Statistical Analysis Plan for Study M21-862

A Phase 2 Dose Finding Study Evaluating the Safety and Efficacy of Linaclotide in Pediatric Subjects 6 Months to Less Than 2 Years of Age with Functional Constipation (FC)

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Version 1.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for linaclotide (Linzess) Study M21-862, Functional Constipation: A Phase 2 Dose Finding Study Evaluating the Safety and Efficacy of Linaclotide in Pediatric Subjects 6 Months to Less Than 2 Years of Age.

Study M21-862 identifies the tolerable, safe, and efficacious dose of linaclotide administered for 4 weeks in pediatric subjects (Part 1), and evaluates the safety and efficacy of 4 weeks of study intervention with linaclotide in pediatric participants (Part 2), 6 months to less than 2 years of age, with FC.

The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analysis.

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.

This SAP includes changes to analyses described in the protocol. Details are outlined in Section 14.1.

2.0 Study Objectives and Design

2.1 Study Objectives

The objective of this study is divided into two parts.

Part 1: To identify a tolerable, safe, and efficacious dose of linaclotide administered for 4 weeks in pediatric subjects, 6 months to less than 2 years of age, with FC for Part 2.

Part 2: To evaluate the safety and efficacy of 4 weeks of study intervention with linaclotide in pediatric subjects, 6 months to less than 2 years of age, with FC.

There are no current, approved therapies to treat children 6 months to less than 2 years of age with functional constipation (FC). Therefore, AbbVie aims to evaluate whether linaclotide can be an effective and safe therapy for FC in this age group.

There is no formal hypothesis corresponding to the objectives.

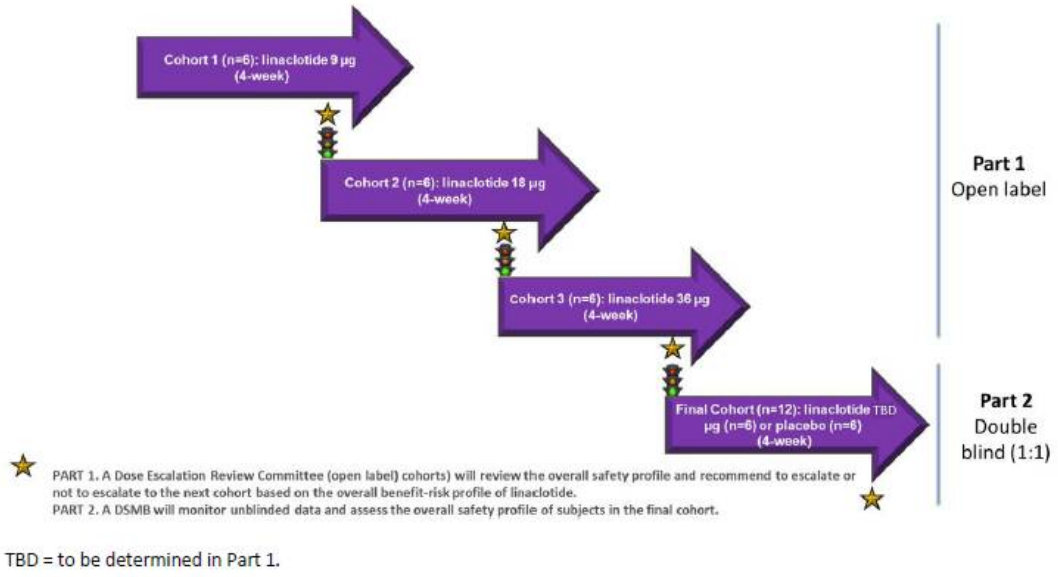
2.2 Study Design Overview

M21-862 is a phase 2 study to assess the safety of linaclotide (Part 1) and to evaluate the safety and efficacy of linaclotide in pediatric subjects (Part 2) (6 months to less than 2 years of age). The schematic of the study is shown in Figure 1 and Figure 2. Further details regarding study procedures are in the Protocol Operations Manual.

This study consists of 2 Parts that include 4 cohorts in total. Part 1 has three open-label cohorts and Part 2 has a double-blind cohort. Part 1 cohorts will be open label and enrolled sequentially with linaclotide in ascending doses. A linaclotide dose will be chosen for Part 2 based on the overall benefit-risk profile of the open-label cohorts in Part 1. Part 2 will include a double-blind cohort to assess the efficacy of linaclotide vs. placebo. All cohorts will have a study intervention period of 4 weeks.

