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Protocol for 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

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SPONSOR:	AbbVie Inc.*	PLANNED NUMBER OF SITES:	Approximately 36 sites (globally)
ABBVIE INVESTIGATIONAL PRODUCT:	Linaclotide	EU CT:	2022-501947-34-00

FULL TITLE: 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).

Incorporating Versions 1.0, 1.1 (EU Only), and 2.0

PRINCIPAL INVESTIGATOR(S): Investigator information on file at AbbVie.

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1 SYNOPSIS

Title: 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)	
Background and Rationale:	There are no current, approved therapies to treat children 6 months to less than 2 years of age with functional constipation (FC). Therefore, we aim to evaluate whether linaclotide can be an effective and safe therapy for FC in this age group.
Objective(s) and Endpoint(s):	**Objective for 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. **Objective for Part 2:** To evaluate the safety and efficacy of 4 weeks of study intervention with linaclotide in pediatric participants, 6 months to less than 2 years of age, with FC. Efficacy endpoints for Part 1 and Part 2: • Change from baseline in 4-week overall Spontaneous Bowel Movement (SBM) frequency rate (SBMs/week) during the Study Intervention Period • Change from baseline in 4-week stool consistency (Bristol Stool Form Scale) reported by LAR/parent/guardian/caregiver during the Study Intervention Period • Change from baseline in 4-week straining reported by LAR/parent/guardian/caregiver during the Study Intervention Period Additional Efficacy Endpoints for Part 1 and Part 2: • Achievement of no longer meeting Rome IV criteria for FC at the end of the 4-week study intervention period • Global change in symptoms and the global severity of symptoms at each week during the study intervention period.
Investigator(s):	Investigator information on file at AbbVie.
Study Site(s):	Approximately 36 sites (globally)
Study Population and Number of Subjects to be Enrolled:	The study population is pediatric subjects with FC between the ages 6 months to less than 2 years old. Up to 30 and at least 18 subjects will be enrolled.
Investigational Plan:	M21-862 is a phase 2 study to assess and evaluate the safety and efficacy of linaclotide in pediatric subjects (6 months to less than 2 years of age). 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 cohort(s) in Part 1. In Part 1, 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. 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.
Key Eligibility Criteria:	A population of pediatric subjects that is well characterized as having FC as defined by Rome IV criteria.
Study Drug and Duration of Treatment:	In Part 1, linaclotide will be administered orally once daily at doses 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 9, 18, or 36 µg) that exhibited the best benefit-risk profile from Part 1; and subjects receiving matching placebo. In Part 2, linaclotide (or matching placebo) will be administered orally once daily. Parts 1 and 2 will both have a 4-week study intervention period.
Date of Protocol Synopsis:	25 November 2024

2 INTRODUCTION

2.1 Background and Rationale

Background

Functional Constipation (FC) is a common healthcare problem in children of all ages, with a worldwide prevalence ranging between 0.7% and 29.6%.[1] The pathophysiology of FC is multifactorial and include genetic predisposition, inadequate fiber and fluid intake, and immobility. The most common etiological factor, especially in younger children, is withholding behavior, which usually develops as a consequence of painful or frightening evacuation of stools.[2] This can lead to a self-reinforcing cycle, where voluntary stool retention leads to increased water absorption from the feces and, thereby, harder stools and inherently more difficult and painful defecation. Colonic dysmotility, a common cause of FC in adults, can be a cause, but also a consequence of FC most likely due to longstanding fecal stasis. Symptoms suggestive of FC include infrequent (≤ 2 bowel movements [BMs]/week) hard or large diameter stools, painful defecation, retentive posturing, and fecal incontinence. If left untreated, FC may have other clinical consequences such as poor appetite, failure to thrive, encopresis, anal fissures, and cystitis. These symptoms can have a severe impact on a child's quality of life and may lead to school absenteeism and substantial costs related to healthcare utilization.

Initial nonpharmacological interventions include education, dietary advice (sufficient fiber and fluid intake), and behavioral modifications. In older children, additional nonpharmacological interventions include toilet training, a reward system, and keeping a stool diary. However, many children ultimately require pharmacological treatment. If a fecal mass is suspected to be present, disimpaction should be attempted through either rectally administered enemas or high doses of oral polyethylene glycol (PEG), followed by maintenance treatment and eventually a weaning phase after a sustained period of symptom relief. Despite chronic pharmacological treatment, approximately 40% of children with FC who are referred to a pediatric gastroenterologist remain symptomatic after 5 years and 20% of children still have symptoms after 10 years of treatment. In some cases, symptoms may persist into adolescence or adulthood. Potential reasons for ineffectiveness of treatment include suboptimal dosage regimens, poor compliance with treatment, or the use of treatments that do not address the underlying pathophysiological mechanism. Children with a longstanding history of untreated constipation may require longer treatment durations to break the vicious pathophysiological cycle associated with chronic withholding long fecal stasis, and subsequent impairment of colonic function.[1]

There are currently no approved therapies for FC in pediatric patients in the European Union (EU) or in pediatric patients less than 6 years of age in the US and Canada; PEG, the current treatment of choice, is used off-label. Reports of potential neurological adverse events have been associated with the use of PEG, which has triggered concerns in patients and caregivers and is currently being further investigated.

Effective treatments are needed to provide symptomatic relief in children with FC that are supported by safety and efficacy data from well controlled studies.

Linaclotide offers a potential therapeutic option to treat these symptoms in this pediatric population, as it is currently indicated for the treatment of irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) in the adult population and for the treatment of FC in children 6 to

17 years of age in US and Canada. In the European Union (EU) linaclotide (CONSTELLA) is indicated for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults. Linaclotide is a 14-amino acid peptide that acts on the apical surface of epithelial cells surrounding the intestinal lumen to stimulate the receptor guanylate cyclase subtype C (GC-C). By activating GC-C, orally administered linaclotide has been found to increase both intestinal fluid secretion and intestinal transit and to also decrease visceral (abdominal) pain. Linaclotide has minimal oral bioavailability (≤ 0.2%) in several animal species and is minimally absorbed with low systemic availability in adults.[3,4]

Pediatric Linaclotide Program

Pediatric subjects (2 to 17 years of age) have been treated with linaclotide in multiple Phase 2 and Phase 3 studies in FC (LIN-MD-62 [FC, NCT02559570], LIN-MD-67 [FC, NCT04110145], and LIN-MD-64 [NCT04026113]) and IBS-C pediatric populations (LIN-MD-63 [IBS-C, NCT02559817] and LIN-MD-64 [NCT04026113]). Overall, linaclotide was well tolerated in pediatric subjects with FC and IBS-C across all doses evaluated.[5] Additional details regarding the completed pediatric FC studies in subjects 2 to 17 years of age with linaclotide are described below.

Phase 2 Study in FC: LIN-MD-62

LIN-MD-62 was a Phase 2 -double-blind, placebo controlled, parallel group, safety and efficacy study of a range of linaclotide doses administered to 173 subjects, 6 to 17 years of age, who fulfilled modified Rome III criteria for FC (refer to Table 1 for dosing information). The objective of LIN-MD-62 was to evaluate the dose response, safety, and efficacy of 4 weeks of study intervention with 1 of 3 linaclotide doses (Dose A, B, and C, defined in Table 1) compared with placebo in pediatric subjects who fulfill modified Rome III criteria for child/adolescent FC with the goal of selecting an optimal dose of linaclotide to evaluate in a confirmatory study.

Overall, linaclotide was well tolerated across all doses and both age groups. The safety profile was consistent with prior adult linaclotide studies for CIC. The most frequently reported treatment-emergent adverse event (TEAE) was diarrhea, which occurred in 7.6% of linaclotide-treated subjects versus 0% in the placebo group. The majority of the TEAEs of diarrhea reported were mild; none were severe. In the 12 to 17 years of age group, 1 subject experienced moderate diarrhea (related) leading to discontinuation in the linaclotide Dose C group.

There were no reported adverse events of special interest (AESIs) (i.e., significant volume depletion and/or significant electrolyte abnormalities and/or Electrocardiogram [ECG] abnormalities that were considered by the investigator or sponsor to be related to diarrhea) or deaths. There were 2 Serious adverse event (SAE) (suicidal ideation and vomiting), each reported in 1 subject 12 to 17 years of age, neither of which were considered related to study intervention. Moreover, in the younger pediatric subjects, 6 to 11 years of age, no SAEs or AEs leading to discontinuation were reported.[5]

Table 1. Dose Levels (µg) by Weight in Pediatric Subjects Treated with Linaclotide in Study LIN-MD-62

		Linaclotide Dose A N = 36	Linaclotide Dose B N = 41	Linaclotide Dose C N = 39
Age Group	**Weight**	**Dose (µg)**		
Subjects 6-11 years[a]				
	18 to < 35 kg	9	18	36
	≥ 35 kg	18	36	72
Subjects 12-17 years[b]				
	--	18	36	72

a. Subjects 6 to 11 years of age received linaclotide or placebo in a liquid oral solution.

b. Subjects 12 to 17 years of age received linaclotide or placebo in a solid oral capsule or a liquid oral solution.

Phase 3 Study in FC: LIN-MD-64

Study LIN-MD-64 was a Phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel group, confirmatory safety and efficacy study comparing linaclotide at 72 µg and placebo in pediatric subjects, 6 to 17 years of age, with a diagnosis of FC based on modified Rome III Child/Adolescent Criteria (i.e., who fulfilled modified Rome III criteria for child/adolescent FC). The objective of this study was to evaluate the safety and efficacy of 12-weeks of linaclotide therapy (72 µg daily) in comparison with placebo in pediatric subjects, 6 to 17 years of age, who fulfilled modified Rome III Criteria for Child/Adolescent FC.

Treatment with linaclotide demonstrated a statistically significant increase in the SBM frequency rate (SBMs/week) from baseline and improvement in stool consistency (as measured by the p-BSFS) from baseline during the 12-week intervention period compared to placebo.

AEs were reported for 28 subjects (17.1%) in the linaclotide group and for 35 subjects (21.3%) in the placebo group. The majority of AEs in each treatment group were nonserious. Treatment-emergent serious adverse events (TESAEs) were reported for 2 subjects (1.2%) in the linaclotide group and 2 subjects (1.2%) in the placebo group. AEs leading to study treatment discontinuation were reported for 2 subjects (1.2%) in the linaclotide group and for 3 subjects (1.8%) in the placebo group. No AEs leading to death were reported.

Linaclotide was well tolerated across 6 to 17-year-olds with no deaths. The majority of TEAEs experienced by subjects were mild or moderate in severity. Overall, no unexpected or clinically relevant changes to vital signs, volume depletion, or ECG abnormalities were reported. There was one AESI of severe diarrhea. Overall, the safety profile of linaclotide in pediatric subjects is consistent with prior linaclotide studies in adults with CIC and IBS-C.

Phase 2 Study in FC: LIN-MD-67

LIN-MD-67 was a Phase 2, randomized, double-blind, placebo-controlled, sequential, ascending, multidose study designed to evaluate the dose response, safety, and efficacy of 4 weeks of linaclotide

compared with matching placebo in 35 pediatric subjects (2 to 5 years of age) who met modified Rome III criteria for childhood FC.[5]

Overall, linaclotide was well tolerated across all doses evaluated. Although there was no clear dose-response relationship, numerically better efficacy results were consistently observed at the linaclotide 72 µg dose group compared to placebo in three out of four key efficacy endpoints: change from baseline in 4-week overall Spontaneous Bowel Movement (SBM) frequency rate (SBMs/week), change from baseline in 4-week stool consistency, and change from baseline in 4-week straining. The safety profile was consistent with that of the prior linaclotide study in 6 to 17 year-old FC subjects (Study LIN-MD-62) and prior linaclotide studies in adults with CIC. There were no deaths, SAE, AESI (i.e., significant volume depletion and/or significant electrolyte abnormalities and/or ECG abnormalities that were considered by the investigator or sponsor to be related to diarrhea), or AE leading to study drug discontinuation. Two subjects receiving 18 µg experienced TEAEs of otitis media, increased blood creatine, and cough (1 [14.3%] subject for each TEAE), no subject receiving 36 µg experienced TEAEs, and 2 subjects receiving 72 µg experienced TEAEs of upper abdominal pain, diarrhea, and an ear infection (1 [7.7%] subject for each TEAE). All TEAEs experienced by subjects were mild or moderate in severity.[5]

These data provide the rationale for the 9 µg, 18 µg, and 36 µg doses being studied in this Phase 2 Study M21-862. Refer to Dose Justification (Section 4.2) for additional details.

Additional information from studies conducted with linaclotide can be found in the most current version of the linaclotide Investigator's Brochure (IB).[5] Refer to Section 2.2 for benefit and risks discussion.

Rationale

AbbVie is conducting this Phase 2 study to investigate the potential therapeutic dose(s) of linaclotide in pediatric subjects age 6 months to less than 2 years with FC. The rationale for conducting the study in this population is that FC is highly prevalent in this age group, there is currently no approved treatment for this population, and safety and tolerability have been established in pediatric subjects 2 to less than 18 years of age.

This dose-ranging study will evaluate if once daily (qd) administration of 9, 18, or 36 µg of linaclotide for a 4-week study intervention period is safe and effective in pediatric subjects, 6 months to less than 2 years of age, with FC.

2.2 Benefits and Risks to Subjects

Linaclotide has the potential to improve FC symptoms. Diarrhea was the most common adverse reaction in studies of adults with IBS-C or CIC and older children with IBS-C and FC. In studies of adults with IBS-C or CIC abdominal pain, flatulence, and abdominal distension were also reported. In completed pediatric studies linaclotide was well tolerated across all doses (LIN-MD-62, LIN-MD-67, LIN-MD-63, and LIN-MD-64), the safety profile was consistent with prior adult linaclotide studies for CIC and IBS-C.[5]

Refer to the IB for a more detailed description of the chemistry, pharmacology, efficacy, and safety of linaclotide, based on studies conducted in animals, healthy volunteers, and in subjects with IBS-C and CIC.

