NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sNDA
Application Number(s)	202811/S-022
Priority or Standard	Priority
Submit Date(s)	5/6/2025
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PDUFA Goal Date	11/6/2025
Division/Office	Division of Gastroenterology
Review Completion Date	11/4/2025
Established/Proper Name	linaclotide
(Proposed) Trade Name	Linzess
Pharmacologic Class	Guanylate cyclase-C agonist
Code name	
Applicant	AbbVie Inc.
Dosage form	capsule
Applicant proposed Dosing Regimen	145 mcg orally once daily
Applicant Proposed Indication(s)/Population(s)	Treatment of irritable bowel syndrome with constipation in pediatric patients 7 to 17 years of age
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	440630006 | Irritable bowel syndrome characterized by constipation (disorder)|
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of irritable bowel syndrome with constipation (IBS-C) in pediatric patients 7 years of age and older
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	440630006 | Irritable bowel syndrome characterized by constipation (disorder)|
Recommended Dosing Regimen	145 mcg orally once daily

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OB=Office of Biostatistics
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
DPMH=Division of Pediatrics and Maternal Health
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DCOA= Division of Clinical Outcome Assessment
PFSS=Patient-Focused Statistical Scientists

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
APS	abdominal pain and spontaneous bowel movement
AR	adverse reaction
BLA	biologics license application
BLQ	below level of quantification
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BSFS	Brostol Stool Form Scale
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFB	change from baseline
CFR	Code of Federal Regulations
CIC	chronic idiopathic constipation
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSBM	complete spontaneous bowel movement
CSR	clinical study report
CSS	Controlled Substance Staff
DBTP	double blind treatment period
DG	Division of Gastroenterology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FC	functional constipation
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GC-C	guanylate cyclase-C
GCP	good clinical practice
GRMP	good review management practice
IBS-C	irritable bowel syndrome with constipation
ICH	International Conference on Harmonisation
IND	Investigational New Drug

ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IVRS	interactive voice response system
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NRI	nonresponder imputation
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PIBSCSD	Pediatric Irritable Bowel Syndrome with Constipation Symptom Diary
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SBM	spontaneous bowel movement
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Trade name: Linzess (linaclotide)

Pharmacologic class: guanylate cyclase-C (GC-C) receptor agonist
Description, formulation, and route of administration: Linzess is supplied as hard gelatin capsules containing linaclotide-coated beads. Currently approved dosage forms are 72 mcg, 145 mcg, and 290 mcg capsules for oral administration.
Mechanism of action: Linaclotide is a peptide and agonist of GC-C. GC-C receptors are expressed on epithelial cells in the intestinal lumen, and agonism of the receptors stimulates secretion of chloride and bicarbonate into the lumen, resulting in increased intestinal fluid and intestinal transit.
Regulatory History: Linzess (linaclotide) was originally approved for adults with irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) on August 30, 2012. Linzess was issued Pediatric Research Equity Act (PREA) postmarketing requirements (PMRs) at the time of approval, including a PMR to conduct safety and efficacy study in pediatric patients with IBS-C. A Best Pharmaceuticals for Children Act Pediatric Written Request (PWR) was issued on March 11, 2016 to evaluate the potential use of linaclotide for the treatment of IBS-C and functional constipation (FC) [1] in pediatric patients. Linzess was approved for pediatric FC in patients 6 years of age and older on June 12, 2023 (Supplement 21). Supplement 22 was submitted on May 6, 2025, seeking the pediatric IBS-C indication for patients 7 years of age and older. This efficacy supplement is intended to fulfill the following PMR and address the three studies listed below that are described in the PWR:

- PMR 1915-3: A safety and efficacy study in pediatric patients with irritable bowel syndrome with constipation ages seven years up to 17 years treated with Linzess (linaclotide).
- PWR Study 02: A randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study for the treatment of irritable bowel syndrome with constipation in children ages 7 to 17 years.
- PWR Study 04: A randomized, double-blind, parallel-group confirmatory safety and efficacy study for the treatment of irritable bowel syndrome with constipation in children and adolescents 7 to 17 years of age.

[1] In clinical practice, chronic idiopathic constipation (CIC) and functional constipation (FC) are used interchangeably to refer to constipation that is characterized by a chronic time course and for which there are no anatomical, structural, or biochemical abnormalities. In pediatric patients, the term functional constipation is used more frequently.

- PWR Study 05: A long-term safety study enrolling children and adolescents with chronic idiopathic constipation or irritable bowel syndrome with constipation who completed Studies 01, 02, 03 or 04.[2]

1.2. Conclusions on the Substantial Evidence of Effectiveness

The multidisciplinary review team recommends approval of this sNDA to expand the indications of linaclotide to include "the treatment of irritable bowel syndrome with constipation (IBS-C) in pediatric patients 7 years of age and older."

Under current regulations [21 CFR 201.57(f)(9)(iv) in the 2008 CFR], pediatric effectiveness claims can be established by extrapolating adult study results when the pathophysiology and drug effects are sufficiently similar between populations. The pathophysiology, clinical characteristics, and disease course of IBS-C are similar in adult and pediatric populations. The disease definitions and treatment response outcomes (including abdominal discomfort associated with changes in stool frequency and improvement with defecation) are also deemed sufficiently similar between adult and pediatric IBS-C populations to permit the extrapolation of efficacy from adequate and well-controlled studies that supported approval of linaclotide in adults with IBS-C. Since linaclotide is minimally absorbed and acts locally in the gut, it is difficult or impossible to rely upon correlation between systemic drug exposures and therapeutic response; therefore, dose ranging data and assessment of dose-response relationship using clinical endpoints are needed as part of the pediatric extrapolation to support substantial evidence of effectiveness (SEE).

The Applicant conducted Study LIN-MD-64, a phase 3, multicenter, randomized, double-blind, study of linaclotide 145 mcg or 290 mcg daily in 108 subjects 7 to 17 years of age who met modified Rome III criteria for child/adolescent IBS-C. In the study, the primary efficacy endpoint was based on the proportion of subjects meeting the combined responder criteria for at least 6 out of 12 weeks during the intervention period: a minimum 30% reduction in abdominal pain from baseline and an increase of at least 2 spontaneous bowel movements (SBM) per week from baseline (i.e., the 6/12 weeks abdominal pain and SBM [APS] + 2 responder). Although the primary analysis failed to meet prespecified success criteria, this failure was driven by high rates of missing data. The missing data were likely due to the burdensome twice-daily eDiary requirement (compared to the once-daily eDiary requirement in the adult studies) and the subsequent use of conservative missing data rules with non-responder imputation. These factors likely resulted in conservative response rates that may have reflected compliance issues rather than poor treatment efficacy.

[2] Study 01 is a randomized, double-blind, placebo-controlled, parallel group, dose-ranging study for the treatment of FC in children ages 6 to 17 years. Study 03 is a randomized, double-blind, parallel group confirmatory safety and efficacy study for the treatment of FC in children ages 6 to 17 years.

Sensitivity analyses using alternative approaches[3] for defining and handling missing data addressed these methodological concerns, demonstrated improved combined responder rates, and met primary endpoint statistical success criteria. The review team therefore concluded that efficacy was demonstrated for the primary endpoint. Study LIN-MD-64 also demonstrated statistically significant improvements in secondary endpoints measuring individual responder components, with both linaclotide dose groups showing increased weekly stool frequency and reduced abdominal pain scores. Exploratory analyses that demonstrated reductions in rescue medication use during the study provided further support for the treatment effect.

The efficacy of linaclotide in pediatric IBS-C is supported by similar results demonstrated in the adult IBS-C population for the 12-week change from baseline in abdominal pain scores and complete spontaneous bowel movement (CSBM) frequency. These consistent results, in conjunction with the similarity of the pathophysiology, clinical characteristics, disease course, and treatment response outcomes of IBS-C in adult and pediatric populations, support pediatric extrapolation and the demonstration of efficacy.

The collective evidence from adult and pediatric studies establishes SEE for linaclotide and supports expanding the indication to include the treatment of IBS-C in patients 7 years of age and older.

[3] This alternative approach modified the criteria for evaluable data from requiring ≥7 complete daily eDiary entries to requiring ≥4 evening eDiary entries per week, while maintaining non-responder imputation for missing data. This approach was appropriate because it: (1) aligned the pediatric study requirements with the adult study methodology (both requiring 4 of 7 entries), (2) addressed concerns about data reliability due to high eDiary non-compliance, and (3) provided conservative estimates of treatment response rates.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Linzess (linaclotide) is a guanylate cyclase-C (GC-C) receptor agonist currently approved for treatment of irritable bowel syndrome with constipation (IBS-C) in adults, chronic idiopathic constipation (CIC) in adults, and functional constipation (FC) in pediatric patients 6 years of age and older. In this NDA supplement, the Applicant proposes the added indication of linaclotide 145 mcg once daily for treatment of IBS-C in pediatric patients 7 years of age and older.

IBS-C, defined by the Rome diagnostic criteria, is a common condition experienced by children and adolescents. The etiology is often multifactorial with no known underlying organic cause. Untreated IBS-C can have clinically significant impacts on the health and well-being of children and adolescents. There are currently no FDA-approved therapies for treating pediatric patients with IBS-C. Treatment typically includes off-label use of nonprescription osmotic laxatives (e.g., polyethylene glycol), selective serotonin reuptake inhibitors (SSRIs) (e.g., citalopram), and antispasmotics (e.g., hyoscyamine).

To support this submission, the Applicant conducted Study LIN-MD-64, a phase 3 randomized, double-blind study of linaclotide 145 mcg and 290 mcg once daily for 12 weeks in subjects 7 to 17 years of age meeting Rome III criteria for IBS-C. The data submitted from Study LIN-MD-64 support the safety and effectiveness of linaclotide in treating IBS-C in pediatric patients 7 to 17 years of age and the use of linaclotide in this population relies upon extrapolation of efficacy from adequate and well-controlled studies that supported approval of linaclotide in adults with IBS-C. The primary efficacy endpoint was a combined responder definition requiring subjects to meet two criteria for at least 6 weeks of the 12-week study intervention period: a minimum 30% reduction in abdominal pain from baseline and an increase of at least 2 spontaneous bowel movements (SBM) per week from baseline (i.e., the 6/12 weeks abdominal pain and SBM [APS] + 2 responder).

Study LIN-MD-64 initially failed to achieve statistical significance on the prespecified primary endpoint, with response rates of 22.6% and 23.4% for the 145 mcg and 290 mcg doses, respectively. This failure was primarily attributed to high rates of missing data caused by burdensome twice-daily electronic diary requirements and subsequent use of conservative missing data rules with non-responder imputation. However, sensitivity analyses using alternative approaches for defining and handling missing data demonstrated improved primary endpoint response rates that met statistical success criteria, with 30% and 32% of subjects being combined responders in the linaclotide 145 mcg and 290 mcg

groups, respectively[4]. This alternative approach was deemed appropriate as it aligned the pediatric study requirements with the adult study methodology (both requiring 4 of 7 entries), addressed concerns about data reliability due to high eDiary non-compliance, and provided conservative estimates of treatment response rates.

Study LIN-MD-64 also demonstrated statistically significant improvements in secondary endpoints measuring individual responder components. The change from baseline (CFB) in 12-week stool frequency was 2.35 SBMs and 2.75 SBMs per week, and the response rates[4] for the 6/12 Weeks SBM + 2 endpoint were 40% and 38% for the linaclotide 145 mcg and 290 mcg groups, respectively. The CFB in 12 week abdominal pain score were each -0.84 points, and the response rates[4] for the 6/12 Weeks APS endpoint were 68% and 62% for the linaclotide 145 mcg and 290 mcg groups, respectively.

The Applicant conducted exploratory analyses to further characterize clinical benefit. Post-hoc analyses evaluated the proportion of subjects meeting clinically relevant thresholds for weekly SBM frequency and stool consistency scores. In the linaclotide 145 mcg and 290 mcg groups, the proportion of subjects with a mean weekly SBM frequency of at least 3 SBMs/week increased from 0% at baseline to 43.4% and 53.2% during treatment, respectively. Additionally, subjects in both linaclotide groups showed decreases in weekly scores for abdominal pain, straining, and bloating during the 12-week treatment period. By the end of treatment, 27.5% and 41.9% of subjects in the linaclotide 145 mcg and 290 mcg groups, respectively, no longer fulfilled the Rome III criteria for IBS-C. Exploratory analyses of rescue medication use revealed progressively lower rates in both linaclotide treatment groups, with the percentage of weeks requiring rescue medication decreasing from 50.9% to 20.8% and from 52.5% to 14.9% for the 145 mcg and 290 mcg groups, respectively.