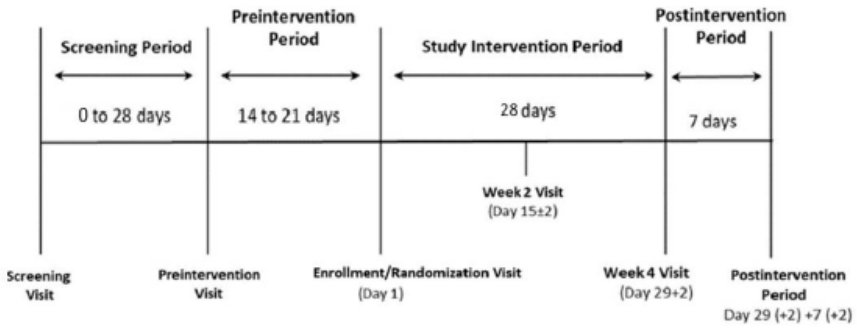
The schematics of the study and the study visit for Parts 1 and 2 are shown in Figure 1 and Figure 2.

Figure 1. Study Schematic



TBD = to be determined in Part 1.

Figure 2. Study Visit Schematic Parts 1 and 2



2.3 Treatment Assignment and Blinding

Approximately 30 subjects, 6 months to less than 2 years of age, will be sequentially enrolled into this study: six subjects in each cohort for Cohorts 1-3 and twelve subjects for

Part 2. Cohorts 1 to 3 will be open label with linaclotide only. Part 2 will be double blinded, and subjects will be randomized at a 1:1 ratio to linaclotide or placebo.

All cohorts will be of 7 to 12 weeks in duration: 0 to 4-week Screening Period (the minimal of 0 to 4-week period only applies to subjects that need wash out from prohibited medications), a 2 to 3-week Preintervention Period, followed by a 4-week Study Intervention Period, and a 1-week Postintervention Period.

In Part 1, linaclotide will be administered orally QD at the dose of 9 µg, 18 µg, and 36 µg for Cohort 1, Cohort 2 and Cohort 3, respectively. Part 2 will include additional subjects at the dose of linaclotide (either the 9, 18, or 36 µg dose) that exhibited the best benefit-risk profile from Part 1; and subjects receiving matching placebo.

In Cohorts 1-3, at least 5 subjects per cohort will need to complete treatment with an acceptable safety profile assessed by an internal Dose Escalation Review Committee which will give special attention to the presence of AESIs for the cohort to be declared safe to escalate to the next dose level.

In each cohort of Part 1, at least 1 subject will need to be ≤ 12 months of age. The study investigator and the legally authorized representative (LAR)/parent/guardian will be given the option for the subject to continue in the next higher cohort (dose escalation) if the safety profile favors a trial cohort at a higher dose. Subjects who are participating in intrasubject dose escalation will need to repeat all screening procedures and eDiaries if > 30 days have elapsed since the subject's last dose in the previous cohort. Note: the screening number assigned by the Interactive response technology (IRT) at the initial screening visit should still be used. If symptoms have improved at the current dose level, the subject will be invited to participate in a long-term safety extension study once the study is active and accepting subjects. An internal Dose Escalation Review Committee will be monitoring the safety of Cohorts 1-3 and will provide a recommendation for the dose escalation to the next cohort or to stop the study based on the overall benefit-risk profile.

Once the best benefit-risk dosing profile from Cohorts 1-3 has been identified, Part 2 (the final cohort) will include 12 subjects at 4 weeks of double-blind study intervention with linaclotide vs. placebo using that selected dose. An independent Data Safety Monitoring Board (DSMB) will review unblinded interim safety data for that cohort. Based on this review, the DSMB will assess the overall safety of the subjects in Part 2.

In Part 1, new subjects will be recruited for each cohort, but existing subjects from previous cohorts (Cohorts 1 and 2) will be given the opportunity to participate in the next cohort (up to Cohort 3) if their symptoms have not improved at that respective dose ($\leq$ 2 SBM per week), the subject has an acceptable tolerability to the study drug, and the LAR/parent/guardian is willing to continue in the study.