There are currently no pharmacologic therapies for the treatment of FC approved in the pediatric population in EU and in children less than 6 years of age in US and Canada. Thus, there is a need for new agents with favorable safety and tolerability profiles that are effective in providing relief for the variety of symptoms associated with FC in pediatrics.

Linaclotide provides an important treatment option for adult subjects with CIC and pediatric subjects with FC (6 to 17 years of age in US and Canada). The sponsors consider the benefit-risk balance favorable and support further clinical development of linaclotide as a treatment for FC in younger children.

See Section 4 for details of study procedures, dose, and study design justification.

Considering the coronavirus disease 2019 (COVID-19) pandemic and based on the information to date, the mechanism of action, and preclinical and clinical information, there is no expected risk for study subjects treated with linaclotide for COVID-19 or for subjects to experience more serious illness if infected.

This study has been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subjects. The study will be monitored throughout its course with routine medical monitoring and pharmacovigilance activities to ensure that the risk threshold, degree of distress, and the risks and benefits are being carefully managed. Details regarding criteria for dose interruptions, criteria for discontinuation of study drug or study, independent Data Safety Monitoring Board (DSMB), Internal Dose Escalation Review Committee, and additional safety considerations can be found in Section 5.4, Section 5.5, Section 5.10, and Section 6.

Taken together, the efficacy and safety data from linaclotide studies to date show a favorable benefit-risk profile for linaclotide and support the continued investigation of linaclotide in pediatric patients less than 6 years of age with FC.

3 OBJECTIVES AND ENDPOINTS

3.1 Objective and Hypothesis

Objective for 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.

Objective for Part 2:

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

There is no formal hypothesis corresponding to the objectives.

3.2 Key Efficacy Endpoints and Estimand

Key efficacy endpoints for Part 1 and Part 2:

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

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

3.3 Additional Efficacy Endpoints

Additional Endpoints For Part 1 and Part 2:

- Achievement of no longer meeting Rome IV criteria for FC at the end of the 4-week Study Intervention Period
- Global change in symptoms and the global severity of symptoms at each week during the Study Intervention Period

3.4 Safety Endpoints

Safety evaluations include frequency of 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.

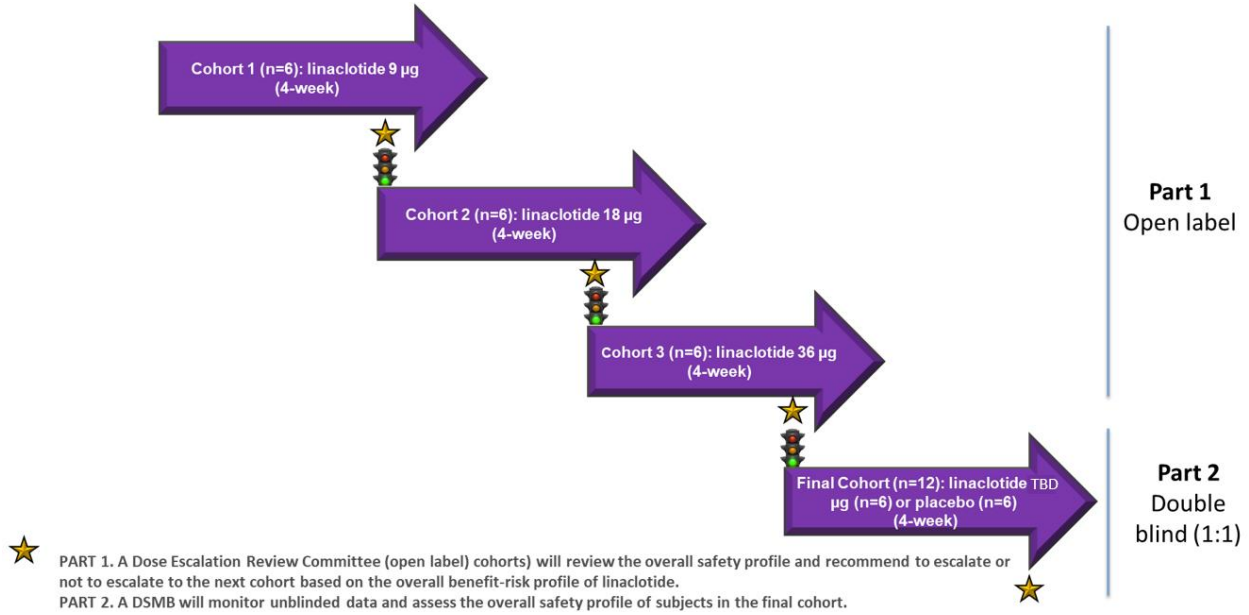
4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

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 located in the Operations Manual.

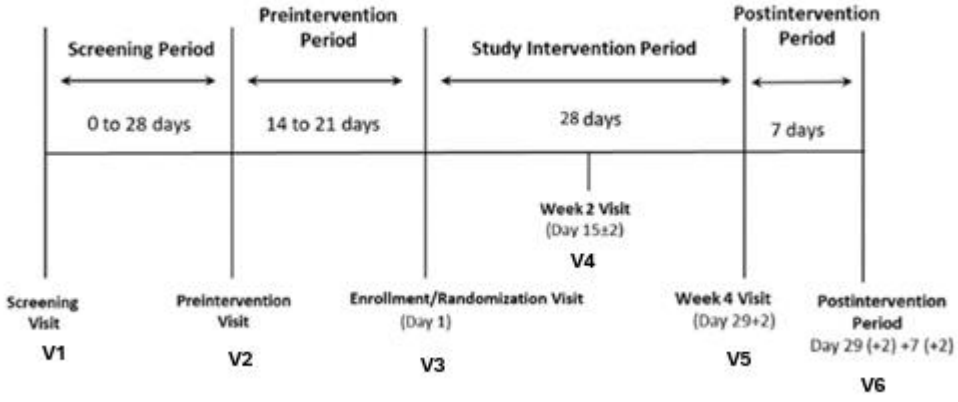
See Section 5 for information regarding eligibility criteria.

Figure 1. Study Schematic



TBD = to be determined in Part 1

Figure 2. Study Visit Schematic for Parts 1 and 2



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 cohort(s) 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.

Up to 30 and at least 18 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 9 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 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. 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 (≤ 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.

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. The dose will be selected based on: 1) the absence of treatment-related AESI within the cohort and 2) an increase in SBM frequency per week compared to baseline with or without improvement of at least 1 point in the Bristol Stool Form Scale (BSFS) scale. The minimum effective dose will be selected.

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 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 2, new subjects will be recruited. Data based on the final selected dose will be analyzed and compared with a 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.

4.2 Discussion of Study Design

Choice of Study Population

The inclusion and exclusion criteria are meant to identify a population of pediatric subjects that is well characterized as having FC as defined by Rome IV criteria.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy and safety-related measurements in this study are standard for assessing disease activity in subjects with FC. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

Despite the fact that children with FC are commonly prescribed various and miscellaneous pharmacologic agents, it is notable that there are no approved products indicated for FC in children less than 6 years of age or well controlled trials of these frequently prescribed agents. Thus, effective treatments are needed to provide symptomatic relief in children less than 6 years of age with FC, with the evidence for safety and efficacy of these based on the results of adequate and well-controlled studies.

This study is being conducted in pediatric subjects aged 6 months to less than 2 years who meet Rome IV criteria for FC based on the linaclotide pediatric developmental program and discussions with regulatory agencies. Section 5.1 outlines the eligibility criteria and the eligible subject population.

Dose Justification

The dose selection in this study is based on extrapolation of efficacy and safety data from Phase 2 studies in FC subjects 2 to 17 years of age, Phase 3 studies in adult subjects with CIC, and a clinical research GC-C ontogeny study in pediatric patients.

In the Phase 2 FC study, Lin-MD-67, children (2- to 5-year-olds), were administered linaclotide doses of 18, 36, and 72 µg for 4 weeks. Those doses correspond to 1.8, 3.6, and 7.2 µg/kg in a 10 kg (22 pound) subject (minimum weight of a 2-year-old), respectively. Overall linaclotide was well tolerated across all doses evaluated in LIN-MD-67, the safety profile being consistent with that of the prior FC study LIN-MD-62 in 6 to 17 year-olds and prior studies in adults with CIC. There were no deaths, SAEs, AESIs (i.e., significant volume depletion and/or significant electrolyte abnormalities and/or ECG abnormalities that were considered by the investigator or sponsor to be related to diarrhea), or AEs leading to study drug discontinuation for LIN-MD-67 with all TEAEs experienced by subjects being mild or moderate in severity.

Additionally, in the GC-C ontogeny study MCP-103-311, GC-C mRNA expression in the small bowel was shown to be flat with no age-dependent trend in patients 6 months to < 18 years of age.[6] The doses of 9, 18, and 36 µg QD being employed in Study M21-862 correspond to 1.8, 3.6 and 7.2 µg/kg in a 5 kg (11 pound) subject (minimum weight of a 6 month old), respectively and are therefore equivalent to the doses tested and safe in 2- to 5- year-old subjects on µg/kg basis and are expected to have an acceptable safety profile. Dose escalation between cohorts will be assessed based on the review of all available safety/tolerability data by an internal Dose Escalation Committee. Regarding risks, patients are closely monitored for AEs including diarrhea and well-defined AESIs. Safety measures are in place including stopping criteria, a safety monitoring plan, and an independent DSMB.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. The Subjects' LAR/parent/guardian must voluntarily sign and date an informed consent, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.
- 2. The LAR/parent/guardian who will be completing the electronic diary (eDiary) is able to read and understand the assessments in the eDiary device and must undergo training
- 3. Subject's LAR/parent/guardian are willing and able to comply with procedures required in this protocol and do not have any neurodevelopmental disabilities that could impact their ability to complete the eDiary and study questionnaires.

Demographic and Laboratory Assessments

- 4. **Individuals** must be 6 months to less than 1 year and 11 months old, at the time the LAR/parent/guardian signs the informed consent in alignment with local requirements.
- 5. Subject has no condition or clinically significant findings on a physical examination, vital sign assessment, ECG, or clinical laboratory tests at Screening (Visit 1), as determined by the investigator, based on consideration of whether the finding could represent a safety concern or a condition that would be exclusionary, could prevent the subject from performing any protocol assessments, or could confound study assessments
- 6. Subject has weight-for-height/length ratio of ≥ 3rd percentile for age 6 months to less than 24 months at the time the LAR/parent/guardian has provided signed consent. (Investigators can choose to use CDC or WHO growth charts based on their current clinical practice).
- 7. Laboratory values meet the following criteria within the screening of assessments period and prior to the first dose of study drug:
  - Serum alanine transaminase (ALT) < 2 × upper limit of normal (ULN);

Per investigator's discretion all other laboratory values obtained in the screening period prior to the first dose of study drug must not be considered clinically significant abnormalities.

- 8. Subject's LAR/parent/guardian must have not been directly or indirectly involved in the conduct and administration of this study as an investigator, study coordinator, or other study staff member. In addition, any subject, LAR/parent/guardian must not have a first-degree family member, significant other, or relative residing with him/her who are directly or indirectly involved in this study.

Disease/Condition Activity

- 9. Subject meets Rome IV criteria for FC as outlined below:

  For at least 1 month before Screening (Visit 1), the subject must meet 2 or more of the following (a-e):

  a) 2 or fewer defecations per week (with each defecation occurring in the absence of any laxative, suppository, or enema use during the preceding 24 hours)

  b) History of excessive stool retention

  c) History of painful or hard bowel movements (BMs)

  d) History of large-diameter stools

  e) Presence of a large fecal mass in the rectum

  Accompanying symptoms may include irritability, decreased appetite, and/or early satiety. The accompanying symptoms disappear immediately following passage of a large stool.

- 10. LAR/Parent/Guardian is willing to discontinue any laxatives used before the Preintervention Visit in favor of the protocol-permitted rescue medicine.

- 11. Based on the eDiary, the LAR/Parent/Guardian/Caregiver reports the subject did not have more than 1 loose, mushy stool (eDiary recorded stool consistency of 6 on the Bristol Stool Form Scale) or any watery stool (eDiary recorded stool consistency of 7 on the Bristol Stool Form Scale) with any SBM that occurred in the absence of laxative use on the calendar day of the BM **or** the calendar day before the BM during the 14 days before and up to enrollment/randomization (including the daily eDiary assessment reported before administration of the first dose of study intervention on the enrollment/randomization day).

- 12. Based on the eDiary, the Subject has an average of ≤ 2 spontaneous bowel movements (SBMs) per week during the 14 days before the enrollment/randomization day and up to the enrollment/randomization (including the morning eDiary assessments reported before administration of first dose of study intervention on the enrollment/randomization day). An SBM is defined as a bowel movement (BM) that occurs in the absence of laxative, enema, or suppository use on the calendar day of the BM or the calendar day before the BM.

- 13. LAR/Parent/Guardian/Caregivers are compliant with eDiary requirements by completing daily assessments for 10 out of the 14 days immediately preceding the enrollment/randomization visit.