In light of the unmet medical need for safe and effective therapies for treating pediatric IBS-C, the review team concluded that the collective evidence of efficacy from adult and pediatric data supported a clinically meaningful benefit for linaclotide in pediatric patients 7 years of age and older with IBS-C. The 290 mcg group demonstrated a numerically higher response rate than the 145 mcg group in patients aged 12 to 17 years, while the opposite trend was observed in patients aged 7 to 11 years. These differences should be interpreted cautiously due to limited subgroup sizes and absence of statistical significance testing. Given conflicting findings across age groups, inherent uncertainties in the data due to small sample sizes, and the lack of clear additional clinical benefit for the 290 mcg dose, the review team recommends the 145 mcg dose for both age groups. This recommendation aligns with the regulatory principle of approving the lowest effective dose that achieves the desired therapeutic outcome while minimizing potential risks associated with dose escalation.

[4] Results based on sensitivity analysis that required ≥ 4 evening eDiary entries per week for the weekly values to be considered non-missing.

The safety of linaclotide was characterized through data obtained from the 12-week phase 3 Study LIN-MD-64 and the long-term safety Study LIN-MD-66. Diarrhea was the most common treatment-emergent adverse event but occurred without significant sequelae of dehydration, volume depletion or electrolyte abnormalities. Only one subject reported severe diarrhea in the submitted datasets (in the 290 mcg treatment group). Dehydration related to diarrhea can have potentially serious outcomes in pediatric patients, which remains an important consideration. The review team concluded that no new safety concerns were identified from the clinical study data nor from the postmarketing safety data, and that the safety profile for linaclotide described from the pediatric studies in this submission was generally consistent with the known safety profile for linaclotide from studies in adults with IBS-C and CIC, and studies in children with functional constipation (FC).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• IBS-C is a common condition experienced by children and adolescents. There is no known underlying organic cause and the etiology is often multifactorial.	• IBS-C can have clinically significant impacts on the health and well-being of children and adolescents.
Current Treatment Options	• No FDA-approved treatment options exist for pediatric patients with IBS-C. • Nonprescription osmotic laxatives (e.g., polyethylene glycol), SSRIs (e.g., citalopram), and antispasmotics (e.g., hyoscyamine) are used off-label for treatment of IBS-C in some pediatric patients.	• There is an unmet medical need for safe and effective therapies for treatment of pediatric IBS-C.
Benefit	•The Applicant conducted a phase 3 randomized, double-blind study of linaclotide 145 mcg and 290 mcg once daily for 12 weeks in subjects 7 to 17 years of age meeting Rome III criteria for IBS-C (study LIN-MD-64). • The primary efficacy endpoint was a combined responder definition that required subjects to meet two criteria for at least 6 weeks of the 12-week study intervention period: (1) a minimum 30% reduction in abdominal pain from baseline and (2) an increase of at least 2 spontaneous bowel movements per week from baseline. The endpoint	•Linaclotide demonstrated improvements in meeting the threshold (18%) of combined responder definition (primary endpoint) as well as improvement in SBM frequency and abdominal pain. •Although the primary analysis did not achieve statistical significance, a post-hoc sensitivity analysis that modified the criteria for non-

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	showed response rates of 22.6% and 23.4% for the 145 mcg and 290 mcg doses, respectively. While these rates were numerically higher than the 18% threshold, they failed to meet the primary statistical success criteria. This failure was primarily attributed to high rates of missing data caused by burdensome twice-daily electronic diary requirements (compared to the once-daily eDiary requirement in adult IBS-C studies) and the subsequent use of conservative missing data rules with non-responder imputation. • Sensitivity analyses using alternative approaches for defining and handling missing data, requiring ≥4 evening eDiary entries per week vs. ≥7 complete twice daily eDiary entries while maintaining non-responder imputation for missing data, addressed these methodological concerns and demonstrated improved primary endpoint response rates that met statistical success criteria, with a response rates of 30% (95% CI: 18%, 44%) and 32% (95% CI: 19.1, 47.1) for the linaclotide 145 mcg and 290 mcg groups, respectively. • The secondary efficacy endpoint results for linaclotide 145 mcg and 290 mcg doses, were as follows: ○ the response rates[4] were 40% and 38% for the 6/12 weeks SBM + 2 endpoint; ○ the response rates[4] were 68% and 62% for the 6/12 weeks APS endpoint; ○ the CFB in 12-week stool frequency was 2.35 SBMs and 2.75 SBMs per week; ○ the CFB in stool consistency was 0.98 and 1.36 points. ○ The CFB in 12-week abdominal pain score was -0.84 points for both doses. • Additional post-hoc analyses showed the following:	missing data demonstrated improved primary endpoint response rates that met statistical success criteria. This sensitivity analysis required ≥ 4 evening eDiary entries per week for the weekly values to be considered non-missing. This alternative approach was deemed appropriate because it (1) aligned the pediatric study requirements with the adult study methodology—both required 4 of 7 entries, (2) addressed concerns about data reliability due to high eDiary non-compliance, and (3) provided conservative estimates of treatment response rates. • Linaclotide also demonstrated improvements in secondary endpoints that included the abdominal pain and SBM responder components of the primary endpoint, as well as changes from baseline (CFB) in abdominal pain scores and SBM frequency during the 12-week study intervention period. • Post-hoc analyses evaluated the proportion of subjects meeting clinically relevant thresholds for weekly SBM frequency and stool consistency scores. Exploratory analyses of rescue medication use revealed progressively lower rates of rescue medication use in both linaclotide treatment groups over the 12-week treatment period.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	○ The proportion of subjects with a mean weekly SBM frequency of at least 3 SBMs/week in the linaclotide 145 mcg and 290 mcg groups increased from 0% in the baseline period to 43.4% and 53.2% in the DBTP. ○ Subjects in both linaclotide groups showed decreases in weekly scores for abdominal pain (including daytime and nighttime symptoms), straining, and bloating during the 12-week treatment period, compared to baseline. • By the end of treatment, 27.5% and 41.9% of subjects in the linaclotide 145 mcg and linaclotide 290 mcg groups, respectively, no longer fulfilled the Rome III criteria for IBS-C. • An exploratory analysis of rescue medication use showed that rescue mediation use was lower in the DBTP, as compared to the baseline period. In the linaclotide 145 mcg group and 290 mcg group, the percentage of weeks with rescue medication decreased from 50.9% to 20.8% and from 52.5% to 14.9%, respectively. • The 290 mcg group demonstrated a numerically higher response rate than the 145 mcg group in patients aged 12 to 17 years, while the opposite trend was observed in patients aged 7 to 11 years. These differences should be interpreted cautiously due to limited subgroup sizes and absence of statistical significance testing.	• The collective evidence of efficacy from adult and pediatric data supported a clinically meaningful benefit for linaclotide in pediatric patients ages 7 to 17 with IBS-C. • Given conflicting findings across age groups, inherent uncertainties in the data due to small sample sizes, and the lack of clear additional clinical benefit for the 290 mcg dose, the review team recommends retaining the 145 mcg dose for both age groups in the proposed labeling. This recommendation aligns with the regulatory principle of approving the lowest effective dose that achieves the desired therapeutic outcome while minimizing potential risks associated with dose escalation.
Risk and Risk Management	• Diarrhea was the most common adverse event but occurred without significant sequelae of dehydration, volume depletion or electrolyte abnormalities. • One subject in the long-term safety study, LIN-MD—66, who received the 290 mcg dosage, reported a case of severe diarrhea. • Dehydration related to diarrhea can have potentially serious outcomes in pediatric patients.	• Diarrhea is a known risk of linaclotide use. Diarrhea was the most commonly reported TEAE. Only one subject reported severe diarrhea in the submitted datasets (in the 290 mcg treatment group). The USPI already includes the risk of diarrhea with Warnings and Precautions language.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		• No new safety concerns were identified from the clinical study data nor from the postmarketing safety data. • The safety profile for linaclotide described from the pediatic studies in this submission was generally consistent with the known safety profile for linaclotide from studies in adults with IBS-C and CIC, and children with FC.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	8.1.1, 8.1.3, 15.5
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

IBS-C is a functional gastrointestinal disorder characterized by recurrent abdominal pain associated with altered bowel movement characteristics, specifically constipation (Drossman, 2006; Hyams et al., 2016; Greer & Sultan, 2025). The overall estimated prevalence of IBS in the pediatric population varies across studies, with IBS affecting approximately 2.8% to 5.1% among US children 4 to 18 years of age, with roughly half of these patients affected by the IBS-C subtype (Lewis et al., 2016; Self et al., 2014; Hyams et al., 2016). The underlying etiology of IBS-C is not completely understood and is likely multifactorial (Drossman, 2006; Hyams et al., 2016; Greer & Sultan, 2025). Contributing and/or related factors can include, but are not limited to, psychosocial factors (stress, anxiety, depression), visceral hypersensitivity, and intestinal inflammation (Drossman, 2006; Chiou & Nurko, 2011; Hyams et al., 2016). Untreated IBS-C can significantly impact a child's quality of life and may lead to school absenteeism and substantial healthcare utilization costs (Lewis et al., 2016; Chiou & Nurko, 2011; Gordon et al., 2025).

Diagnosis of IBS-C is defined by the Rome diagnostic criteria, which are in their fourth edition (Rome IV) at the time of this review. Rome IV defines diagnosis of child and adolescent IBS-C as follows (Hyams et al. 2016):

Table 1. Rome IV Diagnostic Criteria for Child and Adolescent IBS-C

Must include the following criteria for at least 2 months before diagnosis:
1. Abdominal pain at least 4 days per month associated with one or more of the following: a. Related to defecation b. A change in frequency of stool c. A change in form (appearance) of stool
2. In children with constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not irritable bowel syndrome)
3. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

Source: Adapted from Hyams et al. 2016.

Pediatric clinical development for linaclotide preceded publication of Rome IV; therefore, modified Rome III criteria were used in the clinical studies supporting this NDA supplement. However, the definition of IBS-C is similar in Rome IV and Rome III, with the notable difference being that the Rome IV included the criterion of abdominal pain for at least 4 days per month for at least 2 months, whereas Rome III included a criterion of abdominal pain or abdominal discomfort once per week for at least 2 months (Drossman et al., 2006; Hyams et al., 2016).

2.2. Analysis of Current Treatment Options

No FDA-approved treatment options currently exist for pediatric IBS-C. Treatment typically includes dietary modification and off-label medications, such as osmotic laxatives (e.g., polyethylene glycol), antidepressants (e.g., citalopram), and antispasmodics (e.g., hyoscyamine) (Chiou & Nurko, 2011; Patel et al., 2021; Gordon et al., 2025) .

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Linzess (linaclotide) was approved for adults with irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) on August 30, 2012, under NDA 202811. The approved dosage for the treatment of IBS-C is 290 mcg capsule taken orally once daily. The approved dosages for the treatment of CIC are either 145 mcg or 72 mcg capsule taken orally once daily. Following the original NDA approval of the 145 mcg dose for the treatment of CIC, the safety and efficacy of the 72 mcg dose was established for CIC in supplement 10, approved on January 25, 2017. On June 12, 2023, linaclotide 72 mcg once daily was approved for the treatment of functional constipation (FC) in pediatric patients 6 to 17 years of age. This product was co-developed by AbbVie Incorporated and Ironwood Pharmaceuticals, Incorporated.

At the time of original NDA approval, several post-marketing requirements (PMRs) were issued including PMR 1915-3 (“a safety and efficacy study in pediatric patients with irritable bowel syndrome with constipation ages seven years up to 17 years treated with Linzess [linaclotide]”).

On March 11, 2016, in response to the Applicant’s Proposed Pediatric Study Request dated August 3, 2015, FDA issued a Written Request (WR) under the Best Pharmaceuticals for Children Act (BPCA) for pediatric studies to investigate the use of linaclotide for the treatment of IBS-C and FC in pediatric patients. Subsequent Amended WRs were issued on June 10, 2021, November 23, 2023, and September 16, 2024, to reflect agreements on study designs and revise the timeframe for submitting reports of the pediatric studies to May 30, 2025.