In Part 2, new subjects will be recruited. The final selected dose will be analyzed and compared to placebo. Similarly, safety and efficacy will be analyzed across all cohorts (Parts 1 and 2) and to placebo. Those results will be used to support the feasibility of a confirmatory Phase 3 study.

The Phase 2 open-label ascending, multidose dose finding portion of the study (Part 1) will provide a safe and efficient method of identifying a suitable dose to assess in Part 2 of the study, where blinding to randomized controlled treatment can then be employed to provide more confidence on the safety and efficacy of linaclotide in this young pediatric population and to support further research in a Phase 3 study.

2.4 Sample Size Determination

The planned total sample size is approximately 30 subjects. Sample size in this study is not driven by statistical consideration. Instead, this study is designed to enroll enough pediatric subjects to observe the clinical response trends and monitor safety.

3.0 Endpoints

3.1 Key Efficacy Endpoints for Part 1 and Part 2

The key efficacy endpoints for Part 1 and Part 2 are:

- The change from baseline in 4-week overall SBM frequency rate (SBMs/week) during the Study Intervention Period
- The change from baseline in 4-week stool consistency (Bristol Stool Form Scale) reported by LAR/parent/guardian/caregiver during the Study Intervention Period
- The change from baseline in 4-week straining reported by LAR/parent/guardian/caregiver during the Study Intervention Period

The details of the derivation of these efficacy endpoints are provided in Appendix B.

The estimands corresponding to the efficacy endpoints are the mean change from baseline in overall SBM frequency rate, stool consistency, and straining during the study intervention period, regardless of interruption of study drug and without use of rescue medications in the linaclotide and placebo groups in the intent-to-treat (ITT) population.

3.2 Additional Efficacy Endpoints for Part 1 and Part 2

The additional efficacy endpoints for Part 1 and Part 2 are:

- The achievement of no longer meeting modified Rome IV criteria for FC at the end of the 4-week study intervention period
- The global change in symptoms at each week during the study intervention period
- The global severity of symptoms at each week during the study intervention period

3.3 Safety Endpoints

The safety endpoints for Part 1 and Part 2 include AEs (including AESI), clinical laboratory assessments (complete blood count [CBC], clinical chemistry, and urinalysis), vital sign measurements (including postural vital signs whenever possible according to a subject's age), ECG, physical examinations, height, and weight, as measures of safety and tolerability for the entire study duration.

4.0 Analysis Populations

The following population sets will be used for the analyses.

The Intent-to-Treat (ITT) Population includes all subjects who received at least 1 dose of study drug. The ITT Population will be used for all efficacy and baseline analyses. Subjects will be included in the analysis according to the treatment group to which they were assigned/randomized (as randomized).

The Safety Analysis (SA) Population includes all subjects who received at least 1 dose of study drug. Subjects will be included in the analysis according to the study drug that they actually received (as treated). A subject's actual treatment 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 by cohort for Part 1 and treatment group for Part 2:

- Subjects enrolled (Part 1) or randomized (Part 2) in the study;
- Subjects who took at least one dose of study drug;
- Subjects who completed study drug;
- Subjects who prematurely discontinued study drug;

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

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

A listing of subjects enrolled in multiple cohorts for Part 1 will be provided as well.

6.0 Study Treatment Duration and Compliance

6.1 Study Treatment Duration

For the SA Population, duration of treatment will be summarized for each cohort in Part 1 and by treatment group in 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 and Part 2: ≤ 1 week, > 1 - ≤ 2 weeks, > 2 - ≤ 4 weeks, > 4 weeks

6.2 Treatment Compliance

Treatment compliance will be summarized for the entire treatment period for the SA Population in Part 1 (by each cohort) and Part 2 (by treatment group), 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 (6 months to less than 2 years of age) with FC was developed for completion by caregivers on an electronic diary (eDiary). eDiary compliance will be assessed based on the number of days with fully completed eDiary assessments by the caregiver in a specific period. The eDiary will be considered fully completed if the caregiver responded to each question in the eDiary. eDiary compliance will be summarized for the preintervention period, the open label period (Part 1), and the double-blind intervention period (Part 2), 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 the enrollment or randomization day, the clinic diary entry administered before the enrollment or 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, by cohort in Part 1, and by treatment group and overall in Part 2 for the ITT population. Unless otherwise specified, baseline is defined as the last non-missing value prior to the first administration of study drug.