Subject History

- 14. No conditions that could **interfere with drug absorption** including but not limited to short bowel syndrome.
- 15. No history of clinically significant medical conditions or any other reason that the investigator determines would **interfere with the subject's participation** in this study or would make the subject an unsuitable candidate to receive study drug.
- 16. No participation in an interventional study within 30 days before Screening (Visit 1) or plans to receive study intervention (other than that administered during this study)
- 17. No fecal impaction at Visit 2 (Preintervention) after failing outpatient clean-out during the Screening Period OR no fecal impaction at Visit 3 (enrollment/randomization).
- 18. No required manual dis-impaction within 6 months prior to enrollment/randomization
- 19. No current condition of unexplained AND clinically significant alarm symptoms (lower gastrointestinal [GI] bleeding [rectal bleeding or heme-positive stool], iron-deficiency anemia, or any unexplained anemia, or weight loss) and systemic signs of infection or colitis, or any neoplastic process
- 20. No surgery that meets any of the following criteria:
  a) Surgery to remove a segment of the GI tract at any time before Screening (Visit 1)
  b) Surgery of the abdomen, pelvis, or retroperitoneal structures during the 6 months before the Screening Visit
  c) An appendectomy or cholecystectomy during the 60 days before Screening (Visit 1)
  d) Other major surgery during the 30 days before Screening (Visit 1)
- 21. No known or suspected mechanical bowel obstruction or pseudo-obstruction
- 22. No known allergy, allergic reaction, or significant sensitivity to the study intervention or its components and/or other medications in the same drug class
- 23. No history of:
  a) Celiac disease, or positive serological test for celiac disease or the condition is suspected but has not been ruled out by endoscopic biopsy
  b) Cystic fibrosis
  c) Hypothyroidism that is untreated or treated with thyroid hormone at a dose that has not been stable for at least 3 months prior to Screening (Visit 1)
  d) Down's syndrome or any other chromosomal disorder
  e) Active anal fissure (investigator has confirmed an active anal fissure and subject reports known anal fissure symptoms [i.e., streaks of blood on the stool or on diaper or toilet paper and pain/crying with bowel movement within 2 weeks prior to Screening]). (Note: Anal fissures that have resolved at least 2 weeks prior to screening would not be exclusionary). However, if in the investigator's opinion, an anal fissure(s) may be the primary cause of subject's Rome IV FC criteria, the subject would not be eligible to participate in the study.
  f) Anatomic malformations (e.g., imperforate anus, anal stenosis, anterior displaced anus)

g) Intestinal nerve or muscle disorders (e.g., Hirschsprung disease, visceral myopathies, visceral neuropathies)

h) Neuropathic conditions (e.g., spinal cord abnormalities, neurofibromatosis, tethered cord, spinal cord trauma)

i) Lead toxicity, hypercalcemia

j) Inflammatory bowel disease

k) Lactose intolerance that is associated with symptoms which could confound the assessments in this study

l) History of cancer. (Note: Subjects with a history of cancer are allowed provided that the malignancy has been in a complete remission before enrollment/randomization (Visit 3). A complete remission is defined as the disappearance of all signs of cancer in response to treatment)

- 24. No known active SARS-CoV-2 infection. Per local requirements/recommendations SARS-CoV-2 infection should be ruled out before entering the study. Subjects who do not meet SARS-CoV-2 infection eligibility criteria must be screen failed and may re-screen upon recovery from COVID-19.

Concomitant Medications

- 25. Subject did not use a protocol-specified prohibited medicine before the start of the Preintervention Period (Visit 2) or failed to meet the stable-dose requirements of certain medications
- 26. Subject did not use rescue medication on the calendar day before the enrollment/randomization visit and on the day of the enrollment/randomization visit prior to enrollment/randomization.
- 27. Subject did not participate in an interventional study within 30 days before Screening (Visit 1) or is planning to receive study intervention (other than that administered during this study).
- 28. Subject must not have been treated with **any investigational drug** within 30 days or 5 half-lives of the drug (whichever is longer) prior to Screening (Visit 1) or is currently or planning to enroll in another clinical study or was previously enrolled in this study.

5.2 Prohibited Medications and Therapy

All medications listed below (1-day washout and 14-day washout) will be excluded during the Preintervention, Study Intervention, and Postintervention Periods. A 1-day washout means that particular medicine is not allowed during the calendar day before the Preintervention Visit (not permitted 24-hours prior to the Preintervention Visit); a 14-day washout means that the particular medicine is not allowed during the 14 calendar days before the Preintervention Visit. Per investigator's discretion, subjects who are screen failed for failing to meet washout requirements may be re-screened.

1 Day Washout

1. Any over the counter or prescription laxative, suppository, or enema (e.g., polyethylene glycol, lactulose, Fleet enema) and any herbal or natural agent that might be taken for constipation. (Note: The use of fiber, bulk laxatives, stool softeners, and probiotics is acceptable, provided that the subject has been on a stable dose for 30 days before the Screening Visit (Visit 1) and plans to continue stable dosing for the duration of the study)
2. Any medicine used to treat diarrhea (e.g., bismuth subsalicylate, kaolin)

14 Day Washout

1. Drugs with known pharmacologic activity at 5-HT4, 5-HT2b or 5-HT3 receptors (e.g., cisapride, tegaserod, prucalopride, ondansetron, tropisetron, granisetron, dolasetron, mirtazapine)
2. Any of the following treatments either alone or in combination: plecanatide, lubiprostone, colchicine, linaclotide, and misoprostol.
3. Prokinetic agents (e.g., metoclopramide, itopride, domperidone)
4. Anticholinergic agents (e.g., dicyclomine, flavoxate, scopolamine, hyoscyamine, propantheline, oxybutynin, tolterodine, solifenacin, darifenacin, trospium). (Note: inhaled ipratropium and tiotropium are permitted at the discretion of the investigator)
5. Bile acid sequestrants (e.g., cholestyramine, colestipol)
6. Cholinomimetic agents (e.g., bethanechol, pyridostigmine, tacrine, physostigmine). (Note: intraocular cholinomimetic agents such as pilocarpine are permitted at the discretion of the investigator)
7. Antipsychotic agents (e.g., risperidone, haloperidol, droperidol, chlorpromazine, perphenazine and any other phenothiazines~~,~~ quetiapine, olanzapine, clozapine), unless the subject has been on a stable dose for 30 days before the Screening Visit (Visit 1) and plans to continue stable dosing for the duration of the study. (Note: paliperidone is permitted at the discretion of the investigator)
8. Antidepressants, unless the subject has been on a stable dose for 30 days before the Screening Visit (Visit 1) and plans to continue stable dosing for the duration of the trial. Specifically included are the following prohibited antidepressants:
    a) Tricyclic antidepressants (e.g., amitriptyline, imipramine, nortriptyline)
    b) Monoamine oxidase inhibitors (e.g., furazolidone, isocarboxazid, pargyline, phenelzine, selegiline, tranylcypromine)
    c) Selective serotonin reuptake inhibitors (e.g., fluoxetine, sertraline, paroxetine, escitalopram, citalopram, vilazodone)
    d) Serotonin-norepinephrine-reuptake inhibitors (e.g., levomilnacipran, duloxetine, venlafaxine, desvenlafaxine succinate)
    e) Other antidepressants (e.g., trazodone, bupropion)

9. Calcium-channel blocker verapamil, unless the subject has been on a stable dose for 30 days before the Screening Visit (Visit 1) and plans to continue stable dosing for the duration of the study. (Note: all other calcium-channel blockers [e.g., nifedipine, diltiazem, amlodipine, felodipine, nicardipine, nimodipine, nisoldipine] are permitted and may be used without restriction)
10. Oral and parenteral antibiotics; however, 1 standard regimen (up to 10 days) of oral antibiotics is permitted during the Study Intervention and Postintervention Periods
11. Any study intervention or imported drugs that have not been approved for human use.
12. All narcotics (e.g., tramadol, codeine, morphine, propoxyphene, loperamide, diphenoxylate, paregoric), either alone or in combination. Note: narcotics used as anesthesia for a colonoscopy require a 5-calendar day wash-out prior to the subject entering into the Preintervention Period. Dextromethorphan, the cough suppressant in many over-the counter cold and cough medicines, is allowed
13. Any medicine that is known to cause diarrhea or constipation (e.g., acarbose)
14. Proton pump inhibitors (e.g., omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole), unless the subject has been on a stable dose for 30 days before the Screening Visit (Visit 1) and plans to continue stable dosing for the duration of the study
15. Other drugs such as barbiturates (e.g., butalbital, phenobarbital) and chronic oral or parenteral glucocorticoids, which must be discontinued at least 3 months before screening. However, one 10-day course of oral or 1 injection of parenteral glucocorticoids is permitted during the Study Intervention and Postintervention Periods. Pregabalin is acceptable, provided the subject has been on a stable dose during the 30 days before the Screening Visit and plans to continue stable dosing throughout the study.

5.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded from 28 days prior to study drug administration through the 1-week postintervention visit ([Visit 6]).

Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact. Information regarding potential drug interactions with linaclotide can be located in the linaclotide IB.

Subjects must be able to safely discontinue any prohibited medications 5 half-lives or 4 weeks prior to initial study drug administration. Legally authorized representative/parent/guardian must provide consent for the study prior to the subject discontinuing any prohibited medications for the purpose of meeting study eligibility. Protocol-permitted rescue medications are shown in Table 2.

Table 2. Rescue Concomitant Medications/Therapy

Rescue Concomitant Medications/Therapy	Comments/Notes
Lactulose (oral)	Rescue medication may be taken when at least 72 hours have passed since the subject's previous BM or when their symptoms become intolerable.
Glycerin suppositories (rectal)	If fecal impaction is identified at Screening (Visit 1), subjects will receive a disimpaction regimen with either oral or rectal medication managed at the discretion of the investigator. Options will include any over-the-counter or prescription laxative, suppository, or enema (e.g., polyethylene glycol, lactulose, Fleet enema).

BM = bowel movement

5.4 Dose Interruption

Subjects with poor tolerability (as determined by the investigator), can temporarily interrupt the study drug for 3 consecutive days and resume the same dose if tolerability improves. If not, subjects will discontinue the investigational drug per the Discontinuation Criteria Section of this document (Section 5.5 and Section 6.2).

5.5 Withdrawal of Subjects and Discontinuation of Study

A subject whose LAR/parent/guardian gave consent may voluntarily withdraw the subject or the subject can be withdrawn from the study at any time for reasons including, but not limited to, the following:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the Sponsor.
- The investigator believes it is in the best interest of the subject.
- The LAR/parent/guardian requests withdrawal from the study.
- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk.
- The investigator determines the subject is significantly noncompliant with study procedures.

Discontinuation Criteria

A premature discontinuation will occur when a subject (whose LAR/parent/guardian who gave consent) ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

Subjects **must be** prematurely discontinued from the study for reasons of safety including those who experience:

- An SAE considered by the investigator or the sponsor to be possibly related or related to study intervention,
- An AESI (Clinically significant [per investigator's discretion] dehydration due to diarrhea causing hospitalization, significant electrolyte abnormalities related to diarrhea and/or ECG abnormalities related to diarrhea that are considered by the investigator or sponsor to be related to the study drug. Refer to Table 3 and Table 4),
- The presence of intentional overdose or intentional misuse per investigator discretion,
- The occurrence of any other AE that in the opinion of the investigator or the sponsor is possibly related or related to the study intervention that represents a clinically significant safety risk to the subject.

Table 3. Potentially Clinically Significant Electrolyte Values

Parameter	Lower Limit	Upper Limit
Bicarbonate	< 0.9 × LLN	> 1.1 × ULN
Chloride	< 0.9 × LLN	> 1.1 × ULN
Magnesium	< 0.9 × LLN	> 1.1 × ULN
Potassium	< 0.9 ×LLN	> 1.1 × ULN
Sodium	< 0.9 × LLN	> 1.1 × ULN

LLN = lower limit of normal value provided by the laboratory; ULN = upper limit of normal value provided by the laboratory

Table 4. Potentially Clinically Significant ECG Values

Parameter	Higher Limit
QRS interval	QRS ≥ 115 msec
PR interval	PR > 225 msec
QTc	> 480 msec

ECG = electrocardiogram; QTc = QT interval corrected for heart rate

Subjects **may** also be prematurely discontinued from the study for reasons of safety including those who experience:

- A vital sign, ECG, and/or laboratory abnormality judged to be clinically significant by the investigator and that in the opinion of the investigator or the sponsor is possibly related or related to the study intervention
- An intolerable AE (defined as an AE that subjectively would cause a subject to consider study withdrawal), as determined by the investigator or the Sponsor.

Additionally, discontinuation of study intervention for abnormal liver function should be considered by the investigator when a subject meets the criteria for Hy's law or the appearance of abnormal laboratory test results suggesting severe drug-induced liver injury (DILI), or if the investigator believes that it is in best interest of the subject. If Hy's law criteria are met and it is considered, in the opinion of the investigator or the Sponsor, to be possibly related to the study drug, the subject must be discontinued from the study. Refer to Appendix E for additional information.

All enrolled subjects who prematurely discontinue from the study, regardless of cause, should be seen for the assessments to be completed at the End of Treatment (EOT) Visit. The EOT assessments are defined as completion of evaluations scheduled for all subjects.

Subjects who discontinue from the study and do not return to the study site for EOT Visit (Visit 5) must be requested in writing to return to the study site for procedures required at the EOT Visit as defined in the Activity Schedule (Appendix D) and return any unused study intervention. A copy of the letter, together with the source documentation, will be kept in the investigator's files. The reason for premature discontinuation from the study will be recorded on the Study Termination Page of the electronic case report form (eCRF). Study site staff will be contacted by the sponsor after each premature discontinuation to ensure proper characterization of the reason for discontinuation is captured.

See the Activity Schedule (Appendix D) for data to be collected at the time of study intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Subjects in this study who prematurely discontinue study intervention will not be replaced (e.g., no more subjects will be allowed to enter the study once randomization is completed).

Criteria for Consideration of Study Discontinuation

Dosing and enrollment will be immediately paused for all subjects at all sites and a thorough review will be initiated after any one of the following conditions has been met in subjects who have received study intervention at any time in the study:

- Any life-threatening SAE that is considered by the investigator or the sponsor to be possibly related or related to the study intervention.
- Any SAE resulting in death that is considered by the investigator or the sponsor to be possibly related or related to the study intervention.