3.2. Summary of Presubmission/Submission Regulatory Activity

This submission is intended to fulfill PREA PMR 1915-3 and address Study 02 (“randomized, double-blind, placebo-controlled, parallel group, dose-ranging study for the treatment of IBS-C in children ages 7 – 17 years, Study 04 (“randomized, double-blind, parallel group confirmatory safety and efficacy study for the treatment of IBS-C in children ages 7 – 17 years”), and Study 05 (“long-term safety study enrolling children with chronic idiopathic constipation or irritable bowel syndrome with constipation who completed Studies 01, 02, 03 or 04”) of the WR.

Key recommendations and points of discussion specific to the development of Linzess for IBS-C in pediatric patients 7 – 17 years of age are outlined below.

January 26, 2010 – Type C Meeting
FDA recommended that observer reports only include events or behaviors that can be observed for patients who cannot respond for themselves.

April 16, 2013 – Type C Meeting
- FDA recommended development of a simpler PRO instrument that could be better understood and self-reported by younger children and to consider an interviewer-administered form that could be administered to young children by their parents/caregivers.
- FDA agreed with the proposed twice-daily assessments for the child-completed diary to cover a 24-hour recall period.
- FDA recommended the sponsors to re-evaluate the qualitative research findings to inform item modification or reduction, to narrow the scope to items most critical for making an assessment of treatment benefit.

February 5, 2014 – Advice/Information Request Letter
FDA advised narrowing the scope of items in the proposed PRO instruments to minimize risk of missing data and suggested evaluating responder burden, completion rates, and item reduction in a stand-alone validation study prior to use in clinical study.

November 4, 2014 – Type C Meeting
FDA agreed that it was acceptable to perform psychometric validation of the PRO instrument within the phase 2 study with the understanding that the finalized scoring algorithm that will be used in the confirmatory study will be based on the validation data from phase 2.

May 16, 2018 – Type C Meeting
To help with enrollment challenges, FDA recommended modifications to the IBS-C dose-ranging study (LIN-MD-63):
- Utilizing adult IBS-C and CIC data, as well as pediatric data from the FC dose-ranging study (LIN-MD-62), to potentially reduce the number of dose groups for LIN-MD-63
- Increasing the duration of the screening period to 4 weeks to capture patients who may have infrequent symptoms
- Reducing the number of questions in the eDiary
- Administering the eDiary once a day rather than twice per day.

The Sponsor acknowledged the suggestions and stated that the modifications were unlikely to address the patient recruitment challenges.

June 19, 2019 – Type C Meeting
- In light of the Sponsor's recruitment challenges, FDA recommended stopping LIN-MD-63 to analyze data from the currently randomized patients to date to inform dosing for a follow-on, confirmatory safety and efficacy study in the pediatric patients with IBS-C.

- To help with the feasibility of conducting two confirmatory trials (FC and IBS-C) simultaneously, FDA stated that the Sponsor could consider using a master protocol for the IBS-C and FC confirmatory trials.
- FDA agreed with the Sponsors' proposal to drop the lowest dose level (72 mcg) in the phase 3 study, but recommended evaluating a higher dose (290 mcg) to potentially demonstrate a clinically meaningful benefit on both constipation and abdominal pain.
- FDA suggested an alternative study design for the 12-week confirmatory study:
    - Efficacy may be extrapolated from adult efficacy data, allowing for a reduced sample size.
    - Placebo arm could be removed to facilitate enrollment.

April 30, 2020 – Type C Meeting

- FDA agreed that the progression of IBS-C and response to treatment are sufficiently similar in adult and pediatric patients to support extrapolation of efficacy from adult data.
- FDA stated that the proposed Bayesian analysis would be one of several considered during supplemental new drug application (sNDA) efficacy assessment.
- FDA recommended that the Sponsors enroll a minimum of 100 patients in the phase 3 study LIN-MD-64.

September 15, 2023 – PMR Deferral Extension Granted

Deferral extension granted and revised milestone acknowledged for PMR 1915-3 due to delays involving study participants and recruitment.

April 16, 2024 – Type C WRO

FDA acknowledged previous agreement that LIN-MD-64 was designed and conducted without a placebo control, and recommended that detailed justification be included with the sNDA to support interpretability of data.

December 11, 2024 – Type B pre-sNDA Meeting

- FDA stated that assessment of efficacy for the pediatric IBS-C population would be based on strength and confidence of the available data, and provided recommendations of additional analyses for the Sponsors to conduct to support evaluation of efficacy.
- FDA stated that all availability data, including post-hoc analyses performed to investigate influence of missing eDiary entries, would be considered during sNDA efficacy assessment.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Site inspections were conducted at two clinical study sites, Sites #10021 (Dr. Edgar Gonzalez) and #10063 (Dr. Inti Fernandez) to assess the quality and integrity of the data submitted in this

marketing application. Based on inspection results, the clinical data generated by these sites appear suitable to evaluate the proposed indication. Refer to Clinical Inspection Summary finalized in Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) on August 22, 2025.

4.2. Product Quality

The Applicant's request for Categorical Exclusion from the requirement of preparing and submitting an Environmental Assessment under 21 CFR 25.31(a) was found acceptable from the chemistry, manufacturing, and controls standpoint.

There are no changes to the quality information for the drug product, and no changes to the quality-related portions of the United States Prescribing Information (sections 3, 11, and 16).

The supplement is recommended for approval by the Office of Pharmaceutical Quality. See review dated June 18, 2025, by Austin Yu in Panorama.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical studies or information were included in this supplement to support the proposed indication in pediatric patients 7 to 17 years of age. Nonclinical studies with linaclotide supporting the safety of use in the proposed patient population were reviewed in detail under the original NDA 202811, NDA 202811 labeling supplement 4, and/or NDA 202811 labeling supplement 18.

There are no nonclinical concerns with the safety of the levels of excipients used in the manufacture of Linzess capsules at the recommended clinical dose of 145 mcg/day in pediatric patients 7 to 17 years of age with IBS-C. The levels of all excipients are below those used in previously approved, orally administered products as reported in the FDA Inactive Ingredient Database.

6 Clinical Pharmacology

6.1. Executive Summary

Linzess (linaclotide capsules) is a 14-amino acid peptide that acts on the apical surface of epithelial cells in the intestinal lumen to stimulate the receptor GC-C, indicated in adults for treatment of IBS-C and CIC and in pediatric patients 6 years of age and older for treatment of FC. The approved dosage is 290 mcg once daily for IBS-C, 145 mcg or 72 mcg once daily for CIC, and 72 mcg for FC.

In this supplement, the Applicant is seeking approval of Linzess for the treatment of IBS-C in pediatrics 7 years of age and older. This supplement is also intended to fulfill the PREA PMR 1915-3.

The clinical pharmacology program to support this supplement includes Study LIN-MD-63, which was a phase 2, dose-ranging, safety and efficacy study in pediatrics 7 to 17 years of age with IBS-C. The efficacy and safety results from this study were used to guide the dosing regimens for the phase 3 program (i.e., 145 or 290 mcg QD).

Sparse pharmacokinetic (PK) samples were collected in Study LIN-MD-63 to determine the plasma concentrations of linaclotide and its active metabolite MM-419447. The concentrations of linaclotide and MM-419447 were below the limit of quantification (BLQ) in most of the subjects, similar to the nondetectable concentrations in adults.

6.1.1. Recommendations

This supplement is approvable from a clinical pharmacology perspective.

6.1.2. Post-Marketing Requirements/ Commitments

None.

6.1.3. Outstanding Issues

None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Overall Study Design

Study LIN-MD-63 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, safety and efficacy, dose-ranging study comparing 1 of 3 linaclotide doses (A [low dose], B [medium dose], and C [high dose]) or 290 mcg (only in subjects 12 to 17 years of age) with

placebo in pediatrics 7 to 17 years of age with IBS-C (Table 2). See Section 15.4. The objective was to evaluate the dose response, safety, and efficacy of the three linaclotide dose levels compared with placebo. The addition of the 290-mcg dose level in subjects 12 to 17 years of age was for safety and exploratory efficacy evaluation only.

The study included four study periods as follows:

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

The primary efficacy endpoint was the change from baseline (CFB) in 4-week overall spontaneous bowel movement (SBM) frequency rate (SBMs/week) during the Treatment Period.

The secondary efficacy endpoints included the CFB in the following:

- 4-week abdominal pain daytime symptom
- 4-week stool consistency
- 4-week severity of straining
- 4-week abdominal bloating daytime symptoms
- 4-week overall complete SBM frequency rate during the Treatment Period

Dosing Regimen

Subjects 7 to 11 years of age were dosed based on weight, and subjects 12 to 17 years of age were assigned to 1 of 4 linaclotide dose levels (Table 2). Assigned treatment was administered orally once daily, 30 minutes before the evening meal. Subjects were instructed to take the assigned treatment at approximately the same time each day.

Table 2. Linaclotide Doses Evaluated in Study LIN-MD-63

		4-Week Treatment Period			
Age Group	**Weight**	**Linaclotide Dose A**	**Linaclotide Dose B**	**Linaclotide Dose C**	**Approved Adult Dose**
Subjects 7 -11 years[a]					
	18 to < 35 kg	18 mcg	36 mcg	72 mcg	—
		placebo	placebo	placebo	—
	≥ 35 kg	36 mcg	72 mcg	145 mcg	—
		placebo	placebo	placebo	—
Subjects 12 -17 years[b]					
		36 mcg	72 mcg	145 mcg	290 mcg[c]

		placebo	placebo	placebo	placebo

[a] Subjects 7 to 11 years of age received linaclotide or placebo in a liquid oral solution or solid oral capsules.

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

[c] Approved adult dose of 290 mcg was for safety and exploratory efficacy only.

Source: Applicant's Clinical Study Report, Table 9-1

Study Subjects

Of the 397 subjects screened, 83.6% (332/397) of subjects completed screening and entered the Pretreatment Period. Among subjects who entered the Pretreatment Period, 69.6% (231/332) discontinued during the Pretreatment Period. The most frequent reason for discontinuation from the Pretreatment was screen failure (215/332 subjects, 64.8%).

A total of 101 subjects were randomized to receive either one of the linaclotide doses or placebo. The majority (94/101 subjects, 93.1%) of subjects completed the Treatment Period. The most frequent reasons for discontinuation during the Treatment Period were lost to follow-up (2 subjects, 2.0%) and AEs (2 subjects, 2.0% [abdominal pain, anaphylactic reaction, and hematemesis in 1 subject and diarrhea in 1 subject]).

Most of the randomized subjects (95/101 subjects, 94.1%) completed the Post-treatment Period. Six subjects (6/101 subjects, 5.9%) did not report to their disposition statuses during the Post-treatment Period.

Overall, 41 subjects were randomized in the 7 to 11 years of age group and 60 subjects were randomized in the 12 to 17 years of age group. See detailed demographic and baseline characteristics in Table 34.

6.2.2. Pharmacokinetics

Sparse PK samples were collected and analyzed for plasma concentrations of linaclotide and its active metabolite MM-419447. One blood sample was collected from each subject at the randomization visit (Day 1) or at Week 2. Subjects were randomly assigned to one of four PK sampling schedules in a 1:1:1:1 allocation as shown in Table 3. The samples were analyzed using a validated liquid chromatography with tandem mass spectrometry assay. See Section 15.3 for details of the assay and its performance.

Table 3. PK Sampling Schedule

Randomization Visit (Day 1)	
PK Schedule 1	1 to 2 hours postdose
PK Schedule 2	3 to 4 hours postdose
PK Schedule 3	6 to 8 hours postdose
Week 2	
PK Schedule 4	>8 to 24 hours postdose

Source: Reviewer's table based on the Applicant's Clinical Study Report
Abbreviations: PK, pharmacokinetics

There is limited systemic absorption of linaclotide following oral administration. The plasma concentrations of linaclotide and MM-419447 were below the limit of quantitation in most of the pediatric subjects enrolled in this study, and thus no PK parameters were calculated. A total of 3 subjects (3/49, 6.1%) in the 12 to 17 years of age group and 2 subjects (2/33, 6.1%) in the 7 to 11 years of age group had quantifiable plasma concentrations of linaclotide and/or MM-419447 as summarized in Table 4.