Continuous demographic variables include age, weight, and height.

Categorical demographic variables include:

- Sex
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race
- Age (6 - < 12, 12 - 24 months)
- Region (Europe, North America)

Continuous disease characteristics variables include:

- spontaneous bowel movement (SBM) frequency rate (SBMs/week)
- stool consistency
- straining

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 by cohort in Part 1 and treatment group and overall in Part 2. 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 by cohort in Part 1 and treatment group and overall, in Part 2. 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 medial history and concomitant medications summaries will be performed for the Safety Analysis Population (SA).

7.3 Protocol Deviations

Protocol deviations include eligibility criteria violations, receipt of wrong treatment or incorrect dose of study drug, development of withdrawal criteria without being withdrawn, and use of prohibited concomitant medications. A listing of subjects with protocol deviations will be provided.

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 by cohort in Part 1 and treatment group and overall in Part 2:

- Subject entered into 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 drug;
- Subject took prohibited concomitant medication.

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

The key efficacy endpoints (defined in Section 3.2) will be analyzed on the ITT population and subjects with the following potential intercurrent events will be handled as follows:

- The BMs for 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 an SBM during the efficacy analysis.
- Subjects who discontinue prematurely during but prior to the completion of the study intervention period will have their eDiary data included up to the last dose date for the endpoint. The SBM frequency rate based on included eDiary

data up to the last dose date will be considered equivalent to the 4-week SBM frequency rate.

- Subjects who have study drug interruption will have their eDiary data included as observed (i.e., regardless of interruption of study drug).

9.0 Efficacy Analyses

9.1 General Considerations

All efficacy analyses will be conducted on the ITT population descriptively for each cohort in Part 1 and by treatment group in Part 2. No statistical testing will be performed in this study. Additionally, if any cohort has a the same linaclotide dose as the other cohorts, pooled summaries will also be provided.

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 enrollment/randomization up to the time of enrollment/randomization in each cohort.

A SBM is a BM that occurs in the absence of laxative, suppository, or enema use on the calendar day of the BM or the calendar day before the BM. Caregiver-observed SBMs are defined as SBMs reported in the eDiary for which the caregiver identified being with the child for.

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

missing baseline consistency and straining reported by the caregiver will be excluded from the respective consistency and straining change from baseline analyses.

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

9.2 Handling of Missing Data

An as-observed (AO) approach to missing post-baseline data will be applied. The AO analysis will not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled visit will be excluded from the AO analysis for that visit. AO will include all values collected in the study.

9.3 Key Efficacy Endpoints and Analyses

9.3.1 Key Efficacy Endpoints

The key efficacy endpoints for Part 1 and Part 2 are:

- The change from baseline in 4-week overall SBM frequency rate (SBMs/week) during the Study Intervention Period
- The change from baseline in 4-week stool consistency (Bristol Stool Form Scale) reported by LAR/parent/guardian/caregiver during the Study Intervention Period
- The change from baseline in 4-week straining reported by LAR/parent/guardian/caregiver during the Study Intervention Period

The numerator of the SBM rate (SBMs/week) during the Study Intervention Period will be derived based on the total number of SBMs reported by a LAR/parent/guardian/caregiver as being directly observed during this period in the eDiary. Additional analysis will also be performed based on the total number of SBMs reported during the Study Intervention Period (including SBMs not directly observed by the LAR/parent/guardian/caregiver) and the corresponding baseline SBM frequency rate

will be determined based on the total number of SBMs reported during the Preintervention period.

Stool consistency for each LAR/parent/guardian/caregiver-observed BM will be measured daily in the eDiary using the 7-point ordinal BSFS. A participant's BSFS score for the Study Intervention Period will be the average of the non-missing BSFS scores from the caregiver-observed SBMs during the 4-week Study Intervention Period. If no caregiver-observed SBMs are present at baseline, the baseline BSFS score reported by caregiver will be missing and, therefore, that subject will not be included in the change from baseline stool consistency analysis.

Straining for each LAR/parent/guardian/caregiver caregiver-observed BM will be collected daily in the eDiary device, using a 4-point scale based on two questions. The subject's daily straining score for each caregiver-observed BM will be derived based on the average of nonmissing responses of the two straining questions. The participant's straining score in the 4-week Study Intervention Period will be the average of the non-missing daily average straining scores from the caregiver-observed SBMs during the 4-week Study Intervention Period. If a subject has no caregiver-observed SBMs at baseline, then the baseline straining score reported by the caregiver will be missing and, therefore, that subject will not be included in the change from baseline straining analysis.