In the event of a pause in enrollment and dosing, the DSMB will be notified and their recommendation on an appropriate course of action will be sought. This may include resuming enrollment, continuing a hold on enrollment, resuming the study intervention, amending the protocol or stopping the study (refer to Section 5.10 for additional data safety monitoring information). The decision to restart or to stop the study will be made by the sponsor, following a thorough review of all clinical, laboratory, DSMB recommendations, and other available safety data.

Lost to Follow up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject's LAR/parent/guardian and reschedule the missed visit as soon as possible and counsel them on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject's LAR/parent/guardian (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts will be documented in the subject's study record.
- Should the subject's LAR/parent/guardian continue to be unreachable, the subject will be considered to have withdrawn from the study.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at their site if they have safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

5.6 Follow-Up After Subject Discontinuation of Study Drug or from Study

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment due to an AE should continue to be followed for all regularly scheduled visits, unless subject's LAR/parent/guardian has decided to discontinue the study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit (PD visit) should be completed as soon as possible, preferably within 2 weeks of the last visit. In addition, if the LAR/parent/guardian is willing, the 1-week postintervention visit (after the last dose of study drug) may be completed to ensure all treatment-emergent AEs/SAEs have been resolved.

5.7 Study Drug

Study drug will be administered at the study site after confirming eligibility.

Study drug dose preparation and administration instructions will be provided separately.

Linaclotide (or matching placebo for Part 2 only) will be taken orally once daily beginning on Day 1 (Baseline) and should be taken at approximately the same time each day, 15 - 30 minutes before a meal. If subjects should forget to take their study drug dose at their regularly scheduled dosing time, they

should take the forgotten dose as soon as they remember as long as it is at least 15 - 30 minutes before their next meal. Otherwise, they should take the next dose at the next scheduled dosing time; subjects may eat 15 - 30 minutes after dosing. No redosing will be allowed on the same day.

The subject must complete at least 4 weeks (28 days) intervention period before returning for the Week 4/Day 29 End of Treatment (EOT) (Visit 5).

Subject dosing will be recorded on a subject dosing eDiary. The LAR/parent/guardian will be instructed to return all drug containers (even if empty) to the study site personnel at each study visit. If required, the LAR/parent/guardian should also return the receptacle containing unused solution to the study site personnel for destruction. The study site personnel will document compliance.

AbbVie will provide study drug for linaclotide (or matching placebo for Part 2 only). AbbVie provided study drug should not be substituted or alternately sourced unless otherwise directed by AbbVie. Study drug will only be used for the conduct of this study.

If a subject's LAR/parent/guardian is unable to come to the study site to pick up the subject's study drug due to COVID-19, a direct-to-patient (DTP) study drug shipment can be made from the study site to the subject's LAR/parent/guardian if allowed by local regulations. AbbVie will submit any required notifications to the regulatory authority as applicable. Refer to the Operations Manual in Appendix G for details on DTP shipment of study drug.

Linaclotide and matching placebo will be packaged in bottles with quantities sufficient to accommodate study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label. Each kit will contain a unique kit number. This kit number is assigned to a subject via IRT and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Site staff will complete all blank spaces on the label before dispensing to subjects.

Upon completion of or discontinuation from study treatment, all original study drug units (containing unused study drugs) will be returned to the sponsor (or designee) or destroyed on site. All return or destruction procedures will be according to instructions from the sponsor and according to local regulations following completion of drug accountability procedures.

AbbVie will provide instructions to the LAR/parent/guardian for drug preparation.

Table 5. Identity of Study Drug

Study Drug	Linaclotide	Linaclotide	Linaclotide	Placebo for Linaclotide
Dosage Form[a]	Capsule[a]	Capsule[a]	Capsule[a]	Capsule[a]
Strength	72 µg	145 µg	290 µg	N/A
Route of Administration	Oral	Oral	Oral	Oral

N/A = not applicable

a. The entire capsule contents will be used in dose preparation of an **oral solution** to achieve the assigned dosage strength per cohort. The LAR/parent/guardian will prepare the dose prior to subject's administration of the study drug. Complete dosing instructions will be provided to the LAR/parent/guardian.

5.8 Randomization/Drug Assignment

All subjects will be assigned a unique identification number by the IRT at the screening visit. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule.

Cohorts 1-3 will be open label linaclotide. Only Part 2 (the final cohort) will be randomized to either linaclotide or placebo at a 1:1 ratio.

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), the investigator, study site personnel, and the subject's LAR/parent/guardian will remain blinded to each subject's treatment throughout Part 2 of the study. To maintain the blind, the linaclotide capsules and placebo capsules provided for the study will be identical in appearance.

For Part 2, the IRT will provide access to unblinded subject treatment information in the case of a medical emergency. In the event of a medical emergency that requires unblinding of the study drug assignment, the investigator is requested to contact the Emergency Medical Contact (AbbVie Therapeutic Area Medical Director) prior to breaking the blind. However, if an urgent therapeutic intervention is necessary which warrants breaking the blind prior to contacting the AbbVie TA MD, the investigator can directly access the IRT system to break the blind without AbbVie notification or agreement. Unblinding is available in the IRT system via the Unblind Subject transaction, which is available only to the investigator. If the IRT system is unavailable, unblinding may occur by contacting the technical support of the IRT vendor via either phone (preferred) or email (support@endpointclinical.com). For country-specific phone numbers, please see the following website: https://www.endpointclinical.com/support/.

In the event that the blind is broken before notification to the AbbVie TA MD, we request that the AbbVie TA MD be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be conveyed to AbbVie and recorded on the appropriate eCRF.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to COVID-19), the investigator is responsible for notifying independent ethics committee IEC/independent review board (IRB), regulatory authorities (as applicable), and AbbVie. Any deviations that occur as a result of COVID-19 should also be documented in the source records.

5.10 Rescreening

Subjects who initially screen-failed for the study are permitted to rescreen once following reconsent. For additional rescreening, Sponsor approval is required for any subsequent rescreens (i.e., after the first rescreen). As appropriate, sites are encouraged to contact Sponsor to confirm if subjects should or should not be rescreened. All screening procedures will be repeated during rescreening. The subject must meet all the eligibility criteria at the time of rescreening in order to qualify for the study. There should be a 30 day gap period between screen-fail and rescreening.

5.11 Data Safety Monitoring

Part 1 Open Label Cohorts

In Part 1 all AE data and the occurrence of intolerable diarrhea will be reported to the sponsor. The Internal Dose Escalation Review committee will monitor Part 1 and based on the frequency and severity of the events, could recommend halting the administration of the investigational product (more details are described in a separate charter). The Internal Dose Escalation Review committee will also give special attention to the presence of AESIs. A cohort will be stopped if 1 treatment-related AESI occurs. If no treatment-related AESI occurred, the Dose Escalation Review Committee will decide on whether to proceed with the next cohort.

Part 2 Randomized Double Blind Placebo Controlled Cohort

In Part 2 an external DSMB composed of clinicians and statisticians independent of AbbVie and with relevant expertise in their field will review unblinded safety data from the ongoing study. The DSMB is responsible for safeguarding the interests of trial subjects, assessing the safety of the interventions during the trial, as well as for monitoring the integrity and interpretability of the trial. The DSMB will provide recommendations to the sponsor regarding ongoing trial conduct or modifications to the trial as described in a separate DSMB charter.

In order to maintain sponsor blinding, an external Statistical Data Analysis Center is responsible for performing the analyses described in the DSMB charter as well as additional analyses requested by the DSMB and facilitating interpretation and answering questions that arise before, during or after DSMB review. An independent DSMB will review unblinded interim safety data for Part 2.

The DSMB will regularly review unblinded safety data from the ongoing study according to the schedule provided in the DSMB charter, including AEs, laboratory values, vitals sign values and ECG results. The occurrence of intolerable diarrhea will be reported to the sponsor and will be monitored; In addition to all AE data, by an external DSMB, who, based on the frequency and severity of the events, could recommend halting the administration of the investigational product.

A separate DSMB charter will be prepared outside of the protocol and will further describe the roles and responsibilities of the DSMB members, frequency and scope of the data reviews, and expectations for blinded communications.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device damage or not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event.

Reporting will be done via electronic data capture (EDC). The date the product complaint details are entered into EDC and the form is saved represents the date reported to AbbVie. A back-up paper form will be provided for reporting complaints related to unassigned product or in the event of an EDC system issue. If a back-up paper form is used, the date the form is emailed to RD_PQC_QA@abbvie.com represents the date reported to AbbVie.

All follow-up information is to be reported to the sponsor (or an authorized representative) and documented in source as required by the sponsor. Product complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events: Linaclotide

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is

considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol-specific criteria (see Section 6.2 regarding toxicity management), and/or if the investigator considers them to be AEs.

The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and/or the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance as a SAE within 24 hours of the site being made aware of the SAE (refer to Section 4.2 of the Operations Manual for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event along with any suspected transmission of an infectious agent via a medicinal product if no other serious criterion is applicable. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All adverse events reported from the time of study drug administration up to 30 days, after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. After 30 days, following the last dose of study drug or completion of study treatment only spontaneously reported SAEs will be collected (nonserious AEs will not be collected). In addition, study procedure-related serious and nonserious adverse events will be collected from the time the subject signs the study-specific informed consent.

The following definitions will be used for Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR):

SAR	Defined as all noxious and unintended responses to an IMP related to any dose administered that result in an SAE as defined above.
SUSAR	Refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is unexpected (not listed in the applicable Reference Safety Information), and meets one of the above serious criteria.

AbbVie will be responsible for SUSAR reporting for the Investigational Medicinal Product (IMP) in accordance with global and local requirements.

Adverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Events of Special Interest

The following AESI will be monitored during the study:

- Clinically significant (per investigator's discretion) dehydration due to diarrhea causing hospitalization, which is considered by the investigator or sponsor to be related to the study drug.

- Clinically significant (per investigator's discretion) electrolyte abnormalities due to diarrhea, which is considered by the investigator or sponsor to be related to the study drug.
- Clinically significant (per investigator's discretion) ECG abnormalities due to diarrhea, which is considered by the investigator or sponsor to be related to the study drug.

The investigator should contact the sponsor if there is any question whether the criteria for an AESI have been met.

To ensure the safety of the subjects, children will be carefully monitored for safety and tolerability. Legally authorized representative/parents/guardians will be instructed to stop the drug and contact the investigator in case of the onset of any AESI. Additionally, the occurrence of intolerable diarrhea (as assessed by the investigator), will be reported to the sponsor. Intolerable diarrhea and all AE data will be monitored by the DSMB, who, based on the frequency and severity of the events, could recommend halting the administration of investigational product (refer to Section 5.10 for additional details).

Adverse Event Severity and Relationship to Study Drug

The investigator will rate the severity of each AE according to the NCI CTCAE (Version 4.03)

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

6.2 Toxicity Management

The management of specific AEs and laboratory parameters is described in the Operations Manual. This includes AEs of:

- Clinically significant (per investigator's discretion) dehydration due to diarrhea causing hospitalization, which is considered by the investigator or sponsor to be related to the study drug.
- Clinically significant (per investigator's discretion) electrolyte abnormalities due to diarrhea, which is considered by the investigator or sponsor to be related to the study drug.
- Clinically significant (per investigator's discretion) ECG abnormalities due to diarrhea, which is considered by the investigator or sponsor to be related to the study drug.

This also includes the following laboratory abnormalities: Significant electrolyte abnormalities related to diarrhea. For allowed study drug interruption, the following rules apply:

1. Allow study drug interruption up to 3 consecutive days for tolerability, AEs, and emergency surgery.
2. If the subject must undergo emergency surgery, the study drug should be interrupted at the time of the surgery. After emergency surgery, allow reintroduction of study drug once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.
3. Additionally, the occurrence of intolerable diarrhea will be reported to the sponsor and will be monitored, in addition to all AE data, by an internal Dose Escalation Review Committee (open label cohorts Part 1) or an external DSMB (double-blind Part 2 [final cohort]), who, based on the frequency and severity of the events, could recommend halting the administration of investigational product.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on key analyses. Complete and specific details of the statistical analysis, including handling of missing data, will be described in the Statistical Analysis Plan (SAP).

7.2 Definition for Analysis Populations

The ITT Population includes all subjects who received at least 1 dose of study drug. The ITT Population will be used for all efficacy analyses.

The Safety Analysis Set consists of all subjects who received at least 1 dose of study drug.

7.3 Handling 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).

7.4 Statistical Analyses for Efficacy

The efficacy analysis will be summarized in the ITT Population descriptively and no statistical testing will be performed in this study.

Summary and Analysis of the Key Efficacy Endpoints

Analysis of the key efficacy endpoints will be conducted on the ITT population. The key efficacy endpoints will be analyzed via descriptive summary statistics in terms of mean, median, standard deviation, standard error of mean, minimum, and maximum.

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 the 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 average 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 average straining scores from all 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.

Subgroup Analysis for Efficacy

The key efficacy endpoints will be summarized descriptively for age groups from 6-months to less than 1 year and 1 year to 2 years of age.

7.5 Statistical Analyses for Safety

All safety analyses will be conducted on the safety population. No statistical analysis will be performed on any of the safety assessments.

Adverse events, growth parameters of height and weight, vital signs, and clinical laboratory measurements will be summarized using descriptive statistics for continuous variables and frequency distributions for categorical variables. For all safety variables, subject data listings will be provided.

Adverse events will be tabulated using the MedDRA system organ class and Preferred Term. Adverse events will be summarized by the number of subjects with AEs. For clinical laboratory parameters, values outside the normal ranges and clinically significantly abnormal laboratory values will be listed.

All safety endpoints and analyses will be fully defined in the SAP.

7.6 Overall Type I Error Control

No multiplicity adjustment will be applied because there are no statistical hypotheses for the key efficacy endpoints.