Table 4. Summary of Quantified PK Samples

Age Group	Subject ID	LIN Dose Group (dose)	PK Sampling Time Point	Analyte	Concentration (ng/mL)
12 to 17 years	(b) (6)	Dose A (36 mcg)	3 to 4 hr postdose at Day 1	Linaclotide MM-419447	6950 1.57
		Dose B (72 mcg)	6 to 8 hr postdose at Day 1	Linaclotide MM-419447	32,500 6.48
		Dose C (145 mcg)	3 to 4 hr postdose at Day 1	Linaclotide MM-419447	40,700 15.0
7 to 11 years		Dose A (36 mcg)	6 to 8 hr postdose at Day 1	Linaclotide	0.38
		Dose A (18 mcg)	>8 to 24hr postdose at Week 2	Linaclotide	0.37

[a]These three subjects were enrolled at the same clinical study site.
Source: Reviewer's table based on the Applicant's Clinical Study Report
Abbreviations: LIN, linaclotide; PK, pharmacokinetics

The abnormally high concentrations observed in the 3 subjects from the 12 to 17 years age group were further investigated by the Applicant. While no evidence of sample contamination was identified in either bioanalytical or at the clinical site, the Applicant concluded that these samples appeared to be contaminated with linaclotide as these plasma concentrations are theoretically impossible to achieve following oral administration of linaclotide, even under the assumption of 100% drub absorption and systemic bioavailability. The review team concurs with the Applicant's conclusion that these samples appear to have been contaminated. The fact that these 3 subjects were all enrolled at the same clinical study site further supports that these values likely represent error rather than true systemic exposure to linaclotide and MM-419447.

Linaclotide concentrations quantified in the two subjects from the 7 to 11 years age group were low as expected, and were comparable to findings in previous clinical study experiences in adults and pediatrics.

No unexpected safety concerns were observed in the five subjects with quantifiable concentrations of linaclotide and/or its active metabolite.

6.2.3. Summary of Efficacy and Safety Results

As most of PK samples were below the level of quantitation, the selection of phase 3 dose from this study was based on efficacy and safety results.

For the primary efficacy endpoint of change from baseline in 4-week overall SMB frequency rate, numerical improvement was observed with increasing dose compared with placebo. For the key secondary efficacy endpoint of change from baseline in 4-week abdominal pain daytime symptoms, numerical improvement was observed with linaclotide 290 mcg compared with placebo, while results were similar in the other linaclotide groups (Dose A [low dose], B [medium dose], and C [high dose]) compared with placebo. For the other secondary efficacy endpoints, greater numerical improvement was observed in the change from baseline in 4-week stool consistency, severity of straining, and overall CSMB frequency rate in the increasing linaclotide dose groups compared with placebo, while similar responses were observed in all linaclotide groups (Dose A, B, C, 290 mcg) compared with placebo for change from baseline in 4-week abdominal bloating.

Overall, linaclotide was well tolerated across all doses and both age groups and the safety profile were consistent with previous experience in adults with IBS-C.

Based on the efficacy and safety findings from this study, the Applicant chose 145 mcg and 290 mcg to be further evaluated in phase 3 trials. Refer to Sections 8 for additional efficacy and safety data from this study.

6.2.4. Formulations

In the dose-ranging study LIN-MD-63, formulations different from the to-be-marketed were used: liquid oral solution and oral capsule. Subjects 7 to 11 years of age received linaclotide in a liquid oral solution or oral capsules, and subjects 12 to 17 years of age received linaclotide in oral capsules.

Although formulations used in Study LIN-MD-63 were different from the to-be-marketed formulation, a relative bioavailability study to support bridging of formulations were not conducted due to limited systemic absorption of linaclotide following oral administration. The to-be-marketed formulation was used in the phase 3 studies (LIN-MD-64 and -66) in pediatric patients with IBS-C.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 5 lists the clinical studies supporting review of efficacy and safety for NDA 202811/S-022.

Table 5. Listing of Clinical Trials Relevant to this NDA

Study ID	Study Design	Dosing Regimen(s)	Endpoints	Duration	Sample Size	Study Population	Sites
Controlled Studies							
LIN-MD-63	R/DB/PC dose-ranging	LIN or PBO PO QD for 4 weeks Doses studied: 7 to 11 yrs, 18 to <35 kg: 18 mcg; 36 mcg; 72 mcg; PBO 7 to 11 yrs, ≥35 kg: 36 mcg; 72 mcg; 145 mcg; PBO 12 to 17 yrs: 36 mcg; 72 mcg; 145 mcg; 290 mcg; PBO	Primary: Change from baseline in 4-week SBM frequency (SBM/week)	4 weeks	Total: 101 LIN: 82 PBO: 19	Patients aged 8 to 17 years with IBS-C per Rome III criteria	48 sites in the US
LIN-MD-64	R/DB	LIN 145 mcg or 290 mcg PO QD for 12 weeks	Primary: 6/12 weeks APS (abdominal pain and SBM) + 2 responder	12 weeks	Total: 108 LIN 145 mcg: 55 LIN 290 mcg: 53	Patients ages 7 to 17 years with IB-C per Rome III criteria	33 sites in the US
Uncontrolled Studies							
LIN-MD-66	Open-label, long-term safety	LIN 145 mcg or 290 mcg PO QD	Safety	52 weeks	Total: 98 LIN 145 mcg: 22 LIN 290 mcg: 76	Subjects who completed LIN-MD-63 or LIN-MD-64	31 sites in the US

Source: Reviewer's table
Abbreviations: LIN, linaclotide; PBO, placebo; PO, by mouth; R/DB/PC, randomized, double-blind, placebo-controlled; QD, once daily; SBM, spontaneous bowel movement; US, United States

7.2. Review Strategy

This review of safety and efficacy focused on data from the phase 3 randomized, double-blind study LIN-MD-64. The safety review also assessed interim data from the open-label extension study LIN-MD-66, which enrolled subjects who had completed either the phase 2 dose-ranging study LIN-MD-63 or the phase 3 study LIN-MD-64. Although data from the phase 2 study, LIN-MD-63, were assessed because they informed the selection of the proposed to-be-marketed dose, these data did not contribute significantly to the review of safety and efficacy due to the study's relatively small sample size and short 4-week treatment duration.

The review team identified significant methodological concerns with the primary statistical analysis of the primary endpoint for the phase 3 pediatric study, stemming from high rates of missing data from electronic diary (eDiary) non-compliance and the subsequent use of non-responder imputation (NRI). The pediatric study had substantially higher missing data rates compared to three adult studies, largely due to the more burdensome twice-daily eDiary requirement (where both morning and evening entries were needed for an evaluable day) versus the adult studies' single daily phone-based entries. This uneven distribution of missing data, combined with the NRI methodology, likely resulted in conservative pediatric response rates and complicated comparisons of efficacy between pediatric and adult studies, as missing data may have reflected compliance issues rather than poor treatment outcomes. To address these concerns, three post-hoc sensitivity analyses were conducted using alternative approaches for defining and handling missing data, which reduced the disparities in evaluable weeks between the adult and pediatric studies.

In addition, the review team evaluated whether the submitted data fulfilled PMR 1915-3 and addressed Studies 02, 04, and 05 as described in the WR.

8 Statistical and Clinical and Evaluation

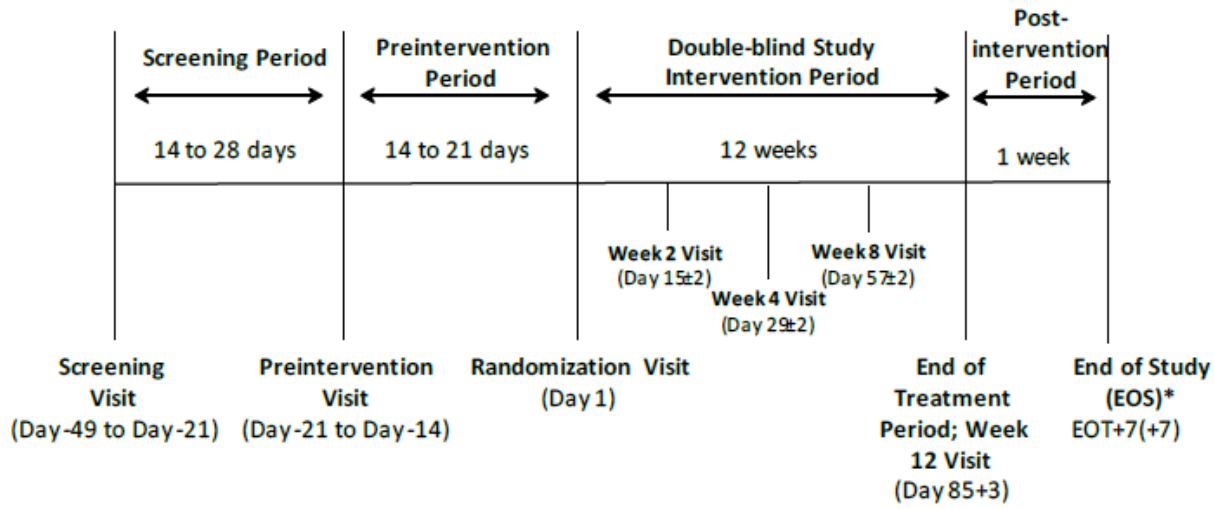
8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. LIN-MD-64

Trial Design

LIN-MD-64 was a phase 3 multicenter, randomized, double-blind, parallel-group study of linaclotide therapy in pediatric participants 7 to 17 years of age with a diagnosis of IBS-C (i.e., fulfill the Rome III criteria for child/adolescent IBS and modified Rome III criteria for child/adolescent functional constipation). The study consisted of a 2-to 4-week Screening Period, a 2- to 3-week Preintervention Period, followed by a 12-week Double-Blind Treatment Period (DBTP) and 1-week Postintervention Period (Figure 1). At the start of the DBTP, subjects were randomized in a 1:1 ratio to receive either 145 mcg or 290 mcg linaclotide, with randomization stratified by age group only (7 to 11 years of age versus 12 to 17 years of age). Primary efficacy assessments were determined based on responses entered in a morning and evening electronic diary (eDiary).

Figure 1: LIN-MD-64 Study Schema



* Participants who rollover to the long-term safety study, LIN-MD-66, before the EOS Visit are not required to have this visit.
Source: Clinical Study Report Figure 1 (page 23).

Inclusion/Exclusion Criteria

Key inclusion criteria:

1. Ages 7 to 17 years (inclusive)
2. ≥ 18 kg
3. Meets Rome III criteria for child/adolescent IBS: At least once per week for at least 2

months before the Screening Visit, the subject experienced abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with 2 or more of the following at least 25% of the time:
- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form (appearance) of stool

4. Subject has an average daytime abdominal pain score of ≥ 1 (at least "a tiny bit") during the 14 days before Visit 3.
5. Subject has an average of fewer than 3 SBMs per week during the 14 days before the randomization day and up to the randomization.

Key exclusion criteria:

1. Celiac disease, or positive serological test for celiac disease and the condition has not been ruled out by endoscopic biopsy.
2. Participant reports having more than 1 loose, mushy stool (eDiary-recorded stool consistency of 6 on the Pediatric Bristol Stool Form Scale [p-BSFS]) or any watery stool (eDiary-recorded stool consistency of 7 on the p-BSFS) 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 the randomization day and up to the randomization (including the morning eDiary assessments reported before administration of first dose of double-blind study intervention on the randomization day)
3. Participant used rescue medication on the calendar day before the Randomization Visit and on the day of the Randomization Visit until randomized.

Study Endpoints

Primary Endpoint

The primary efficacy endpoint is the 6/12 weeks APS (abdominal pain and SBM) + 2 responder. A 6/12 weeks APS + 2 responder is a subject that meets the weekly APS + 2 responder criteria for at least 6 out of the 12 weeks of the DBTP. A weekly APS +2 responder is a subject who has an increase of at least 2 in the spontaneous bowel movement (SBM) weekly rate from baseline, AND a decrease of at least 30% in the mean abdominal pain score from baseline, during that study intervention week. Baseline values were derived from the eDiary collected during the 14-day period immediately prior to randomization.

The number of BMs (used to defined SBMs) and abdominal pain are reported in the Pediatric Irritable Bowel Syndrome with Constipation Symptom Diary (PIBSCSD) daily eDiary. The PIBSCSD is a patient-reported outcome (PRO) measure that is designed to assess abdominal symptoms (pain, bloating) and bowel movement characteristics (frequency, consistency, straining, and complete evacuation). Refer to Section 8.1.3 for additional discussion of the PIBSCSD.