9.3.2 Main Analysis of Key Efficacy Endpoints

The estimands corresponding to the key efficacy endpoints are the mean change from baseline in overall SBM frequency rate, stool consistency, and straining, regardless of interruption of study drug and without use of rescue medications in the linaclotide and placebo groups in the intent-to-treat (ITT) population.

The key efficacy endpoints will be analyzed based on the AO approach. Descriptive statistics (mean, median, standard deviation, standard error, minimum, and maximum) will be provided.

The attributes of the estimand corresponding to the key efficacy objectives are summarized in Table 1.

Table 1. Summary of the Estimand Attributes Corresponding to the Key Efficacy Objectives

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Key	Part 1: linaclotide Part 2: linaclotide or placebo (see Section 3.1)	Change from baseline in 4-week overall SBM frequency rate (SBMs/week) during the study intervention period	ITT	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 after IE3 will be used.	Mean change from baseline in 4-week overall SBM frequency rate (SBMs/week) during the study intervention period in linaclotide (Part 1), or linaclotide or placebo (Part 2)
Key	Part 1: linaclotide Part 2: linaclotide or placebo (see Section 3.1)	Change from baseline in 4-week stool consistency (Bristol Stool Form Scale) reported by LAR/parent/guardian/caregiver during the study intervention period	ITT	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 after IE3 will be used.	Mean change from baseline in 4-week stool consistency reported by LAR/parent/guardian/caregiver during the study intervention period in linaclotide (Part 1), or linaclotide or placebo (Part 2)

Estimand Label	Attributes of the Estimand				
	Treatment	Endpoint	Population	Handling of Intercurrent Events	Statistical Summary
Key	Part 1: linaclotide Part 2: linaclotide or placebo (see Section 3.1)	Change from baseline in 4-week straining reported by LAR/parent/guardian/caregiver during the study intervention period	ITT	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 after IE3 will be used.	Mean change from baseline in 4-week straining reported by LAR/parent/guardian/caregiver during the study intervention period in linaclotide (Part 1), or linaclotide or placebo (Part 2)

9.4 Additional Efficacy Endpoints and Analyses

9.4.1 Additional Efficacy Endpoints

The additional efficacy endpoints for Part 1 and Part 2 are defined in Section 3.2.

The additional efficacy endpoints will be analyzed based on the AO approach. Descriptive statistics will be provided for continuous (mean, median, standard deviation, standard error, minimum, and maximum) and categorical (count, percentage) efficacy endpoints.

9.5 Efficacy Subgroup Analyses

The following subgroup analyses will be conducted for the key efficacy endpoints. Descriptive statistics (number and percentage) will be provided.

- Age (6 - < 12, 12 - 24 months)

10.0 Safety Analyses

10.1 General Considerations

Safety analyses will be performed on the safety analysis population in the 4-week OL period (Part 1) and the 4-week DB period (Part 2). Safety summary will be presented for each cohort in Part 1 and by treatment group in Part 2. Additionally, if any cohort has a the same linaclotide dose as the other cohorts, pooled summaries will also be provided.

The Baseline for safety analysis is defined as the last available measurement before the first study drug administration for each cohort, except the following:

- For subjects enrolled in 2 cohorts (Cohort 1 and Cohort 2; or Cohort 2 and Cohort 3), if subjects enroll into the next cohort within 28 days of last dose of the previous cohort, the baseline of the first cohort will be used the baseline for the second cohort.
- For subjects enrolled in all 3 cohorts (Cohort 1, Cohort 2, and Cohort 3), if subjects enroll into the second cohort and the third cohort within 28 days of last dose of the previous cohort, the baseline of Cohort 1 will be used the baseline for the second and third cohort.

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 AE event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported for the corresponding cohort.

10.2.1 Treatment-Emergent Adverse Events

The Treatment-Emergent Adverse Events (TEAEs) for the SA population are defined as follows.