7.7 Sample Size Determination

The planned total sample size is up to 30 and at least 18 subjects. Sample size in this study is not driven by statistical consideration. Instead, this study is designed to enroll a sufficient number of pediatric subjects to observe the clinical response trends and monitor safety.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Independent Ethics Committee/Institutional Review Board (IEC/IRB) for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

For the personal data that AbbVie, and for sites in the EU AbbVie Deutschland GmbH & Co, controls and maintains, AbbVie has developed a robust security program focused on due diligence in design, managed change, and information security governance. Information security policies govern the information security functions including identity and access management, operations, infrastructure, application, and third-party security requirements. The risk-based AbbVie Data Classification Tool dictates the level of scrutiny and control required for the relevant activities per AbbVie's information security policies taking into account the sensitivity of the data.

Before subject data are shared with AbbVie, the study doctor and staff will replace any information that could directly identify a subject (such as name, address, and contact information) with a generic code which AbbVie cannot link to that subject's identity to protect the confidentiality of the data.

AbbVie has a data protection impact assessment (DPIA) program to ensure and document the appropriate controls and safeguards stated above are in place for clinical trial data that it controls and maintains, and these processing activities respect the privacy of clinical trial subjects. AbbVie also maintains robust security incident response policies and procedures, including requirements for the containment of any data related incidents, the mitigation measures where needed, and notification to authorities or affected individuals where required.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s). During the COVID-19 pandemic remote data review/verification may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 START AND COMPLETION OF THE STUDY

The start-of-study is defined as the date of the first site activated.

The end-of-study is defined as the date of end of study participation by the last subject in the last country where the study was conducted.

12 REFERENCES

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	Adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
AST	aspartate aminotransferase
BMs	bowel movements
BSFS	Bristol Stool Form Scale
CBC	complete blood count
CIC	chronic idiopathic constipation
COVID-19	coronavirus disease - 2019
DILI	drug-induced liver injury
DPIA	data protection impact assessment
DSMB	data Safety Monitoring Board
DTP	direct-to-patient
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	Electronic data capture
eDiary	electronic diary
EOT	End of Treatment
EU	European Union
EudraCT	European Clinical Trials Database
FC	functional constipation
GC-C	guanylate cyclase subtype C
GCP	Good clinical practice
GFR	glomerular filtration rate
GI	gastrointestinal
IB	investigator's Brochure
IBS-C	irritable bowel syndrome with constipation
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IEC/IRB	Independent Ethics Committee/Institutional Review Board

Abbreviation	Definition
IMP	Investigational Medicinal Product
INR	international normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
ITT	intent-to-treat
IWRS	Interactive web response system
LAR	legally authorized representative
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger RNA
PD visit	premature discontinuation visit
PEG	polyethylene glycol
PK	Pharmacokinetic(s)
qd	once daily
QTc	QT interval corrected for heart rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	serious adverse reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBM	Spontaneous Bowel Movement
SUSAR	Suspected unexpected serious adverse reactions
TA MD	Therapeutic Area Medical Director
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol 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).

Protocol Date: 25 November 2024

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and local laws and regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/IEC, except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the IB/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly (within one (1) calendar day to AbbVie), the ethics committees/institutional review boards (as required) and other appropriate individuals (e.g., coordinating investigator, institution director):
    - All changes in the research activity and all unanticipated problems involving risks to human subjects or others
    - Any departure from relevant clinical trial law or regulation, GCP, or the trial protocol that has the potential to affect the following:
        - Rights, safety, physical or mental integrity of the subjects in the clinical trial
        - Scientific value of the clinical trial, reliability or robustness of data generated
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]		Clinical Development Statistics

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities. The individual activities are described in detail in the **Operations Manual**. Allowed modifications due to COVID-19 are detailed in the Operations Manual.

Study Activities Table – All

Activity	Screening	Preintervention	Study Intervention Period (28 days)		EOT visit or premature discontinuation	Postintervention (7 days)
			Enrollment / Randomization	Week 2	Week 4	1 Week Postintervention visit
	Day –28 to Day 0	Day –21 to Day –14	Day 1	Day 15 (± 2 Days)	Day 29 (+ 2 Days)	Day 29 + 7 days (+ 2)
Visit	**1**	**2**	**3**	**4**	**5**	**6**
INTERVIEWS & QUESTIONNAIRES						
LAR/Parent/guardian Informed consent	✓					
Eligibility criteria	✓	✓	✓			
Rome IV Assessment	✓				✓	
Assess Rome IV status			✓	✓	✓	
Medical/surgical history	✓					
Lifestyle Modification Information given to LAR/Parent/Guardian		✓				
Adverse event assessment	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓
OBSERVER-REPORTED OUTCOMES						
eDiary and Instructions Given to the LAR/Parent/Guardian/Caregiver		✓				
Review eDiary data and complete manual review of subject eligibility			✓			
eDiary Compliance			✓	✓	✓	✓
Return eDiary Device						✓

Activity	Screening	Preintervention	Study Intervention Period (28 days)		EOT visit or premature discontinuation	Postintervention (7 days)
			Enrollment / Randomization	Week 2	Week 4	1 Week Postintervention visit
	Day –28 to Day 0	Day –21 to Day –14	Day 1	Day 15 (± 2 Days)	Day 29 (+ 2 Days)	Day 29 + 7 days (+ 2)
Visit	**1**	**2**	**3**	**4**	**5**	**6**
EXAMS						
ECG (single)	✓				✓	
Height	✓					
Vital signs (including weight) and Postural Vital Signs	✓	✓	✓	✓	✓	✓
Physical examination	✓		✓	✓	✓	
Fecal Impaction Assessment	✓	✓	✓			
CENTRAL LABS						
Clinical chemistry, Hematology (CBC)	✓				✓	
Optional Blood samples for PK assay (refer to Appendix G)				✓ (optional)	✓ (optional)	
TREATMENT						
IWRS (registration of screening and enrollment)	✓		✓			
Randomization/drug assignment (Part 2 only)			✓			
Rescue Medication	✓	✓	✓	✓	✓	
Study drug administered in the clinic			✓			
Study drug Dispensed			✓			
IP Compliance and Accountability				✓	✓	

AE = adverse event; ECG = electrocardiogram; eDiary = electronic diary; EOS = end of study; EOT = end of treatment; IWRS = interactive Web response system; LAR = legally authorized representative; ObsRO = observer reported outcome

APPENDIX E. LIVER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

Close monitoring should be initiated for the following subjects:

- Subjects with normal baseline serum AT who develop an increase of serum AT ≥ 2 × ULN
- Subjects with elevated baseline AT who develop an increase of serum AT > 2 × the baseline value

The subject should return to the study site and be evaluated for potential drug-induced liver injury (DILI) as soon as possible, preferably within 48 to 72 hours from the time the investigator becomes aware of the abnormal results. Evaluation should typically include repeat testing of all 4 of the usual serum biochemical measures (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) to confirm the abnormalities and to determine if they are increasing or decreasing.

If it is difficult for the subject to return to the study site promptly, the subject should be retested locally, but normal laboratory ranges should be recorded, results should be made available to sponsor's study physician and the investigator immediately, and the data should be included in the eCRF. If repeat testing within this time frame is not possible, the study intervention should be discontinued.

It is critical to initiate close monitoring immediately upon detection and confirmation of signals of potential DILI as early as possible and not to wait until the next scheduled visit or monitoring interval. Close monitoring of the subject should be initiated in conjunction with the sponsor and consideration given to the following:

- Obtain a more detailed history of symptoms and prior or concurrent diseases.
- Obtain a history of concomitant drug use, including nonprescription medications, herbal products and dietary supplements, alcohol and recreational drug use, and special diets.
- Obtain a history of exposure to environmental chemical agents.
- Initiation of appropriate evaluations including applicable laboratory tests (e.g., direct bilirubin, international normalized ratio [INR]), physical assessments, and other assessments (e.g., imaging)
    - Rule out other potential causes of biochemical abnormalities, e.g., acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; non-alcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Consider gastroenterology or hepatology consultations.

If any of the following criteria are met, discontinuation of study intervention should be considered (if indicated, prior to receipt of confirming retest biochemistry laboratory test results) and the Sponsor notified of the discontinuation:

- ALT or AST ≥ 2 × ULN and the subject is symptomatic with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> 5%)
- ALT or AST ≥ 2 × ULN and total bilirubin > 2 × ULN or INR > 1.5
- ALT or AST ≥ 2 × ULN for more than 2 weeks
- ALT or AST ≥ 2 × ULN

If Hy's law criteria are met and it is considered, in the opinion of the investigator or the Sponsor, to be possibly related to the study drug, the subject must be discontinued from the study.

APPENDIX F. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	19 December 2022
Version 1.1 (EU Only)	08 September 2023

The purpose of this version is to address the following concerns:

- **Throughout**: update minor clerical errors.
- **Title Page and throughout as applicable**: adjust number of sites to approximately 36.
- **Title Page and throughout as applicable in protocol and operations manual**: update Sponsor emergency medical contact to Shelly Gupta.
- **Section 2.1 Background and Rationale**: Clarify approved therapies for FC and indications for Linaclotide in various regions for various age ranges.
- **Section 2.1 Background and Rationale**: add a results for Study LIN-MD-64 to pediatric linaclotide program summary.
- **Section 2.2 Benefits and Risks to Subjects**: Added language to benefit-risk clarifying safety monitoring during the study and referencing additional sections in the protocol.
- **Section 4.1 Overall Study Design and Plan and throughout as applicable in protocol and operations manual**: Clarified up to 30 subjects and a minimum of 18 will be enrolled. Added text regarding criteria for selecting dose level (Part 2 [the final cohort]). Additionally, Figure 2 was updated to incorporate changes for protocol version 2.0.
- **Section 4.2 Dose Justification**: Added text to Dose Justification to discuss potential risks to subjects and safety monitoring.
- **Section 5.1 Eligibility Criteria**: Clarification of weight-for-height/length ratio added.
- **Section 5.5 Discontinuation Criteria and Appendix E**: Revised text for Hy's Law discontinuation criteria.
- **Section 5.8 Randomization/Drug Assignment**: Added text regarding emergency unblinding procedure.
- **Section 5.10 Rescreening**: section added to define criteria for rescreening after screen-fail. This includes a 30 day gap period between screen-fail and rescreening.
- **Section 5.11 Data Safety Monitoring**: Clarified criteria for the termination of the dose escalation.
- **Section 6.1 Adverse Events of Special Interest**: update instructions for investigator rating of AEs. Additionally, change of AE grading scale from Vaccine grading scale to CTCAE to align with the scale built in EDC.
- **Section 8.3 Subject Confidentiality**: Revised subject confidentiality and mitigation language.

- **Appendix C. List of Protocol Signatories**: Revised protocol signatories, added Shelly Gupta, MD
- **Appendix D. Activity table:** Adjust eDiary data review process to remove review of eCOA eligibility report and include eDiary data manual review for subject eligibility.
- **Operations Manual - Section 1 Contacts**: contacts updated to reflect current roles.
- **Operations Manual – throughout as applicable**: adjust eDiary review to include manual review for eligibility.
- **Operations Manual – Section 3 Rescue Medication**: add rescue medication records clarification to be recorded in the EDC and eDiary.
- **Operations Manual – Section 3.8 Optional Pharmacokinetic Sampling:** clarify blood should be collected from a vein. Blood collected from heel, finger or ear stick may contain interstitial/tissue fluid and therefore is not acceptable.
- **Operations Manual – Section 4.2 Reporting Adverse Events and Intercurrent Illnesses:** Update emergency medical contact to Shelly Gupta, MD.
- **Operations Manual – Appendix B Acceptable Protocol Modifications:** update to specify unforeseen circumstances and clarify what protocol activities can be modified.

APPENDIX G. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol 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

SPONSOR:	AbbVie Inc.	ABBVIE INVESTIGATIONAL PRODUCT:	Linaclotide

FULL TITLE: 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).

1 CONTACTS

Sponsor/ Emergency Medical Contact	[redacted], MD AbbVie Inc. 1 N Waukegan Road North Chicago, IL 60064-1802 **EMERGENCY 24-hour Number:** **+1 (973) 784-6402**	Mobile: [redacted] Email:
Safety Questions	Internal Medicine Safety Team	Email: SafetyManagement_InternalMedicine @abbvie.com
SAE Reporting outside of EDC	Email: PPDINDPharmacovigilance@abbvie.com	Fax: +1 (847)-806-2062 Back-up: +1 (847) 935-2844
Protocol Deviations and Product complaints	[redacted] AbbVie Inc. 100 Park Avenue Florham Park, NJ 07932	Office: Cell: Email: [redacted]
Certified Clinical Lab	LabCorp 1447 York Ct Burlington, NC 27215-3361	Phone: +1 (336) 584-5171
PK Sample Lab	Charles River Laboratories Massachusetts Attn: Sample Management 334 South Street Shrewsbury, MA 01545	Phone: +1 (508) 925-6808
Observer-Reported Outcome	Signant Health 785 Arbor Way Blue Bell, PA 19422	Phone: +1 (267) 422-1700
ECG eResearch Technology	Clario Analytics 1818 Market St Suite 2600 Philadelphia, PA 19103	Phone: +1 (215) 972-0414 Email: customercare@ert.com
IRT	Endpoint Clinical 701 Edgewater Dr Suite 320 Wakefield, Massachusetts 01880	Phone: +1 (877) 810-4786 Email: support@endpointclinical.com
EDC system	Medidata RAVE 350 Hudson Street New York, NY 10014	Phone: +1 (866) 633-4328 Email: helpdesk@mdsol.com

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2 PROTOCOL ACTIVITIES BY VISIT

2.1 Individual Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Treatment Period Activity Schedule.

Activities are grouped by category (Interview, Exam, etc.). Further information about each activity is provided in Section 3.