An SBM is a BM that occurs in the absence of laxative, suppository, or enema use on the

calendar day of the BM or the calendar day before the BM. The weekly SBM frequency is calculated as 7 x (total number of SBMs reported during the specific period)/(number of days during the specific period).[5] See Section 15.5 for eDiary questions related to number of SBMs.

The abdominal pain score was based on a 5-point scale ranging from 0 to 4, with higher scores indicating more pain. The abdominal pain combination score for a 24-hour period was defined as follows. If both morning and evening eDiary entries were completed, the daily abdominal pain combination score is equal to the average of both scores. If only the morning or evening eDiary entry was completed, the daily abdominal pain combination score is equal to the reported score. The subject's abdominal pain combination score for a specific period was derived as the mean of the non-missing abdominal pain combination scores within the corresponding diaries during the specific period. Unless otherwise indicated, the abdominal pain score will refer to the abdominal pain combination score. See Section 15.5 for eDiary questions related to the abdominal pain score.

Secondary Endpoints

The secondary efficacy endpoints include:

1. Change from baseline (CFB) in 12-week SBM frequency rate (SBMs/week) during the DBTP. See above section for the definition of the SBM frequency rate.
2. CFB in 12-week abdominal pain score during the DBTP. See above section for the definition of the abdominal pain score.
3. CFB in 12-week stool consistency during the DBTP. Stool consistency was measured twice daily in the eDiary using the 7-point ordinal pediatric Bristol Stool Form Scale (p-BSFS) for each BM. The stool consistency will be calculated as the mean of all non-missing, SBM-associated p-BSFS scores during that specific time period.[6] See Section 19.8 for the definition of the p-BSFS score.
4. 6/12 weeks SBM + 2 responder. A 6/12 weeks SBM + 2 responder is a subject who meets the weekly SBM + 2 responder criteria for at least 6 out of the 12 weeks of the DBTP. A weekly SBM + 2 responder is a subject who had an increase of at least 2 in the SBM weekly rate from baseline during that study intervention week.
5. 6/12 weeks abdominal pain responder. A 6/12 weeks abdominal pain responder is a subject who meets the weekly abdominal pain responder criteria for at least 6 out of the 12 weeks of the DBTP. A weekly abdominal pain responder is a subject who had a decrease of at least 30% in the mean abdominal pain score from baseline during

[5] When calculating the number of days within a specific period, (i) the randomization day with an evening diary will be considered a half day for the DBTP, (ii) the randomization day with morning and/or clinic diary will be considered a half day for the Preintervention Period, (iii) the day after last dose will be considered a half day for the DBTP, and (iv) Week 12 spans Day 78 to one day after the last dose.

[6] If the subject had no SBM during the baseline period, the stool consistency (p-BSFS score) during the baseline period will be missing and the participant will be excluded from the change from baseline analysis for this secondary endpoint. For subjects who reported no SBMs during a study period, the stool consistency assessments would be considered missing for that study period in the analyses.

that study intervention week.

Exploratory Endpoints:

Key exploratory endpoints included :

1. CFB in 12-week straining during the study intervention period
2. CFB in 12-week abdominal bloating during the study intervention period
3. CFB in 12-week abdominal pain score (daytime symptoms) during the study intervention period
4. CFB in 12-week abdominal pain score (nighttime symptoms) during the study intervention period
5. Proportion of subjects who no longer fulfill Rome III criteria for IBS-C at the end of the DBTP.
6. 9/12 weeks APS + 2 responder

See Section 15.5 for eDiary questions related to straining and abdominal bloating.

Statistical Analysis Plan

Analysis Populations

The Randomized Population consists of all subjects who underwent the screening visit, received a participant identification number, and were randomized to a study intervention group. The Safety Population and original Modified Intent-to-Treat (mITT) Population consist of all subjects in the Randomized Population who received at least 1 dose of double-blind study intervention. For efficacy analyses, subjects are summarized according to the randomized study intervention and for safety analyses, subjects are summarized according to their actual study intervention.

Significant non-compliance was identified at an investigational site (Site ID 10049) that had enrolled 3 subjects. Additionally, an issue was discovered in July 2021 by the eDiary vendor where the inclusion criterion related to abdominal pain was not displayed in the eligibility report. Because of this, 8 subjects (including the 3 subjects at Site 10049) were incorrectly randomized without meeting the abdominal pain criterion. As a result of these findings and as of Amendment 1 of the SAP, these 8 subjects were excluded from the mITT Population and efficacy data from these participants were excluded from the statistical analyses.

Estimand for the Primary Endpoint

The target population is subjects with IBS-C, ages 7 – 17 year olds who meet the inclusion and exclusion criteria. The primary variable of interest is 6/12 weeks APS + 2 response defined above and the population summary is the proportion of subjects meeting the 6/12 weeks APS + 2 responder criteria. The following intercurrent events were considered for the primary efficacy analyses.

1. The BMs for the subjects who took a laxative, enema, or suppository on the calendar day of the BM or the calendar day before the BM are not be considered as SBMs for the analysis.
2. Subjects who prematurely discontinue treatment have their eDiary data included up to the morning diary following the last dose date. Subjects are considered non-responders for the weeks following treatment discontinuation.
3. eDiary responses following the onset of dose de-escalation are not included. The subjects with dose de-escalation are considered non-responders for the subsequent study intervention weeks.

Primary Analysis for the Primary Endpoint

The primary statistical analysis was based on a Bayesian method that borrows information from adult IBS-C populations enrolled into the phase 2b study MCP-103-202 and phase 3 registration studies LIN-MD-31 and MCP-103-302 for linaclotide. The Applicant's Bayesian approach appears reasonable based on the similarities of the IBS-C disorder in adult and pediatric subjects, and the expected similarity in response to linaclotide treatment. The details of the Bayesian analysis are discussed below.

The primary objective was to show that the 2.5^{th} percentile of the posterior distribution of the response rate, Θ, in pediatric subjects exceeds 0.18. A meta-analysis of the three late-stage studies estimated the response rate (95% CI) in adult placebo subjects to be 0.16 (0.13 – 0.18), and the upper-bound of that CI was chosen as the benchmark for this study.

The prior distribution of Θ was based on a meta-analysis of adult subjects receiving 266 mcg to 300 mcg of linaclotide in the three late-stage studies. Across these three studies, there were 340 responders and 550 non-responders. The prior distribution was then defined by $\Theta \sim \text{Beta}(\alpha = w \times 340, \beta = w \times 550)$, where w is a prespecified weighting factor that downweights the importance of the adult subjects relative to the pediatric subjects. The prespecified range for w was 0.0067 to 0.02, which corresponds to the adult data providing the informational equivalent of approximately 6 to 20 pediatric subjects. The likelihood function for the number of responders, X, among the number treated, N, in each pediatric arm was defined by $X \sim \text{Binominal}(\Theta,N)$. The resulting posterior distribution is $\Theta \sim \text{Beta}(\alpha = X + w \times 340, \beta = N - X + w \times 550)$.

Missing Data Handling for the Primary Endpoint

BM frequency is considered as zero for a diary period (morning or evening diary) that is missing that data. Rescue Medication (RM) is assumed to have not been used during a diary period that is missing data, with the exception that missing RM is considered "used" if the other available assessment during that day is "yes". Missing abdominal pain scores are not imputed.

For the primary analysis, a subject had to have at least 4 completed diary days per study

intervention week to be considered non-missing for that week. Otherwise, the subject was considered missing and imputed as a non-responder for that week. A completed diary day is a day in which both morning and evening eDiary entries are filled out by the subject.

The approaches for handling missing data are consistent with the approaches used in the phase 3 adult trials; however, in the adult phase 3 trials, PRO data were collected once per day instead of twice per day.

Supplemental/Sensitivity Analyses of the Primary Endpoint

A significant issue was identified with the primary statistical analysis for the primary endpoint after the study had been completed. There was a large amount of missing data due to eDiary non-compliance in the study and the use of non-responder imputation (NRI) likely resulted in a conservative estimate of the pediatric response rate. The rates of missing data due to diary non-compliance were substantially higher for the primary endpoint in this pediatric study, as compared to the three adult studies. As the primary analysis was defined as a comparison between the rates observed in the pediatric and adult studies, the use of NRI complicates the interpretation of the results. The rates observed in the pediatric study would be more conservative because of the higher rates of missing data and the estimated differences in response rates may not reflect true differences in the efficacy of the drug. Because of this, the primary endpoint analysis is not considered to be the most appropriate approach for evaluating efficacy. This conclusion is predicated on the Agency's belief that missing data may not indicate that a subject had poor efficacy outcomes (e.g., reasons for missingness may be unrelated to symptoms), particularly if the subject remained enrolled in the study and using the study drug. A noteworthy issue is that differences in the methods for collecting diary entries may have contributed to the differential rates of diary compliance and missing data. Pediatric studies used twice-daily eDiaries and an evaluable day required both entries to be completed, whereas adult studies used a once-daily diary entry conducted by an Interactive Voice Response System (i.e., phone call) and an evaluable day only required that one entry to be completed. A total of 4 evaluable days were needed in order for a week to be considered non-missing. The use of twice-daily diaries adds additional burden to participants that could result in higher rates of missing data. Even if a similar percentage of PRO data were missing in the pediatric and adult trials, the pediatric trial would likely still have more missing data due to the requirement of needing both a morning and evening diary entry for at least 4 days in order to be considered non-missing.

Given the above significant concerns with the use of non-responder imputation, three sensitivity analyses were specified and performed after the completion of the study to evaluate the impact of methods for defining and handling missing data. The three analyses were similar to the primary analysis, but the analyses either changed the method for handling missing data (i.e., non-responder imputation) or the requirement for data to be considered non-missing (i.e., ≥ 4 days with complete eDiary entries).

1. MI: The FDA proposed an analysis[7] that used multiple imputation (MI) assuming data was missing at random (MAR). Weekly values for weeks with fewer than 4 completed diary days (i.e., completed both morning and evening diaries) were still set to missing, but missing weekly values were now handled by MI instead of NRI. The Applicant had prespecified and performed a similar sensitivity analysis that used MI. However, the FDA slightly modified the Applicant's approach[8] to enhance the validity of the missing data imputation process and strengthen the robustness of the statistical inferences.
2. ≥ 4 evening entries: The Applicant proposed a sensitivity analysis that used non-responder imputation as implemented in the primary analysis, but only required subjects to have at least 4 evening eDiary entries in a week to be considered non-missing.
3. ≥ 8 entries: This analysis is similar to the ≥ 4 evening entries above. However, subjects were required to have at least 8 eDiary entries (morning or evening) in a week to be considered non-missing.

As will be discussed in the results section, using either alternative criterion for defining missing weekly values (i.e., ≥ 4 evening entries, ≥ 8 total entries) reduced the differences in the percentage of evaluable weeks between the adult and pediatric studies.

Finally, these sensitivity analyses attempt to address potential biases caused by using NRI to handle missing weekly values. The analyses do not address potential biases caused by imputing missing morning and evening SBM counts as 0 during evaluable weeks. However, for CFB endpoints, the biases in the baseline period and DBTP may partially offset each other.

Analysis of Secondary Endpoints

[7] The MI procedure used the fully conditional specification (FCS) method with predictive mean matching and models that included treatment, age group, baseline values, and all prior weekly values for both sets of imputed variables (i.e., weekly SBM frequency, weekly abdominal pain scores). Additionally, the meta-analyses in adult subjects used to estimate the benchmark for comparison (e.g., 0.18) and the parameters for the prior distribution in the primary analysis now also handled missing data using MI. For frequentist inference, results across multiply imputed datasets were combined according to Rubin's rules and for Bayesian inference, the overall posterior distribution was a mixture of the beta distributions from each imputed dataset. For this analysis, the intercurrent event (ICE) of dose de-escalation was handled using a treatment policy strategy.

[8] The Applicant's MI procedure used a two step approach. In the first step, Markov-Chain Monte Carlo (MCMC) was used to impute to a monotone missing pattern. Imputation was performed separately for weekly SBM frequency and weekly abdominal pain score, with models including all weekly values. In the second step, a regression model was used to impute the remaining values. Again, imputation was performed separately for weekly SBM frequency and weekly abdominal pain score. Regression models included age group, baseline value, and all prior weekly values and were based on subjects in the linaclotide 145 mcg group. Moreover, the Applicant's approach handled missing data in the meta-analyses in adult studies using non-responder imputation. FDA requested that the weekly SBM frequency and weekly abdominal pain score be imputed jointly to avoid assuming those outcomes are conditionally independent. FDA also requested missing data in the adult studies use MI to determine an appropriate benchmark.

