that specific period.

Straining

If the primary 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:

For the bowel movement #X you were with the child for, did he/she grunt like he/she was straining?

- 0 No, not at all
- 1 Yes, a little
- 2 Yes, a lot
- I don't know

For the bowel movement #X you were with the child for, did he/she make a face like he/she was straining?

- 0 No, not at all
- 1 Yes, a little
- 2 Yes, a lot
- I don't know

"I don't know" is considered as a missing response. The subject's average straining score for each primary caregiver-observed BM will be derived based on the average of nonmissing responses of the two straining questions. The subject's straining score will be the average of the nonmissing average straining scores for all the primary caregiver-observed SBMs during the specific period.

Fecal Incontinence (For Subjects 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, modified daily diary, or clinic diary and responses will be carried through to the completion of the study.

Caregivers will be asked the following:

Is the child (please select one):

- Toilet trained for bowel movements both during the day and in bed at night
- Toilet trained for bowel movements during the daytime only
- Not toilet trained for bowel movements

Caregivers who choose the first response option for toilet training status ("Toilet trained for bowel movements both during the day and in bed at night") at the start of the study will be presented with the following question assessing daily fecal incontinence throughout the course of the study:

Did the child have a pooping accident (pooped in his/her underwear) in the past 24 hours?

- Yes
- No
- I don't know

Caregivers who choose the second option for toilet training status ("Toilet trained for bowel movements during the daytime only") at the start of the study will be presented with the following question assessing daily fecal incontinence throughout the course of the study:

Did the child have a pooping accident (pooped in his/her underwear) today?

- Yes
- No
- I don't know

"I don't know" is considered as a missing response. Any "yes" response for the question related to the occurrence of a pooping accident will be counted as presence of fecal incontinence in the corresponding day.

The proportion of days with fecal incontinence during the analysis week and the study intervention period will be derived based on number of non-missing reported days with fecal incontinence responses during the analysis week and the study intervention period in the denominator, respectively.

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 study intervention period and the global change item will be completed beginning at one week after Randomization through the study intervention period.

Global Change Item

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

Please choose the response below that best describes the overall change in your child's constipation since he/she started taking the study medication.

- 0 Much better
- 1 A little better
- 2 No change
- 3 A little worse
- 4 Much worse

Global Severity Item

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

How would you rate the severity of the child's constipation over the past 7 days?

- 0 None
- 1 Mild
- 2 Moderate
- 3 Severe
- 4 Very severe

Appendix C. Potentially Clinically Important Criteria for Safety Endpoints

The criteria for Potentially Clinically Important (PCI) laboratory findings are described in Table C-1, Table C-2, and Table C-3, and the PCI criteria for vital sign findings are described in Table C-4.

Table C-1. Criteria for Potentially Clinically Important Hematology Values

		Definition of Potentially Clinically Important	
Hematology Variables	**Units**	**Very Low**	**Very High**
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

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

Table C-2. Criteria for Potentially Clinically Important Chemistry Values

		Definition of Potentially Clinically Important	
Chemistry Variables	**SI Units**	**Lower Limit**	**Higher Limit**
Albumin	g/L	< 0.9 × LLN	> 1.1 × ULN
Alanine aminotransferase (ALT)	U/L	—	≥ 3 × ULN
Alkaline phosphatase (ALP)	U/L	—	≥ 1.2 × ULN
Aspartate aminotransferase (AST)	U/L	—	≥ 3 × ULN
Bicarbonate	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Bilirubin, total	µmol/L	—	> 1.5 × ULN
Calcium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Chloride	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Cholesterol, Total	mmol/L	—	> 1.6 × ULN
Creatinine	µmol/L	—	> 1.3 × ULN
Glucose, random, serum	mmol/L	< 0.8 × LLN	> 1.4 × ULN
Magnesium	mmol/L	< 0.9 × LLN	> 1.1 × 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

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

Table C-3. Criteria for Potentially Clinically Important Urinalyses Values

		Definition of Potentially Clinically Important	
Urinalyses Variables	**Units**	**Very Low**	**Very High**
pH	—	< 0.9 × LLN	> 1.1 × ULN
Specific gravity	—	—	> 1.1 × ULN

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

Table C-4. Criteria for Potentially Clinically Important Vital Sign Values

Urinalyses Variables	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, mmHg (Supine)	High	Age 2 5 (inclusive): ≥ 125	Increase of ≥ 20
	Low	Age 2 5 (inclusive): ≤ 70	Decrease of ≥ 20
Diastolic Blood Pressure, mmHg (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

Urinalyses Variables	Flag	Criteria[a]	
		Observed Value	Change From Baseline
Weight, kg	High		Increase of ≥ 10%
	Low		Decrease of ≥ 5%

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

* Change from supine value standing value supine value.

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

Table C-5. Criteria for Potentially Clinically Important 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