SCREENING: (Day -28 to Day 0 [Visit 1])

INTERVIEW	• LAR/parent/guardian Informed Consent[a] • Eligibility Criteria[b] • Rome IV Assessment	• Medical/Surgical history • Adverse event assessment • Prior/concomitant therapy
EXAMS	• ECG (single) • Height • Vital signs (including weight) and Postural vital signs[e]	• Physical Examination[c] • Fecal Impaction Assessment[d]
CENTRAL LAB	• Clinical Chemistry, Hematology (CBC)[f]	• Register subject in IWRS
TREATMENT	• Rescue Medication[g]	

NOTE: All procedures must be performed onsite. All assessments must be recorded in the source records in addition to the eCRF.

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

b. This only applies to subjects that are on prohibited medications and need to have their 1 or 14 day-wash out from those medications. Subjects that are not on any prohibited medications can immediately continue to Visit 2. Similarly, subjects that are on a prohibited medication but only need 1 day washout, they can proceed to Visit 2 once the 1-day washout has been completed. Subjects who are participating in intrasubject dose escalation in Part 1 of the study will need to repeat all screening procedures and eDiaries if > 30 days have elapsed since the subject's last dose in the previous cohort.

c. Physical examinations will be performed by medically qualified site personnel at Screening (Visit 1), enrollment/randomization (Visit 3), Week 2 (Visit 4), and Week 4 (Visit 5), physical exams may be repeated at the investigator's discretion. If fecal impaction (as defined in footnote d below) is documented during an optional repeat physical examination, the study physician must be notified.

d. Fecal impaction is defined as a hard mass in the lower abdomen identified on physical examination or a dilated rectum filled with a large amount of stool on rectal examination. If a rectal examination is performed, the medically qualified site personnel should assess for and document the presence of anal wink and normal anal tone.

e. Vital signs include weight, temperature, and respiratory rate. Postural vital signs (supine and standing whenever possible according to subject's age) include pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting. At all visits, postural vital signs must be obtained after subjects have been in a supine position for at least 2 to 3 minutes, followed by a standing position for at least 1 minute. If possible, temperature should be obtained using the same method at each visit.

f. Clinical laboratory tests consist of clinical chemistry and hematology. All laboratory tests requiring blood draws should be collected at the same time.

g. Protocol-permitted rescue medication (outlined in Section 5.3 of the protocol) will be assessed at screening; rescue medication will be site-supplied or site-dispensed from preintervention to Week 4 (Visits 2-5). The LAR/parent/guardian may choose a different protocol-permitted rescue medication at any subsequent visit, where available. Additional protocol permitted rescue medications may be site-supplied or site-dispensed as needed at any subsequent visits, where available. Rescue medication will be recorded, refer to Section 3.3 for further information.

Preintervention (Day -21 to Day -14 [Visit 2]):

INTERVIEW	• Confirm Eligibility criteria	• Adverse event assessment • Prior/concomitant therapy • Lifestyle modification information given[b]
Observer Reported Outcome	• eDiary and Instructions Given to LAR/Parent/Guardian/Caregiver[a]	
EXAMS	• Fecal Impaction Assessment[c] • Vital signs (including weight) and Postural vital signs[d]	
TREATMENT	• Rescue Medication[e]	

NOTE: All procedures must be performed onsite. All assessments must be recorded in the source records in addition to the eCRF.

a. At the Preintervention Visit, LAR/parent/guardian/caregivers will be trained on the use of the eDiary device and instructed to complete the daily evening assessment. At subsequent visits, study site staff will verify compliance with the eDiary and remind LAR/parent/guardian/caregivers to complete their assessments daily. Assessment of global change in symptoms and global severity of symptoms will be completed in the weekly Diary. The global severity items will be completed beginning at the Preintervention Period through the 1-week postintervention visit (Visit 6), and the global change items will be completed from one week after enrollment/randomization through the 1-week postintervention visit (Visit 6).

b. During the Preintervention Period, subjects and their LAR/parent/guardian will receive information regarding lifestyle modifications. See Section 3.4 for further information regarding lifestyle modifications.

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

d. Vital signs include weight, temperature, and respiratory rate. Postural vital signs (supine and standing whenever possible according to subject's age) include pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting. At all visits, postural vital signs must be obtained after subjects have been in a supine position for at least 2 to 3 minutes, followed by a standing position for at least 1 minute. If possible, temperature should be obtained using the same method at each visit.

e. Protocol-permitted rescue medication (outlined in Section 5.3 of the protocol) will be site-supplied or site-dispensed from preintervention to Week 4 (Visits 2-5). The LAR/parent/guardian may choose a different protocol-permitted rescue medication at any subsequent visit, where available. Additional protocol permitted rescue medications may be site-supplied or site-dispensed as needed at any subsequent visits, where available. Rescue medication will be recorded, refer to Section 3.3 for details.

DAY 1: (Study Intervention Period – Enrollment/Randomization – Visit 3)

INTERVIEW	• Eligibility criteria • Assess Rome IV status[a]	• Adverse event assessment • Prior/concomitant therapy
Observer Reported Outcome	• eDiary Compliance[b] • Manual review of eDiary subject eligibility[c]	
EXAMS	• Vital signs (including weight) and Postural Vital Signs[d] • Physical examination • Fecal Impaction Assessment[e]	
TREATMENT	• Rescue Medication[f,g] • Randomization/drug assignment (Part 2 only) • Study drug administered in the clinic[h]	• Study drug dispensed • IWRS registration of enrollment

NOTE: All procedures must be performed onsite. All assessments must be recorded in the source records in addition to the eCRF.

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

b. The clinic eDiary will be completed on the day of enrollment/randomization. Study site staff will verify compliance with the eDiary and remind LAR/parent/guardian/caregivers to complete their assessments daily. Assessment of global change in symptoms and global severity of symptoms will be completed in the weekly Diary. The global severity items will be completed beginning at the Preintervention Period through the 1-week postintervention visit (Visit 6), and the global change items will be completed from one week after enrollment/randomization through the 1-week postintervention visit (Visit 6).

c. Manual review of eDiary subject eligibility must be completed prior to enrollment/randomization.

d. Vital signs include weight, temperature, and respiratory rate. Postural vital signs (supine and standing whenever possible according to subject's age) include pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting. At all visits, postural vital signs must be obtained after subjects have been in a supine position for at least 2 to 3 minutes, followed by a standing position for at least 1 minute. If possible, temperature should be obtained using the same method at each visit.

e. A fecal impaction assessment is performed at the enrollment/randomization Visit (Visit 3) prior to enrollment/randomization and dosing for all subjects. If there is no fecal impaction at the enrollment/randomization Visit (Visit 3) (defined as a hard mass in the lower abdomen identified on physical examination or a dilated rectum filled with a large amount of stool on rectal examination), the subject may enter the enrollment/randomization period. If fecal impaction is present upon examination, the subject will not be eligible for enrollment/randomization.

f. Protocol-permitted rescue medication (outlined in Section 5.3 of the protocol) will be site-supplied or site-dispensed from preintervention to Week 4 (Visits 2-5). The LAR/parent/guardian may choose a different protocol-permitted rescue medication at any subsequent visit, where available. Additional protocol permitted rescue medications may be site-supplied or site-dispensed as needed at any subsequent visits, where available. Subject must not have used rescue medication until randomized; this includes the calendar day before the enrollment/randomization visit and on the day of the enrollment/randomization visit prior to enrollment/randomization.

g. Rescue medication will be recorded, refer to Section 3.3 for details.

h. IWRS will be contacted to obtain the study drug (bottle number) to be dispensed. Study drug will be prepared by parent/caregiver at the site after instructions how to prepare IP solution have been explained and video reviewed. LAR/parent/guardian will administer first study drug at the study site. Site will document training and first dose preparation by parent/caregiver, as also administration. Subjects may eat 15 - 30 minutes after dosing.

WEEK 2 (Study Intervention Period – Visit 4 Day 15 [± 2 Days]):

INTERVIEW	• Assess Rome IV status[a]	• Adverse event assessment • Prior/concomitant therapy
Observer Reported Outcome	• eDiary Compliance[b]	
EXAMS	• Vital signs (including weight) and Postural Vital Signs[c]	• Physical examination
CENTRAL LAB	• Blood samples for PK assay (optional)[d]	
TREATMENT[e]	• Rescue Medication[f,g] • IP Compliance and Accountability	

NOTE: All procedures must be performed onsite. All assessments must be recorded in the source records in addition to the eCRF.

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

b. Study site staff will verify compliance with the eDiary and remind LAR/parent/guardian/caregivers to complete their assessments daily. Assessment of global change in symptoms and global severity of symptoms will be completed in the weekly Diary. The global severity items will be completed beginning at the Preintervention Period through the 1-week postintervention visit (Visit 6), and the global change items will be completed from one week after enrollment/randomization through the 1-week postintervention visit (Visit 6).

c. Vital signs include weight, temperature, and respiratory rate. Postural vital signs (supine and standing whenever possible according to subject's age) include pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting. At all visits, postural vital signs must be obtained after subjects have been in a supine position for at least 2 to 3 minutes, followed by a standing position for at least 1 minute. If possible, temperature should be obtained using the same method at each visit.

d. The optional PK sample can be collected either before or after subjects receive study drug. Optional PK samples should be collected at the same time as clinical labs. This visit should be scheduled at approximately the same time as when subjects take their daily dose. Refer to Section 3.8 for additional details.

e. The subject must complete at least 4 weeks (28 days) of intervention period before returning for the Week 4/Day 29 EOT or premature discontinuation visit (Visit 5). The study drug will be administered at approximately the same time as on other days of study drug administration.

f. Protocol-permitted rescue medication (outlined in Section 5.3 of the protocol) will be site-supplied or site-dispensed from preintervention to Week 4 (Visits 2-5). The LAR/parent/guardian may choose a different protocol-permitted rescue medication at any subsequent visit, where available. Additional protocol permitted rescue medications may be site-supplied or site-dispensed as needed at any subsequent visits, where available.

g. Rescue medication will be recorded, refer to Section 3.3 for details.

WEEK 4 (Visit 5 Day 29 EOT or premature discontinuation [+ 2 Days]):

INTERVIEW	• Rome IV Assessment • Assess Rome IV status[a]	• Adverse event assessment • Prior/concomitant therapy
Observer Reported Outcome	• eDiary Compliance[b]	
EXAMS	• Vital signs (including weight) and Postural Vital Signs[c] • Physical examination[d]	• ECG (single)
CENTRAL LAB	• Blood samples for PK assay (optional)[f]	• Clinical chemistry, Hematology (CBC)[e]
TREATMENT	• Rescue Medication[h,i] • IP Compliance and Accountability	

NOTE: All procedures must be performed onsite. All assessments must be recorded in the source records in addition to the eCRF.

a. Prior to dosing, the investigator or appropriate site staff member will assess if Rome IV criteria for FC was met and record the outcome in the eCRF. Eligibility for the study is not based on this assessment. Refer to Section 3.5 for details.

b. Study site staff will verify compliance with the eDiary and remind LAR/parent/guardian/caregivers to complete their assessments daily. Assessment of global change in symptoms and global severity of symptoms will be completed in the weekly Diary. The global severity items will be completed beginning at the Preintervention Period through the 1-week postintervention visit (Visit 6), and the global change items will be completed from one week after enrollment/randomization through the 1-week postintervention visit (Visit 6).

c. Vital signs include weight, temperature, and respiratory rate. Postural vital signs (supine and standing whenever possible according to subject's age) include pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting. At all visits, postural vital signs must be obtained after subjects have been in a supine position for at least 2 to 3 minutes, followed by a standing position for at least 1 minute. If possible, temperature should be obtained using the same method at each visit.

d. Physical examinations will be performed by medically qualified site personnel at Screening (Visit 1), enrollment/randomization (Visit 3), Week 2 (Visit 4), and Week 4 (Visit 5), physical exams may be repeated at the investigator's discretion. If fecal impaction (defined as a hard mass in the lower abdomen identified on physical examination or a dilated rectum filled with a large amount of stool on rectal examination) is documented during an optional repeat physical examination, the study physician must be notified.

e. Clinical laboratory tests consist of clinical chemistry and hematology. All laboratory tests requiring blood draws should be collected at the same time.

f. The optional PK sample can be collected either before or after subjects receive their last dose of study drug. Optional PK samples should be collected at the same time as clinical labs. This visit should be scheduled at approximately the same time as when subjects take their daily dose.

g. Protocol-permitted rescue medication (outlined in Section 5.3 of the protocol) will be site-supplied or site-dispensed from preintervention to Week 4 (Visits 2-5). The LAR/parent/guardian may choose a different protocol-permitted rescue medication at any subsequent visit, where available. Additional protocol permitted rescue medications may be site-supplied or site-dispensed as needed at any subsequent visits, where available. Subject must not have used rescue medication until randomized; this includes the calendar day before the enrollment/randomization visit and on the day of the enrollment/randomization visit prior to enrollment/randomization.

h. All enrolled/randomized subjects who prematurely discontinue from the study, regardless of cause, should be seen for the assessments completed at EOT (Visit 5, Week 4).

i. Rescue medication will be recorded, refer to Section 3.3 for details.

2.2 Individual Post-Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Post-Treatment Period Activity Schedule.

Activities are grouped by category (Interview, Exam, etc.). Further information about the activities is presented in Section 3.