The SAP specified that the secondary endpoints would only be summarized descriptively and did not prespecify any statistical tests or comparisons with the adult population. Methods for handling intercurrent events are similar to those used for the primary endpoint. Post-hoc, the FDA proposed comparing the results for the continuous SBM, abdominal pain, and stool consistency endpoints (i.e., CFB in 12-week SBM frequency rate, CFB in 12-week abdominal pain, CFB in 12-week stool consistency) with the results for adult placebo subjects. The means in LIN-MD-64 were compared with the upper-bounds of the 95% CI from meta-analyses of adult placebo subjects using a one-sided t test.

Protocol and SAP Amendments

The Canada-specific Protocol Amendment CA-3 (dated May 2021) was the final version of protocol. The SAP amendment #2 (dated February 2024) was the last version of the SAP. Changes in the protocol and SAP amendment did not generally affect the interpretation of the study results. However, as discussed above, as of Amendment 1 of the SAP (dated January 2022) and before the unblinding of any data, 8 subjects who did not meet the abdominal pain criterion at baseline were excluded from the mITT Population.

8.1.2. Study Results (LIN-MD-64)

Compliance with Good Clinical Practices

The Applicant asserts that this study was conducted in compliance with Good Clinical Practice. The review team did not identify any concerns regarding compliance with Good Clinical Practices.

Financial Disclosure

The Applicant submitted adequate financial disclosures regarding the clinical investigators for studies LIN-MD-63, LIN-MD-64, and LIN-MD-66 (see Appendix 15.2). The review team did not identify any concerns from any of the financial disclosures.

Patient Disposition

Subject disposition for the Randomized Population is summarized in Table 6. Of the 108 subjects in the Randomized Population, 98 subjects (90.7%) completed the DBTP. The most common reason for study discontinuation during the DBTP was withdrawal by subject (6 subjects, 5.6%). No subject who withdrew from the study experienced a treatment-related adverse event. A slightly larger percentage of subjects in the linaclotide 290 mcg group (13.2%) discontinued the study, as compared to subjects in the linaclotide 145 mcg group (5.5%). However, given the small sample size of each treatment group, this difference in discontinuation rates could be attributable to chance. All 8 subjects in the Randomized Population who were omitted from the mITT population completed the DBTP without dose de-escalation.

Table 6: Disposition of Subjects (Randomized Population, LIN-MD-64)

	Linaclotide 145 mcg N = 55	Linaclotide 290 mcg N = 53	Total N=108
Number of subjects completed DBTP	52 (94.5)	46 (86.8)	98 (90.7)
Number of subjects completed DBTP without dose de-escalation[a]	50 (90.9)	45 (84.9)	95 (88.0)
Number of subjects discontinued from DBTP	3 (5.5)	7 (13.2)	10 (9.3)
Lack of efficacy	0	1 (1.9)	1 (<1)
Lost to follow-up	1 (1.8)	0	1 (<1)
Physician decision	1 (1.8)	0	1 (<1)
Withdrawal by subject	1 (1.8)	5 (9.4)	6 (5.6)
Other[b]	0	1 (1.9)	1 (<1)
Related to COVID-19	1 (1.8)	0	1 (<1)

Source: Clinical Study Report Table 3 (page 29). Verified by reviewer using ADSL.xpt.
[a] All three subjects with a dose de-escalation completed the DBTP. For IBS-C participants experiencing an intolerable AE that may be related to the use of linaclotide, the protocol allowed dose reductions from 145 mcg to 72 mcg linaclotide and from 290 mcg to 145 mcg in a double-blinded fashion during the course of the study at the investigator's discretion.
[b] Reason listed as possible pregnancy
Abbreviations: N=number of subjects in population treatment group

Protocol Violations/Deviations

Protocol deviations are summarized in Table 7. As noted in Section 8.1.1, 8 subjects did not meet the inclusion criteria and were excluded from the mITT population. Additionally, two subjects received a prohibited concomitant medication.

Table 7: Protocol Deviations (Randomized Population, LIN-MD-64)

	Linaclotide 145 mcg N = 55	Linaclotide 290 mcg N = 53	Total N=108
Overall	2 (3.6)	8 (15.1)	10 (9.3)
Inclusion criteria not met	2 (3.6)	6 (11.3)	8 (7.4)
Prohibited concomitant medication taken	0	2 (3.8)	2 (1.9)

Source: Clinical Study Report Table 4 (page 30). Verified by reviewer using ADSL.xpt, DV.xpt.
Abbreviations: N=number of subjects in population treatment group

Demographic and Baseline Characteristics

Baseline demographic characteristics are summarized in Table 8. The majority of subjects were female (61.0%), White (70.0%), and between 12 and 17 years old (60.0%). All subjects in the mITT population were at sites within the United States.

Table 8: Demographic Characteristics (mITT population, LIN-MD-64)

	Linaclotide 145 mcg N=53	Linaclotide 290 mcg N=47	Total N=100
Age, years			
Mean (SD)	12.7 (3.2)	12.6 (2.8)	12.6 (3.0)
Median	13.0	13.0	13.0
IQR	10.0, 16.0	11.0, 15.0	10.0, 15.0
Min, Max	7, 17	7, 17	7, 17
Age Group, n (%)			
7-11 Years	22 (41.5)	18 (38.3)	40 (40.0)
12-17 Years	31 (58.5)	29 (61.7)	60 (60.0)
Sex, n (%)			
Female	30 (56.6)	31 (66.0)	61 (61.0)
Male	23 (43.4)	16 (34.0)	39 (39.0)
Race, n (%)			
Asian	2 (3.8)	1 (2.1)	3 (3.0)
Black or African American	13 (24.5)	11 (23.4)	24 (24.0)
White	38 (71.7)	32 (68.1)	70 (70.0)
Multiple	0	1 (2.1)	1 (1.0)
Missing	0	2 (4.3)	2 (2.0)
Ethnicity, n (%)			
Hispanic or Latino	18 (34.0)	14 (29.8)	32 (32.0)
Not Hispanic or Latino	35 (66.0)	33 (70.2)	68 (68.0)
Weight, kg			
Mean (SD)	53.3 (17.1)	53.8 (16.2)	53.5 (16.6)
Median	54.4	52.3	53.4
IQR	41.7, 63.3	44.5, 63.1	43.5, 63.2
Min, Max	22, 110	21, 88	21, 110

Source: Clinical Study Report Table 6 (page 32). Verified by reviewer using ADSL.xpt.
Abbreviations: IQR = interquartile range; max=maximum; min=minimum; N=number of subjects in population treatment group; n=number of subjects in subgroups; SBM = spontaneous bowel movement; SD=standard deviation.

Baseline Disease Characteristics

Baseline disease characteristics are summarized in Table 9. The average number of SBM per week was 1.3, the average abdominal pain score was 1.9, the average stool consistency score was 2.6, and the average abdominal bloating score was 1.7.

Table 9: Baseline Disease Characteristics (mITT population, LIN-MD-64)

	Linaclotide 145 mcg N=53	Linaclotide 290 mcg N=47	Total N=100
SBM weekly frequency			

Mean (SD)	1.3 (0.8)	1.3 (0.9)	1.3 (0.9)
Median	1.4	1.4	1.4
IQR	0.5, 1.9	0.5, 1.9	0.5, 1.9
Min, Max	0, 3	0, 3	0, 3
Abdominal pain			
Mean (SD)	1.9 (0.8)	1.9 (0.8)	1.9 (0.8)
Median	1.8	1.6	1.7
IQR	1.3, 2.6	1.2, 2.6	1.3, 2.6
Min, Max	1, 4	1, 4	1, 4
Stool consistency			
Mean (SD)	2.5 (0.9)	2.8 (1.1)	2.6 (1.0)
Median	2.3	2.6	2.3
IQR	2.0, 3.0	2.0, 3.2	2.0, 3.0
Min, Max	1, 6	1, 5	1, 6
Missing	6	8	14
Abdominal bloating[a]			
Mean (SD)	1.8 (1.1)	1.6 (1.0)	1.7 (1.0)
Median	1.5	1.4	1.5
IQR	0.9, 2.7	0.7, 2.6	0.8, 2.7
Min, Max	0, 4	0, 3.5	0, 4

Source: Clinical Study Report Table 14.1-4.2 (page 80). Verified by reviewer using ADEFF.xpt.
[a] Based on morning and evening assessments.
Abbreviations: IQR = interquartile range; max=maximum; min=minimum; N=number of subjects in population treatment group; n=number of subjects in subgroups; SBM = spontaneous bowel movement; SD=standard deviation.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Dosing compliance was generally high. The mean dosing compliance was 98.5% for the linaclotide 145 mcg group and 98.6% for the linaclotide 290 mcg group during the DBTP.

Rescue medication was assessed daily using the eDiary[9] and is summarized in Table 10. Rescue mediation use was lower in the DBTP, as compared to the baseline period. In the linaclotide 145 mcg group and 290 mcg group, the percentage of weeks with rescue medication decreased from 50.9% to 20.8% and from 52.5% to 14.9%, respectively. During the 12-week DBTP, the percentage of subjects requiring rescue medication use also decreased from 28.3% to 13.2% and from 25.5% to 12.8% for the linaclotide 145 mcg and 290 mcg groups, respectively (see Table 11).

[9] Based on questions "From bedtime last night until now, did you take any medicine to help you poop, other than the study medicine?" "From when you got up this morning until now, did you take any medicine to help you poop, other than the study medicine?

Table 10: Rescue Medication Use (mITT population, LIN-MD-64)

	Linaclotide 145 mcg N = 53	Linaclotide 290 mcg N = 47
Percentage[a] of weeks with rescue medication usage, mean (SD)		
Baseline Period	50.9 (45.1)	52.5 (45.4)
Double-Blind-Treatment-Period	20.8 (28.0)	14.9 (21.9)
Percentage[a] of days with rescue medication usage, mean (SD)		
Baseline Period	9.8 (11.6)	10.3 (10.5)
Double-Blind-Treatment-Period	4.8 (7.9)	4.1 (8.2)

Source: Created by reviewer using ADEFF.xpt.
[a] Percentage is based on days prior to treatment discontinuation. Missing eDiary entries are imputed as no rescue medication usage.
Abbreviations: SD = standard deviation

Table 11. Rescue Medication Use During the Treatment Period (mITT population, LIN-MD-64)

	Subjects using rescue medication (%)	
Treatment period week	**Linaclotide 145 mcg N = 53**	**Linaclotide 290 mcg N = 47**
1	15 (28.3%)	12 (25.5%)
2	16 (30.2%)	11 (23.4%)
3	13 (24.5%)	8 (17%)
4	10 (18.9%)	9 (19.1%)
5	8 (15.1%)	3 (6.4%)
6	9 (17%)	5 (10.6%)
7	12 (22.6%)	5 (10.6%)
8	9 (17%)	4 (8.5%)
9	11 (20.8%)	5 (10.6%)
10	9 (17%)	7 (14.9%)
11	11 (20.8%)	5 (10.6%)
12	7 (13.2%)	6 (12.8%)

Source: Reviewer generated

Electronic Diary Compliance

Electronic diary (eDiary) compliance was relatively low in LIN-MD-64, especially in comparison with the adult linaclotide studies. As discussed in the Section 8.1.1, this low compliance rate and the use of non-responder imputation significantly complicated the validity and interpretability of the results from the primary analysis of the primary endpoint.

Electronic diary compliance is summarized in Table 12 and the reported statistics, unless otherwise stated, are based only on the days/weeks in the DBTP prior to study discontinuation

or treatment de-escalation. The mean percentage of days with complete (i.e., morning and evening) eDiary entries was only 64% and the mean percentage of evaluable weeks (i.e., weeks with ≥ 4 days of complete eDiary entries) was only 71%. Moreover, a substantive proportion (24%) of the mITT population completed 12 weeks of the DBPT without having 6 evaluable weeks for assessing the primary endpoint. Finally, the mean percentage of complete days was higher in the Preintervention Period (84%), as compared to the DBTP (64%), as expected.