Part 1

Cohort 1: TEAEs are defined as events that begin either on or after the first dose of OL linaclotide study drug in Cohort 1 and whichever are earlier of the following:

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

Cohort 2: TEAEs are defined as events that begin either on or after the first dose of the study drug in Cohort 2 and whichever are earlier of the following:

- the first dose of study drug in Cohort 3
- 30 days after the last dose administration of the study drug in Cohort 2

Cohort 3: TEAEs for Cohort 3 are defined as events that begin either on or after the first dose of the study drug in Cohort 3 and 30 days after the last dose administration of the study drug in Cohort 3.

Part 2

TEAEs for Part 2 are defined as events that begin either on or after the first dose of 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 drug start date are assumed to be treatment-emergent. All treatment-emergent AEs 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 cohort in Part 1 and by treatment group for Part 2.

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

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

Treatment-emergent serious adverse events (SAEs) (including deaths), TEAEs leading to premature discontinuation of study drug, and TEAEs leading to death will be summarized by SOC and PT.

Tabular listings will be provided for all deaths, all SAEs, TESAEs, TEAEs leading to death, TEAEs leading to premature discontinuation of study drug, and TEAEs leading to study drug interruptions.

10.2.5 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 and /or 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.

10.3 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 subject with PCI postbaseline values will be provided.

Potential Hy's Law

Potential Hy's Law criteria within a 24-hour window is 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 for each intervention 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 Investigator's overall interpretation of the ECG will be presented by treatment group within each cohort for the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant. A tabular display showing subjects with postbaseline clinically significant ECG abnormalities according to the Investigator's overall interpretation will be provided.

11.0 Other Analyses

Not applicable.

12.0 Interim Analyses

No Interim Analysis is planned.

12.1 Internal Dose Escalation Committee

In Part 1, an internal dose escalation review committee (IDERC) will be monitoring the safety of Cohorts 1-3 and will provide a recommendation for the dose escalation to the next cohort or to stop the study based on the overall benefit-risk profile.

12.2 Data Monitoring Committee

In Part 2, an external Data Safety Monitoring Board (DSMB) 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 DSMB will be to protect the safety of the subjects participating in this study.

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

13.0 Overall Type-I Error Control

There is no hypothesis testing for this study. No multiplicity adjustment will be applied.

14.0 Version History

Table 2. SAP Version History Summary

Version	Date	Summary
1.0	17 May 2023	Initial version

14.1 Changes to Planned Analyses in the Protocol

NA

15.0 References

1. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med. 1985;4:213-26.
2. Johnston KM, Lakzadeh P, Donato BMK, et al. Methods of sample size calculation in descriptive retrospective burden of illness studies. BMC Med Res Methodol. 2019;19(1):9.
3. Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics. 1997;53(3):983-97.
4. 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. 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]	[redacted]	Author
[redacted]	[redacted]	Clinical Statistics
[redacted]	[redacted]	Statistical Programming
[redacted]	[redacted]	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 Enrollment/Randomization Visit

Missing responses in an incomplete clinic diary on enrollment/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:
- Enrollment/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 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) =

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

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

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

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

Stool Consistency

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

"Choose the option that is most like 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.

A subject's stool consistency score for the study intervention period will be the average of the non-missing BSFS scores for the caregiver-observed SBMs during that specific period.

Straining

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

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

- No, not at all
- Yes, a little
- 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?

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

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

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 Enrollment/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.

- Much better
- A little better
- No change
- A little worse
- 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?

- None
- Mild
- Moderate
- Severe
- 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, mm Hg (Supine)	High	Age 6-24 months (inclusive): ≥ 125	Increase of ≥ 20
	Low	Age 6-24 months (inclusive): ≤ 70	Decrease of ≥ 20
Diastolic Blood Pressure, mm Hg (Supine)	High	Age 6-24 months (inclusive): ≥ 85	Increase of ≥ 15
	Low	Age 6-24 months (inclusive): ≤ 35	Decrease of ≥ 15
Pulse Rate, bpm (Supine)	High	Age 6-24 months, boy (inclusive): ≥ 165 Age 6-24 months, girl (inclusive): ≥ 188	Increase of ≥ 15
	Low	Age 6-24 months, boy (inclusive): ≤ 87 Age 6-24 months, girl (inclusive): ≤ 85	Decrease of ≥ 15
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 (6-24 months (inclusive))
PR interval	msec	PR > 225 msec (6-24 months (inclusive))
QTc(F)	msec	> 480

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