1-week postintervention Visit [(Visit 6, Day 29) 7 days + 2 Days]:

INTERVIEW	• Adverse event assessment • Prior/concomitant therapy
Observer Reported Outcome	• eDiary Compliance[a] • Return eDiary device[b]
EXAMS	• Vital signs (including weight) and Postural Vital Signs[c]

NOTE: All procedures must be performed onsite. All assessments must be recorded in the source records in addition to the eCRF. Rescue medication will be recorded, refer to Section 3.3 for further information.

a. At the Preintervention Visit, LAR/parent/guardian/caregivers will be trained on the use of the eDiary device and instructed to complete the daily evening assessment. At subsequent visits, study site staff will verify compliance with the eDiary and remind LAR/parent/guardian/caregivers to complete their assessments daily. The global severity items will be completed beginning at the Preintervention Period through the 1-week postintervention visit (Visit 6), and the global change items will be completed from one week after enrollment/randomization through the 1-week postintervention visit (Visit 6).

b. The subject's LAR/parent/guardian/caregiver will return the eDiary device.

c. Vital signs include weight, temperature, and respiratory rate. Postural vital signs (supine and standing whenever possible according to subject's age) include pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting. At all visits, postural vital signs must be obtained after subjects have been in a supine position for at least 2 to 3 minutes, followed by a standing position for at least 1 minute. If possible, temperature should be obtained using the same method at each visit.

3 STUDY PROCEDURES

3.1 Study Subject Information and Informed Consent

The investigator or their representative will explain the nature of the study, including the use and assessment of any investigational devices (e.g., the eDiary) to the LAR/parent/guardian/caregiver of the subject, the benefits and risks anticipated from participation in the study, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject or any medications being discontinued by the subject in order to participate in this study, the informed consent statement will be reviewed, signed, and dated by the subject's legally authorized representative (LAR)/Parent/guardian, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed informed consent will be given to the subject's LAR/parent/guardian and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding benefits for subjects and information regarding provisions for treating and/or compensating subjects who are harmed because of participation in the study can be found in the informed consent form.

Samples for optional pharmacogenetic analyses or other exploratory analyses will only be collected if the LAR/parent/guardian of the subject has voluntarily signed and dated a separate written consent form for this testing that has been approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The separate written consent may be part of the main consent form. If the subject does not consent to the testing, it will not impact the subject's participation in the study.

3.2 Medical History

A complete medical history including demographics will be taken at screening. The subject's medical history will be updated at the Study Day 1 visit. This updated medical history will serve as the baseline for clinical assessment.

3.3 Rescue Medications

Refer to Table 2 of Protocol Section 5.3 for the protocol-permitted rescue medications. Of note,

- Any laxatives are to be discontinued prior to the Preintervention Visit in favor of the site-supplied, protocol-permitted rescue medications.
- Rescue medication is not to be used on the calendar day before enrollment/randomization (Visit 3) and on the day of the enrollment/randomization Visit (Visit 3) until randomization/enrollment.
- Rescue medication (name of medication, dose, and route of administration) records will include medication given by the caregiver/parent/guardian/LAR as well as information from secondary caregivers if the participant was in the care of others. Rescue medication is recorded in the EDC and the eDiary.
- Rescue medication may be taken when at least 72 hours have passed since the subject's previous BM or when their symptoms become intolerable.

3.4 Lifestyle Modifications

During the Preintervention Period, LAR/parent/guardians will be advised to have subjects adopt the following nonpharmacologic habits and instructed to maintain them throughout the study.

- Adequate fluids: The investigator will discuss the fluid intake necessary to maintain a hydrated state (intake requirements may vary amongst children e.g., child athletes, children in hot climates).
- A high-fiber diet: High-fiber foods include beans, whole grains, fruits, and vegetables. Start slowly, adding just several grams of fiber a day over the Screening Period to reduce the amount

of gas and bloating that can occur in someone who is not used to consuming high-fiber foods. The optimum intake of dietary fiber for infants and children younger than two years of age is not known. Studies of weaning diets with the gradual introduction of solid foods, including increased fiber, suggest that an intake of 5 g per day is beneficial provided the children ingest adequate calories, vitamins, and minerals. [1,2]

- Increased physical activity: Subjects should be physically active throughout the day. Caregivers of subjects should encourage active play that includes a variety of activity types.
- Adequate time for bowel movements:
  - LAR/parents/guardians will be requested not to start the toilet training process with their child during the child's participation in the study. Changes in toileting skills may impact bowel habits and accurate reporting of bowel movements and fecal incontinence.

3.5 Rome IV Assessment

As outlined in Section 5.1 of the protocol, the subject meets the Rome IV criteria for FC.

For at least 1 month before Screening (Visit 1), the subject must meet 2 or more of the following symptoms:

- history of excessive stool retention;
- history of painful or hard bowel movements (BMs);
- presence of a large fecal mass in the rectum;
- history of large-diameter stools;
- 2 or fewer defecations per week [with each defecation occurring in the absence of any laxative, suppository, or enema use during the preceding 24 hours].

Accompanying symptoms may include irritability, decreased appetite, and/or early satiety. The accompanying symptoms disappear immediately following passage of a large stool.

3.6 Adverse Event Assessment

Please refer to Section 4.1.

3.7 Observer-Reported Outcomes

An observer-reported outcome (ObsRO) eDiary instrument assessing key signs and symptoms of FC for use in children (6 months to 5 years of age) with FC was developed by AbbVie and Ironwood Pharmaceuticals based on extensive qualitative research with LAR/parent/guardian/caregivers of children with FC, as well as feedback from pediatric gastroenterologists, measurement experts, and health authorities. The ObsRO instrument was developed for completion by LAR/parent/guardian/caregivers on an electronic diary (eDiary) and is being employed in this study for

use in subjects 6 months to less than 2 years of age. Data collected in the eDiary will be used to derive the efficacy endpoints.

All efficacy assessments will be determined by responses entered in the eDiary by the LAR/parent/guardian/caregiver. The LAR/parent/guardian/caregiver is identified as the individual who completes the eDiary and should be the same individual throughout the course of the study and must be able to read and understand the eDiary as a condition for study participation (inclusion criterion). At the start of the Preintervention Period, LAR/parent/guardian/caregivers will receive full training on the use and completion of the eDiary at the study visit in which they are given the eDiary device. If the LAR/parent/guardian/caregiver completing the diary changes, the study team should be notified and should document the date when it changed and who the new LAR/parent/guardian/caregiver is. The new LAR/parent/guardian/caregiver must also provide written informed consent before the initiation of any study-specific procedures.

The key efficacy assessments, which will be used to determine the efficacy parameter of SBM frequency, are the items assessing BM frequency and rescue medication use in the daily eDiary, once a day in the evening.

Assessments of global change in symptoms and global severity of symptoms will be completed weekly in the eDiary. The global assessments consist of 2 items; 1 assessing global change in the child's symptoms and 1 assessing the global severity of the child's symptoms. Both global items will be completed weekly on the eDiary by the LAR/parent/guardian/caregiver. The global severity item will be completed beginning at the Preintervention Period through the 1-week post intervention visit.

At the enrollment/randomization visit, the LAR/parent/guardian/caregiver should complete the clinic eDiary before any clinical assessments and before any interaction with site personnel has occurred to avoid biasing the LAR/parent/guardian/caregiver's response. All other eDiary entries are to be completed at home.

See Appendix A for further information on eDiary completion.

3.8 Optional Pharmacokinetic Sampling

An important consideration is whether oral bioavailability of linaclotide is similar in this study population (6 months to less than 2 years of age) as in adults and pediatric subjects of 2 to 17 years of age, or whether systemic exposure may be higher in this study population (6 months to less than 2 years of age).

Optional PK sampling will therefore be included in this study to assess the PK of linaclotide in pediatric subjects of 6 months to less than 2 years of age. Blood samples for analysis of linaclotide and its metabolite MM-419447 in plasma will be collected at time points specified in Section 2.1. With the consent of the LAR/parent/guardian, the maximum volume of blood collected for each subject over the duration of the study for optional PK will not exceed 4 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the sample.

Additional information on the collection, handling/processing, disposition, and measurement methods can be found in the lab manual. Please note: Blood should be collected from a vein; blood collected

from heel, finger or ear stick may contain interstitial/tissue fluid and therefore is not acceptable. Samples will be shipped to the lab per the Lab Manual.

3.9 Electrocardiogram

Electrocardiogram (Single Only)

Resting ECGs will be obtained singly as specified in specified in Section 2.1. 3-Lead or 12-Lead ECGs may be utilized per investigator's discretion.

The ECG acquired prior to dosing will serve as the baseline measurements for clinical assessment.

When an ECG is scheduled at the same time as a blood collection, the ECG will be obtained prior to the blood collection. ECGs occurring near meals will take place prior to meals.

ECGs will be acquired after the subject has been in the supine position for at least 5 minutes. Subjects will be instructed to remain completely stationary (no talking, laughing, deep breathing, sleeping, or swallowing) for approximately 10 seconds during the ECG recording. While ECGs are being acquired, subjects and staff are prohibited from having devices (e.g., cellular telephones, fans, heaters, etc.) that emit electrical interference in the room.

ECG Safety Review

Each ECG will be evaluated by an appropriately trained physician, preferably a cardiologist (the "local reader"). This reading of the ECG will be used by the investigator for subject safety assessments, including adverse event determination and management and decision on whether a subject will be discontinued from the study.

The local reader will sign and date the safety ECG and provide a global interpretation using the following categories:

- Normal ECG
- Abnormal ECG Not clinically significant (NCS)
- Abnormal ECG Clinically significant (CS)
- Unable to evaluate

All local reader evaluations of safety ECGs will be entered into the source documents. If the global interpretation is Abnormal (NCS or CS), the local reader will provide further information (e.g., sinus bradycardia, arrhythmia). The QT interval corrected for heart rate will be calculated and documented for all ECGs.

All ECG source documentation will be retained at the study site. The automatic cardiograph reading (i.e., cardiograph-generated measurements and interpretations) will not be collected for analysis.

3.10 Height and Weight

Height will be measured at screening only and body weight will be measured at scheduled visits as specified in Section 2.1. The subject will wear lightweight clothing and no shoes during weighing. Where locally permitted, height will be measured at the Screening Visit (with shoes off).

3.11 Vital Signs (including weight) and Postural Vital Signs

Vital signs and postural vital signs will be obtained and documented as noted in Section 2.1. Vital signs will be assessed as follows:

Vital signs include weight, temperature, and respiratory rate; postural vital signs (supine and standing whenever possible according to subject's age) include pulse rate and systolic and diastolic blood pressure. If possible, temperature should be obtained using the same method throughout the course of the study. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting.

At all visits, postural vital signs must be obtained after subjects have been in a supine position for at least 2 to 3 minutes, followed by a stationary position for at least 1 minute. Measurements should be assessed consistently throughout the study. Vital signs measurements determined prior to dosing on Day 1 will serve as baseline.

Measurements should be assessed consistently throughout the study. Vital signs measurements determined prior to dosing on Day 1will serve as baseline.

3.12 Physical Examination

A complete physical examination, including height (at Screening only), will be performed at the designated study visits as specified in Section 2.1. The physical examination performed on Study Day 1 will serve as the baseline physical examination for the entire study. Physical examination abnormalities noted at the Baseline Visit prior to the first dose of study drug should be recorded in the subject's medical history. Any significant physical examination findings after the first dose will be recorded as AEs. All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate eCRF page.

At any time, a symptom-directed physical examination can be performed as deemed necessary by the investigator.

3.13 Fecal Impaction Assessment

A fecal impaction assessment will be performed for all subjects at the designated study visits as specified in Section 2.1. Fecal impaction is defined as a hard mass in the lower abdomen identified on physical examination or a dilated rectum filled with a large amount of stool on rectal examination. If a rectal examination is performed, the medically qualified site personnel should assess for and document the presence of anal wink and normal anal tone.

If fecal impaction is identified at Screening (Visit 1), subjects will receive a disimpaction regimen with either oral or rectal medication. The choice of treatment will be determined by the investigator after discussing the options with the subject and the LAR/parent/guardian. Options will include any over-the-counter or prescription laxative, suppository, or enema (e.g., polyethylene glycol, lactulose, Fleet enema). After the subject has received treatment for the impaction, the investigator must re-evaluate the subject for the presence of fecal impaction at the Preintervention Visit (Visit 2). If there is no fecal impaction at the Preintervention Visit, the subject may enter the Preintervention Period after adhering to any washout requirements (Protocol Section 5.3). If fecal impaction is present upon reexamination, the subject will not be eligible for the study (i.e., they have failed their outpatient clean-out regimen).

If fecal impaction is present upon examination at enrollment/randomization (Visit 3), the subject will not be eligible to be randomized into the study.

3.14 Dispense Study Drug

Study drug will be dispensed to subject's LAR/parent/guardian as specified in Section 2.1. The first dose of study drug will be administered after all other baseline (Day 1) procedures are completed. At the visits specified in Section 2.1, the site personnel will review returned study drug kits, and empty study drug packaging to verify compliance.

Study drug (i.e., linaclotide) capsules should be prepared by the LAR/parent/guardian and the dose should be administered to the subject at approximately the same time each day, 15 - 30 minutes before a meal; subjects may eat 15 - 30 minutes after dosing.

3.15 Clinical Laboratory Tests

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests. Laboratory reference ranges, including reference ranges from the local laboratory (to be used in the event of a safety event or if lab kits from the central laboratory are not available), will be obtained prior to the initiation of the study.

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory. Please note: Blood collection from heel-, finger-, or ear-stick may contain interstitial/tissue fluid, and therefore are not acceptable. Blood should only be collected from a vein, blood should not be collected from a heel-, finger-, or ear-stick.

If a laboratory test value is outside the reference range and the investigator considers the laboratory result to be clinically significant, the investigator will:

- repeat the test to verify the out-of-range value;
- follow the out-of-range value to a satisfactory clinical resolution; or
- discontinue the subject from the study or require the subject to receive treatment; in this case, the laboratory result will be recorded as an adverse event.

Clinical Chemistry

A fast is not necessary for blood samples to be drawn for chemistry.

The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

The maximum volume of blood collected from each subject over the duration of the study for clinical laboratory testing (which includes chemistry and hematology panels) will not exceed 13.5 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the sample.