The mean percentage of evaluable weeks (i.e., weeks with ≥ 4 days with a complete eDiary entries) in LIN-MD-64 was notably lower than the mean percentage of evaluable weeks (i.e., weeks with ≥ 4 days with a completed Interactive Voice Response System [IVRS] diary response) in the three adult trials. For these adult studies, the Applicant stated that the mean percentage of evaluable weeks was 88.7% (MCP-103-202, N = 85), 92.4% (LIN-MD-31, N = 395), and 89.9% (MCP-103-302, N = 403). However, if we modified the criterion for evaluable weeks in LIN-MD-64 to be ≥ 4 evening entries, the mean percentage of evaluable weeks in LIN-MD-64 (87.7%) was roughly similar to the percentages observed in the adult studies. Moreover, this ≥ 4 evening entries criterion for pediatric subjects may be a more equitable requirement to the ≥ 4 days with a completed IVRS criterion used for adult studies; each criterion required completing 4 of 7 entries.

Table 12: Electronic Diary Compliance (mITT Population, LIN-MD-64)

	Linaclotide 145 mcg N=53	**Linaclotide 290 mcg N=47**	**Total N=100**
Double Blind Treatment Period			
Percentage of complete days[a], %			
Mean (SD)	64.13 (21.54)	63.00 (22.54)	63.60 (21.91)
Median	69.32	70.24	69.78
IQR	47.06, 81.46	51.19, 79.31	48.07, 80.06
Min, Max	15.5, 98.8	16.7, 97.1	15.5, 98.8
Percentage of weeks[a] with ≥ 4 complete days, %			
Mean (SD)	71.95 (29.07)	70.29 (29.49)	71.17 (29.13)
Median	83.33	83.33	83.33
IQR	50.00, 100.00	50.00, 100.00	50.00, 100.00
Min, Max	8.3, 100.0	0.0, 100.0	0.0, 100.0
Number of weeks[a] with ≥ 4 complete days, n[b] (%)			
0-5	13 (24.53)	11 (23.40)	24 (24.00)
6-7	5 (9.43)	6 (12.77)	11 (11.00)
8-9	6 (11.32)	3 (6.38)	9 (9.00)
10-11	11 (20.75)	12 (25.53)	23 (23.00)
12	16 (30.19)	11 (23.40)	27 (27.00)
Early discontinuation[c]	2 (3.77)	4 (8.51)	6 (6.00)
Percentage of weeks[a] with ≥ 4 evening entries, %			
Mean (SD)	89.04 (17.77)	86.14 (18.23)	87.68 (17.95)

Median	100.00	91.67	100.00
IQR	83.33, 100.00	75.00, 100.00	80.00, 100.00
Min, Max	25.0, 100.0	25.0, 100.0	25.0, 100.0
Percentage of weeks[a] with ≥ 8 entries, %			
Mean (SD)	86.84 (21.68)	81.18 (25.37)	84.18 (23.54)
Median	100.00	91.67	100.00
IQR	83.33, 100.00	58.33, 100.00	75.00, 100.00
Min, Max	16.7, 100.0	16.7, 100.0	16.7, 100.0
Preintervention Period			
Percentage of complete days			
Mean (SD)	86.47 (9.07)	86.79 (8.73)	86.62 (8.87)
Median	86.21	86.21	86.21
IQR	79.31, 93.10	79.31, 93.10	79.31, 93.10
Min, Max	72.4, 100.0	72.4, 100.0	72.4, 100.0

Source: Based on Clinical Study Report Table 14.2-5 (page 258) and Table 2 from an Information Request dated June 16, 2025. Created by reviewer using ADSL.xpt, ADEFF.xpt, ADDDIARY.xpt.

[a] Excludes days/weeks after study discontinuation or dose de-escalation

[b] n is the number of subjects who completed the DBTP and had the specified number of weeks with ≥ 4 complete days of eDiary entries. Subjects who prematurely discontinued the study prior to day 84 are categorized separately.

[c] Four subjects who prematurely discontinued the study after Day 84 are not included in this category.

Abbreviations: IQR = interquartile range; max=maximum; min=minimum; N=number of subjects in population treatment group; n=number of subjects in subgroups; SD=standard deviation.

Efficacy Results – Primary Endpoint

Primary Analysis

The results from the primary analysis of the primary endpoint are summarized in Table 13. The proportion of pediatric subjects achieving a response on the primary endpoint was similar in both linaclotide treatment groups, 22.6% in the linaclotide 145 mcg treatment group and 23.4% in the linaclotide 290 mcg treatment group. The proportion of responders in both treatment groups was numerically higher than the prespecified threshold of 18%. However, the study failed to achieve its primary objectives. The 2.5th percentile of the posterior distributions of the response rate for both treatment groups was below the benchmark of 18% over the prespecified range of values for the parameter w.

Table 13: Primary Efficacy Analysis, Proportion of Subjects with 6/12 Weeks APS (Abdominal Pain and SBM) + 2 Responder (mITT Population, LIN-MD-64)

	Linaclotide 145 mcg N = 53	**Linaclotide 290 mcg N = 47**
Responder Rate, n/N (%)	12/53 (22.6%)	11/47 (23.4%)
95% CI	12.3%, 36.2%	12.3%, 38.0%

	2.5th Percentile[a]	Probability > 18%[a]	2.5th Percentile[a]	Probability > 18%[a]
w=0.0067	14.3	87.2%	14.5	88.9%
w=0.008	14.6	88.5%	14.8	90.1%
w=0.01	15.0	90.2%	15.3	91.7%
w=0.012	15.5	91.7%	15.7	93.0%
w=0.014	15.9	93.0%	16.2	94.1%
w=0.016	16.3	94.1%	16.6	95.1%
w=0.018	16.6	95.0%	17.0	95.9%
w=0.02	17.0	95.8%	17.4	96.6%

Source: Based on Clinical Study Report Table 7 (page 36). Verified by reviewer using ADEFF.xpt.

[a] Lower 2.5th percentile and probability are calculated from the posterior Beta(X + w*a, N - X + w*b) distribution, where a = 340 and b = 550.

Abbreviations: N=number of subjects in population treatment group; n=number of responders; SBM = spontaneous bowel movement

Sensitivity Analyses

As discussed in the above section defining the sensitivity analyses, the large amount of missing data due to eDiary non-compliance in this study and the use of NRI raised concerns about the reliability of the results from the primary statistical analysis. Therefore, three post-hoc sensitivity analyses were performed that modified either the criteria required for data to be non-missing (e.g., ≥ 4 days with complete eDiary entries) or the method for handling missing data (i.e., NRI). The results from these sensitivity analyses are presented in Table 16 and Table 17. Importantly, the metric for success (i.e., 2.5th percentile of the posterior distribution exceeding a benchmark based on adult placebo subjects) was met in each of these sensitivity analyses.

The first sensitivity analysis used MI instead of NRI. In this analysis, the estimated response rates (frequentist 95% CI) in the linaclotide 145 mcg and linaclotide 290 mcg groups were 32.5% (19.1, 45.9) and 35.5% (21.1, 50.0), respectively (Table 14). As expected, these rates were notably higher than the rates estimated in the primary analysis that used NRI to handle missing data. Moreover, the 2.5th percentile of the posterior distributions of the response rates based on these analyses using MI exceeded the benchmark of 19.8% (i.e., upper bound of the 95% CI from the meta-analysis in adult placebo subjects using MI) for both treatment groups when using the smallest evaluated value of w in the Bayesian analysis (Table 15).

Table 14: Frequentist Results from Sensitivity Analyses, Proportion of Subjects with 6/12 Weeks APS (Abdominal Pain and SBM) + 2 Responder (mITT Population, LIN-MD-64)

		Adult Placebo Subjects N = 883		**Adult Linaclotide Subjects N = 890**		**Linaclotide 145 mcg N = 53**		**Linaclotide 290 mcg N = 47**
	n[a]	% (95% CI[b])	n[a]	% (95% CI[b])	n[a]	% (95% CI[c])	n[a]	% [a] (95% CI[c])

Primary	139	15.7% (13.1, 17.9)	340	38.2% (34.9, 41.3)	12	22.6% (12.3, 36.2)	11	23.4% (12.3, 38.0)
MI	152	17.2% (14.8, 19.8)	360	40.5% (37.2, 43.6)	17	32.5% (19.1, 45.9)	17	35.5% (21.1, 50.0)
≥ 4 Evening[d]	139	15.7% (13.1, 17.9)	340	38.2% (34.9, 41.3)	16	30.2% (18.3, 44.3)	15	31.9% (19.1, 47.1)
≥ 8 Total[d]	139	15.7% (13.1, 17.9)	340	38.2% (34.9, 41.3)	15	28.3% (16.8, 42.3)	14	29.8% (17.3, 44.9)

Source: Based on Clinical Study Report Table 14.2-1.8 (page 114) and Table 14.2-1.9 (page 115), and Table 1 from a response to Information Request dated July 29, 2025. Verified by reviewer using ADEFF.xpt, ADPRD.xpt, ADSL.xpt.

[a] For methods using MI, the value of n is rounded to the nearest integer.

[b] Frequentist 95% CI based on meta-analysis for adult subjects.

[c] Frequentist 95% CI based on either an exact CI or, when using MI, based on the assumption of normality and Rubin's rules.

[d] For the meta-analyses of adult placebo subjects, weekly values were missing if subjects had < 4 IVRS diary entries/week, identical to the approach used for the primary analysis.

Abbreviations: CI = confidence interval; IVRS = Interactive Voice Response System; MI = multiple imputation; N=number of subjects in population treatment group; n=number of responders; SBM = spontaneous bowel movement

Table 15: Bayesian Results with w = 0.0067 from Sensitivity Analyses, Proportion of Subjects with 6/12 Weeks APS (Abdominal Pain and SBM) + 2 Responder (mITT Population, LIN-MD-64)

			Linaclotide 145 mcg N = 53		**Linaclotide 290 mcg N = 47**
	Adult Benchmark (B)	2.5th Percentile[a]	Probability > B[a]	2.5th Percentile[a]	Probability > B[a]
Primary	18.0%	14.3	87.2%	14.5	88.9%
MI	19.8%	21.4	98.9%	23.2	99.6%
≥ 4 Evening	18.0%	20.0	99.1%	20.8	99.4%
≥ 8 Total	18.0%	18.5	98.1%	19.2	98.6%

Source: Based on Clinical Study Report Table 14.2-1.8 (page 114) and Table 14.2-1.9 (page 115), and Table 9-9.3.1a from a response to Information Request dated July 29, 2025. Verified or generated by reviewer using ADEFF.xpt, ADPRD.xpt, ADSL.xpt., ADEFFMI3.xpt

[a] Lower 2.5th percentile and probability are calculated from the posterior Beta(X + w*a, N - X + w*b) distribution, where a and b are estimated from adult studies and w = 0.0067.

Abbreviations: MI = multiple imputation; N=number of subjects in population treatment group; n=number of responders; SBM = spontaneous bowel movement

The other two sensitivity analyses required either ≥ 4 evening or ≥ 8 total eDiary entries per week for the weekly values to be considered non-missing, but continued to use non-responder imputation. The response rates in these analyses also increased substantively, as compared to the primary analysis. In the analysis only requiring ≥ 4 evening entries, the estimated response rates (frequentisit 95% CI) in the linaclotide 145 mcg and linaclotide 290 mcg groups were 30.2% (18.3, 44.3) and 31.9% (19.1, 47.1) respectively (Table 14). The 2.5th percentile of the posterior distributions exceeded the benchmark of 18% for both treatment groups and for the smallest evaluated value of w (Table 15). Similar results were observed for the analysis requiring ≥ 8 total eDiary entries.

The results included in labeling will be based on the sensitivity analysis that used non-responder imputation and required ≥ 4 evening eDiary entries for weekly values to be considered non-missing. The use of non-responder imputation agrees with the prespecified

method for handling missing data in the adult studies and, as discussed above, the requirement of ≥ 4 evening eDiaries is better aligned with the requirement of ≥ 4 IVRS diary entries in the comparative adult studies. Moreover, on weeks with ≥ 4 evening eDiaries entries, the average number of morning eDiary entries (5.38 entries/week) is only slightly less than the average number of evening eDiary entries (5.94 entries/week) so the results still largely capture both morning and evening responses (Table 16). Finally, reducing the required number of eDiaries and imputing missing SBM values with 0 would be conservative with respect to the number of SBMs per week for subjects with a large amount of missing morning diaries. Similarly, as abdominal pain scores tended to be slightly higher in the evening (Table 17) and the daily abdominal pain score is computed as the average of the two diaries (when both are non-missing), allowing for more missing morning eDiaries when calculating an observed weekly abdominal pain score likely provides a slightly conservative estimate of the weekly abdominal pain score. Therefore, this method would be expected to provide a conservative estimate of the response rate for pediatric subjects.