Clinical Laboratory Tests[a]		
Hematology	**Clinical Chemistry[b]**	**Other Screening Tests**
Platelet count (estimate not acceptable) Red blood cell (RBC) count Hematocrit Hemoglobin RBC indices: MCV MCH MCHC White blood cell (WBC) count with differential absolute: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	Blood urea nitrogen (BUN/Urea) Creatinine Glucose non-fasting Potassium Sodium Chloride Bicarbonate/CO_2 Magnesium Phosphate Total protein Total bilirubin Calcium Alanine transaminase (SGPT/ALT) Aspartate transaminase (SGOT/AST) Alkaline phosphatase Total, direct and indirect bilirubin Total cholesterol Albumin	

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean cell volume of RBC; RBC = red blood cell; WBC = white blood cell

a. All study-required laboratory assessments will be performed by a central laboratory.

b. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are provided in the protocol.

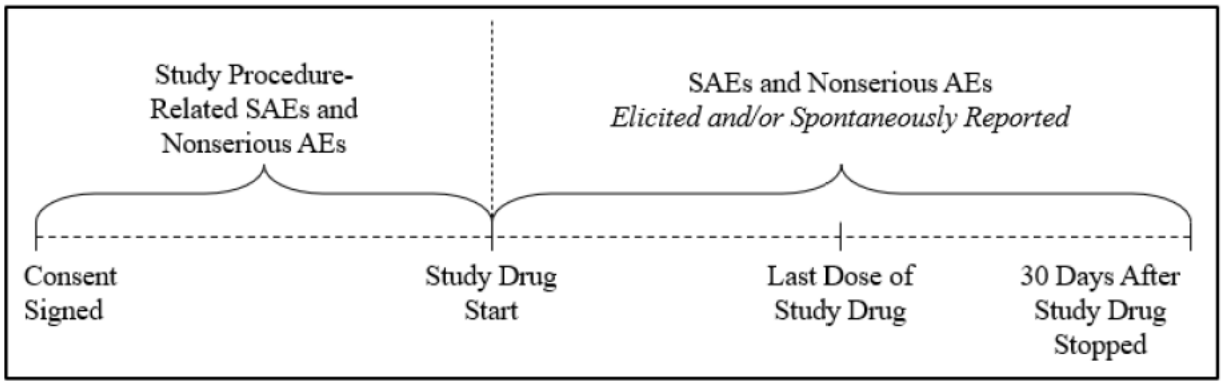
3.16 Subject Withdrawal

All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment, irrespective of whether the subject decides to continue participation in the study.

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All serious and nonserious adverse events which could be related to study procedures, (e.g., infection at liver biopsy site, done during screening) will be collected from the time the subject signed the study-specific informed consent until study drug administration. From the time of study drug administration up to 30 days after the last dose of study drug or study treatment, all nonserious and serious adverse events will be collected whether solicited or spontaneously reported by the subject. After 30 days following the last dose of study drug or completion of study treatment only spontaneously reported SAEs will be collected (nonserious AEs will not be collected).



AE = adverse event; SAE = serious adverse event

4.2 Reporting Adverse Events and Intercurrent Illnesses

In the event of an SAE, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the electronic data capture (EDC) system. SAEs that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE nonCRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

Email: PPDINDPharmacovigilance@abbvie.com
FAX to: +1 847-806-2062 Backup: +1 847 935-2844

For safety questions, contact the Internal Medicine Safety Team at:

Internal Medicine Safety Team
Email: SafetyManagement_Internal Medicine @abbvie.com

For any subject safety concerns, please contact the physician listed below:

[redacted]

EMERGENCY MEDICAL CONTACT:

[redacted], **MD**

AbbVie Inc.

1 N Waukegan Road

North Chicago, IL 60064-1802

Contact Information:

Office: [redacted]

Email:

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie Therapeutic Area Medical Director:

HOTLINE: +1 (973) 784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local requirements.

5 COUNTRY-SPECIFIC REQUIREMENTS

Any coded data (as defined under General Data Protection Requirements) that is transferred to AbbVie's parent company, AbbVie Inc., in the United States, or other AbbVie affiliates is done under internal agreements, which include an EU approved model contract pertaining to data transfers to controllers. A copy can be obtained by sending an email to privacyoffice@abbvie.com. Any transfers of Coded Data to AbbVie's research partners outside the EU will be done in compliance with the international data transfer restrictions that apply under EU data protection laws.

5.1 SUSAR Reporting

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines and Section 6.6 of the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

5.2 Treatment After End of Study

For subjects enrolled in Part 1 (Cohorts 1-3) or randomized to Part 2, subjects will continue study treatment throughout the study for a period of up to 28 days per cohort or until premature

discontinuation of study drug. At the subject's last study visit, the investigator will discuss the appropriate subsequent treatment with the subject. If symptoms improve at the current dose level, the subject will be given the option to participate in a long-term safety extension study, once the study is active and accepting subjects.

6 STUDY DRUG

6.1 Treatments Administered

The study drug linaclotide (or matching placebo for Part 2 only) will be dispensed in the form of a capsule at the visits listed in Section 2.1. Subjects will be trained on how to prepare the appropriate dose and instructed to take prepared dose at approximately the same time each day 15 - 30 minutes before a meal; subjects may eat 15 - 30 minutes after dosing.

Linaclotide (or matching placebo for Part 2 only) will be provided by AbbVie. Sites are responsible for obtaining or prescribing any protocol permitted rescue medications to dispensed as outlined in Section 2.1.

Study drug dose preparation and administration instructions will be provided separately.

Study drug must not be dispensed without contacting the IRT system. Study drug may only be dispensed to subjects enrolled in the study through the IRT system. At the end of the Treatment Period or at the Premature D/C visit, the site will contact the IRT system to provide visit date information and study drug return information for each kit.

6.2 Packaging and Labeling

Linaclotide and matching placebo capsules will be supplied in bottles with quantities sufficient to accommodate the study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. All blank spaces should be completed by site staff prior to dispensing to the subject. Each kit will contain a unique kit number. This kit number is assigned to a subject via IRT and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit.

6.3 Storage and Disposition of Study Drug

Study drug must be stored at room temperature (20° to 25°C [68° to 77°F], with permitted excursions 15° to 30°C [59° to 86°F]).

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or destroyed on site as appropriate.

Sites are responsible for maintaining the investigational study drug according to the storage conditions specified on the clinical label and monitoring for temperature excursions with the use of a

calibrated continuous temperature monitoring device (for example, chart recorders and/or acceptable calibrated min/max thermometers) or continuous monitoring systems. Specific guidance on appropriate temperature monitoring and temperature excursions reporting requirements will be provided separately.

6.4 Method of Assigning Subjects to Treatment Groups

This study consists of 2 Parts that include 4 cohorts in total. Part 1 has three open label cohorts (Cohorts 1-3), and Part 2 has a double-blind cohort. Part 1 cohorts will enroll sequentially and receive open-label 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 efficacy of linaclotide vs placebo.

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

At the screening visit, all subjects will be assigned a unique subject number using the IRT system. For subjects who do not meet the study selection criteria, the site personnel must contact the IRT system and identify the subject as a screen failure.

Subjects who are enrolled will retain their subject number assigned at the screening visit throughout the study. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

Contact information and user guidelines for IRT use will be provided to each site.

6.5 Selection and Timing of Dose for Each Subject

One capsule of linaclotide (or placebo for Part 2 only) will be dosed orally as a prepared solution once daily. All subjects should take the study drug 15 - 30 minutes before any meal around the same time each day. Separate dosing instructions will be provided to the LAR/parent/guardian. Study drug will be prepared by LAR/parent/guardian at the site after instructions for how to prepare IP solution have been explained and video reviewed.

7 REFERENCES

1. Agostoni C, Riva E, Giovannini M. Dietary Fiber in Weaning Foods of Young Children. Pediatrics. 1995;96(5):1002-5.

2. Davidsson L, Mackenzie J, Kastenmayer P, et al. Dietary fiber in weaning cereals: a study of the effect on stool characteristics and absorption of energy, nitrogen, and minerals in healthy infants. J Pediatr Gastroenterol Nutr. 1996;22(2):167-79.

APPENDIX A. EDIARY COMPLETION

During this study, LAR/parent/guardian/caregiver will complete daily and weekly entries in an eDiary:

- Daily: The daily eDiary will be completed by the LAR/parent/guardian/caregiver during the Preintervention Period through the 1-week postintervention visit in the evening except on the day of the preintervention visit and the day of the enrollment/randomization visit. The modified daily eDairy will be completed in the evenings of the preintervention visit and the enrollment/randomization visit.
- Weekly: Assessments of global change in symptoms and global severity of symptoms will be completed weekly in the eDiary. The global severity items will be completed beginning at the Preintervention Period through the 1-week postintervention visit, and the global change items will be completed from 1 week after enrollment/randomization through the 1-week postintervention visit.

In addition, a clinic eDiary will be completed in the clinic before administration of first dose of study intervention on the day of enrollment/randomization.

APPENDIX B. ACCEPTABLE PROTOCOL MODIFICATIONS

Due to unforeseen circumstance (e.g., natural disasters, pandemics, geopolitical conflict such as the conflict in Ukraine and surrounding impacted regions), it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional temporary verbal consent from the parent/guardian/LAR may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations. An appropriately signed and dated informed consent form should be obtained from the parent/guardian/LAR afterwards, as soon as possible.

Protocol Activities by Visit

if it is not possible for all study procedures to be performed as specified due to travel restrictions or other reasons, the following modifications are allowed:

- Some study visits and/or activities may be performed by a local clinic/hospital/laboratory. These are indicated by a plus sign (+) in the appropriate visit tables in Section 2. All procedures performed at local facilities must be performed by appropriately qualified personnel. See Section 3.15 for additional details specific to clinical laboratory assessments.

ECGs

The Sponsor and investigator will discuss availability of resources for ECG collection in the event of unforeseen circumstances in conjunction with severe diarrhea AESI.

Dispense Study Drug

Study drug may be shipped from the study site directly to the study subject's home if all the following criteria are met:

- Direct-to-patient (DTP) shipment of study drug is allowed by local regulations and the relevant IRBs or ethics committees
- Study drug can be administered by the subject's LAR/parent/guardian at home
- Subject's LAR/parent/guardian agrees to have the study drug shipped directly to their home
    - Shipments may also include other study supplies (e.g., drug dosing diaries, paper copies of the ObsROs). Instructions will be provided by AbbVie as to how a study site can initiate a DTP shipment using Marken, a global vendor selected by AbbVie to provide this service when necessary. Shipments of study drugs from the study site to a subject's home will be appropriately temperature controlled (qualified shipper or temperature monitoring) within the labeled storage conditions. Signature is required upon delivery; due to COVID-19-related social distancing, this may be provided by the courier after delivery. Documentation of the shipment is to be retained by the clinical site.
    - AbbVie will not receive subject identifying information related to these shipments, as the site will work directly with the courier.

The study site is responsible for meeting IRB/IEC reporting requirements related to DTP shipments of study drug, and for obtaining consent to provide delivery information to the courier and documenting this consent in source documents.

Clinical Laboratory Tests

If travel restrictions or other changes in local regulations prevent the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local laboratory, hospital, or other facility. Local laboratory results should be obtained along with reference ranges and kept within the subjects' source documentation. The investigator should review local laboratory results as soon as possible.

If laboratory samples cannot be obtained, study drug administration may be continued, provided the investigator has reviewed all prior laboratory results and confirms and discusses with the parent/guardian/LAR that there is no safety concern for the subject to continue use of the study drug in the absence of current laboratory results. The subject should be scheduled for laboratory draws as soon as feasible within the visit windows specified in Section 2 (i.e., Visit 4 + 2 days).

Reporting Adverse Events and Intercurrent Illnesses

Supplemental study case report form (CRF) should be completed in the event of COVID-19 related missed/virtual visits, study drug interruptions or discontinuations, or AEs (including capture of specific signs/symptoms of infection and testing results).

COVID-19 infections should be captured as AEs. If the event meets the criteria for an SAE, then follow the SAE reporting directions per the protocol and above. The following COVID-19-related supplemental eCRFs should be completed (for both serious and nonserious events):

- COVID-19 Supplemental Signs/ Symptoms
- COVID-19 Status Form

Reactions known to be associated with the SARS-CoV-2 vaccine should be reported as adverse events. If the event meets the criteria for an SAE, then follow the SAE reporting directions. All adverse events associated with the SARS-CoV-2 vaccine will be linked to the vaccine on the COVID-19 Vaccine eCRF.

COVID 19 Pandemic Related Vaccination Guidance

Given the ongoing COVID-19 pandemic, vaccines to prevent SARS-CoV-2 infection may be administered during screening, the treatment period, or follow-up, as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject.

If vaccination is available, it should not interfere with eligibility. These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines in subjects with functional constipation and as more data are collected in real-world scenarios and clinical trials. Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine eCRF.

Document Approval

Study M21862 - 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) - Operations Manual for Protocol Version 2-0 - 25Nov2024

Version: 1.0 **Date:** 02-Dec-2024 **Company ID:** 20241202-0900f9f688a65651-1.0-en

Signed by:	Date:	Meaning of Signature:
[redacted]	02-Dec-2024 18:34 UTC	Approver
	25-Nov-2024 22:56 UTC	Approver - Statistics

Document Approval

Study M21862 - 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) - Protocol Version 2-0 - EU CT 2022-501947-34-00 - 25Nov2024

Version: 1.0 **Date:** 02-Dec-2024 **Company ID:** 20241202-0900f9f688a6565f-1.0-en

Signed by:	Date:	Meaning of Signature:
[redacted]	02-Dec-2024 18:34 UTC	Approver
	25-Nov-2024 22:56 UTC	Approver - Statistics