Table 16: Electronic Diary Compliance by Time of Day in Weeks with ≥ 4 Evening Entries (mITT Population, LIN-MD-64)

	Linaclotide 145 ug N=53	Linaclotide 290 ug N=47	Total N=100
Number of evening entries[a]			
Mean (SD)	5.94 (0.61)	5.93 (0.60)	5.94 (0.60)
Median	6.08	5.92	6.00
IQR	5.44, 6.42	5.36, 6.42	5.43, 6.42
Min, Max	5, 7	5, 7	5, 7
Number of morning entries[a]			
Mean (SD)	5.40 (1.14)	5.35 (1.36)	5.38 (1.24)
Median	5.75	5.75	5.75
IQR	4.75, 6.08	4.67, 6.25	4.70, 6.17
Min, Max	1, 7	2, 7	1, 7
Proportion of weeks ≥ 4 morning entries [a]			
Mean (SD)	0.88 (0.19)	0.87 (0.21)	0.87 (0.20)
Median	1.00	1.00	1.00
IQR	0.83, 1.00	0.80, 1.00	0.82, 1.00
Min, Max	0, 1	0, 1	0, 1

Source: Generated by reviewer using ADDIARY.xpt, ADSL.xpt

[a] Based on weeks with ≥ 4 evening eDiaries for abdominal pain and bowel moment questions.

Abbreviations: IQR = interquartile range; max=maximum; min=minimum; N=number of subjects in population treatment group; n=number of subjects in subgroups; SD=standard deviation.

Table 17: Abdominal Pain Scores by Time of Day (mITT Population, LIN-MD-64)

	Linaclotide 145 ug N=53	Linaclotide 290 ug N=47	Total N=100
12-week abdominal pain, morning			
Mean (SD)	1.05 (1.00)	0.96 (0.92)	1.01 (0.96)
Median	0.71	0.67	0.69
IQR	0.39, 1.62	0.29, 1.36	0.34, 1.47
Min, Max	0, 4	0, 4	0, 4
12-week abdominal pain, evening			
Mean (SD)	1.18 (0.98)	1.20 (1.00)	1.19 (0.99)
Median	0.95	0.84	0.94
IQR	0.51, 1.79	0.48, 1.77	0.49, 1.78
Min, Max	0, 4	0, 4	0, 4

Source: Generated by reviewer using ADDIARY.xpt, ADSL.xpt
Abbreviations: IQR = interquartile range; max=maximum; min=minimum; N=number of subjects in population treatment group; n=number of subjects in subgroups; SD=standard deviation.

Subgroup Analyses

The response rates for the primary endpoint and corresponding 95% confidence intervals were estimated in subgroups defined by age, sex, race, and ethnicity (Table 18) based on the Applicant's prespecified primary analysis requiring ≥ 4 complete days for weekly values to be non-missing. The sample sizes within subgroups were relatively small and therefore response rates within subgroups have a high level of variability. However, response rates were generally similar across all subgroups within each treatment group.

Table 18: Subgroup Analyses, Proportion of Subjects with 6/12 Weeks APS (Abdominal Pain and SBM) + 2 Responder (mITT Population, LIN-MD-64)

		Linaclotide 145 mcg N = 53		Linaclotide 290 mcg N = 47
	n/N[a]	% (95% CI[b])	n/N[a]	% (95% CI[b])
Age Group				
7-11 years	4/22	18.2% (5.2,40.3)	2/18	11.1% (1.4,34.7)
12-17 years	8/31	25.8% (11.9,44.6)	9/29	31.0% (15.3,50.8)
Sex				
Female	7/30	23.3% (9.9,42.3)	8/31	25.8% (11.9,44.6)
Male	5/23	21.7% (7.5,43.7)	3/16	18.8% (4.0,45.6)
Race				
White	11/38	28.9% (15.4,45.9)	8/32	25.0% (11.5,43.4)
Black or African American	1/13	7.7% (0.2,36.0)	3/11	27.3% (6.0,61.0)
Asian	0/2	(0, 84.2%)	0/1	0% (0, 97.5%)

Multiple	--		0/1	0% (0, 97.5%)
Ethnicity				
Hispanic or Latino	5/18	27.8% (9.7,53.5)	3/14	21.4% (4.7,50.8)
Not Hispanic or Latino	7/35	20.0% (8.4,36.9)	8/33	24.2% (11.1,42.3)

Source: Based on Clinical Study Report Table 14.2-4.1 (pages 219-224). Generated or verified by reviewer using ADEFF.
[a] Weekly values for all weeks with < 4 complete days of eDiary entries were set to missing and all missing data was handled by NRI according to the prespecified primary analysis.
[b] CI were based on the exact binomial method.
Abbreviations: CI = confidence interval; N=number of subjects in population treatment group or subgroup; n=number of responders; NRI = non-responder imputation; SBM = spontaneous bowel movement

In the pediatric population aged 12 to 17 years, the 290 mcg dose demonstrated a numerically higher response rate compared with the 145 mcg dose. However, in the younger pediatric cohort aged 7 to 11 years, the opposite trend was observed, with no apparent advantage for the higher dose (see Table 20). These differences must be interpreted with caution due to limited subgroup sizes and the absence of formal statistical significance testing for this specific comparison.

Given these conflicting findings across age groups, the inherent uncertainties in the data due to small sample sizes, and the lack of clear additional clinical benefit for the 290 mcg dose, the review team recommends retaining the 145 mcg dose for both age groups in the proposed labeling. This approach aligns with the regulatory principle of approving the lowest effective dose that achieves the desired therapeutic outcome while minimizing potential risks associated with dose escalation.

Data Quality and Integrity

The data were of sufficient quality to permit a substantive review.

Efficacy Results – Secondary endpoints

The results for the secondary endpoints are summarized in Table 19. In the linaclotide 145 mcg and linaclotide 290 mcg groups, the CFB in 12-week stool frequency was 2.35 SBMs and 2.75 SBMs per week, respectively. Of note, CFB in 12-week stool frequency was also the primary endpoint of the randomized, placebo-controlled trial evaluating the efficacy of linaclotide 72 mcg in pediatric subjects 6 to 17 years of age with functional constipation (FC). While comparisons across these two trials should be interpreted with great caution due to differences in the populations (e.g., different indications), the mean CFB in the linaclotide groups were generally similar across the two trials, and larger than the CFB in the placebo group of the FC trial. Refer to Integrated Review dated June 12, 2023, for the results from the FC trial.

The response rates for the 6/12 Weeks SBM + 2 endpoint for the linaclotide 145 mcg and 290 mcg groups were 30.2% and 29.8%, respectively. In the linaclotide 145 mcg and 290 mcg groups, the CFB in 12-week abdominal pain score were each -0.84 points, and the response rates for the 6/12 Weeks APS endpoint were 49.1% and 42.6%, respectively. Finally, in the linaclotide 145 mcg and 290 mcg groups, the CFB in stool consistency was 0.98 and 1.36 points,

respectively.

Table 19: Secondary Efficacy Endpoint Analyses (mITT Population , LIN-MD-64)

	Linaclotide 145 mcg		Linaclotide 290 mcg	
	Baseline	**Change from baseline**	**Baseline**	**Change from baseline**
12-week SBM frequency				
Mean (SD)	1.34 (0.84)	2.35 (3.33)	1.26 (0.90)	2.75 (2.89)
Median	1.45	1.48	1.45	1.56
IQR	0.48, 1.93	0.47, 2.97	0.48, 1.93	0.80, 4.13
Min, Max	0.00, 2.90	-2.64, 18.39	0.00, 2.90	-1.54, 10.95
n[a]	53	53	47	47
12-week abdominal pain				
Mean (SD)	1.94 (0.77)	-0.84 (0.93)	1.92 (0.84)	-0.84 (0.88)
Median	1.82	-0.94	1.57	-0.8
IQR	1.30, 2.57	-1.31, -0.40	1.25, 2.63	-1.25, -0.23
Min, Max	0.87, 4.00	-2.83, 2.76	0.87, 4.00	-3.39, 0.78
n[a]	53	53	47	47
12-week stool consistency				
Mean (SD)	2.46 (0.95)	0.98 (1.29)	2.79 (1.07)	1.36 (1.13)
Median	2.33	1.12	2.60	1.32
IQR	2.00, 3.00	0.11, 1.98	2.00, 3.17	0.69, 2.30
Min, Max	1.00, 6.00	-1.90, 3.52	1.00, 5.25	-1.86, 3.60
n[a]	47	47	39	39
		Responder Rate, n/N		**Responder Rate, n/N**
6/12 Weeks SBM + 2 Responder		16/53 (30.2%)		14/47 (29.8%)
6/12 Weeks APS Responder		26/53 (49.1%)		20/47 (42.6%)
6/12 Weeks SBM + 2 Responder, sensitivity analysis[b]		21/53 (39.6%)		18/47 (38.3%)
6/12 Weeks APS Responder, sensitivity analysis[b]		36/53 (67.9%)		29/47 (61.7%)

Source: Clinical Study Report Table 8 (page 39). Verified by reviewer using ADEFF.

[a] Subjects with analysis values at both baseline and postbaseline during the specified time period.

[b] Results based on sensitivity analysis that only required 4 evening eDiaries for subjects to be potentially considered as a responder.

Abbreviations: IQR = interquartile range; max=maximum; min=minimum; N=number of subjects in population treatment group;

n=number of subjects in subgroups; SBM = spontaneous bowel movement; SD=standard deviation.

In post-hoc analyses, the results for the three continuous secondary endpoints in Study LIN-MD-64 were compared to the results from the adult studies (Table 20). Specifically, the mean values in LIN-MD-64 were compared to the conservative bounds from the 95% CIs estimated in the meta-analyses of adult placebo subjects. In both LIN-MD-64 groups, the mean CFB for each of these endpoints was, in absolute value, larger than the conservative estimates of CFB observed in adult placebo subjects. In the linaclotide 290 mcg group, the corresponding p-values for each endpoint was nominally significant. In the linaclotide 145 mcg group, only the p-value for the abdominal pain endpoint was nominally significant; however, the p-value for SBM frequency was close to nominally significant (0.053).

Table 20: Comparison of Secondary Efficacy Endpoints with Adult Subjects (mITT Population, LIN-MD-64)

	Adult Placebo Subjects N = 883	**Adult 290 ug Subjects N = 890**	**Linaclotide 145 mcg N = 53**		**Linaclotide 290 mcg N = 47**	
	Change from Baseline (95% CI)	Change from Baseline (95% CI)	Change from Baseline (95% CI)	p-value[a]	Change from Baseline (95% CI)	p-value[a]
12-week SBM frequency (SBMs/week)	1.30 (1.16, 1.44)	4.08 (3.81, 4.34)	2.35 (1.43, 3.27)	0.0530	2.75 (1.90, 3.59)	0.0032
12-week abdominal pain	-21.71% (-23.73, -19.68)	-35.89% (-38.00, -33.77)	-42.91% (-58.10, -27.72)	0.0143	-43.44% (-55.13, -31.74)	0.0014
12-week stool consistency[b]	0.68 (0.61, 0.75)	2.09 (1.99, 2.19)	0.98 (0.60, 1.36)	0.2288	1.36 (0.99, 1.72)	0.0018

Source: Created by reviewer using ADEFF.xpt and adult results reported in the response Information Request dated June 16, 2025 and the response to Information Request dated July 29, 2025.
[a] p-value based on a one-sided t-test compared with the appropriate bound (i.e., upper bounds for SBM frequency and stool frequency; lower bound for abdominal pain) of the 95% CI for adult placebo subjects.
[b] Stool consistency was assessed by the p-BSFS in pediatric subjects and BSFS in adult subjects.
Abbreviations: BSFS = Bristol Stool Form Scale; CI = confidence interval; N=number of subjects in population treatment group; p-BSFS = pediatric BSFS; SBM = spontaneous bowel movement

A second set of post-hoc analyses evaluated the proportion of subjects meeting clinically relevant thresholds for weekly SBM frequency and stool consistency scores. The proportion of subjects with a mean weekly SBM frequency of at least 3 SBMs/week in the linaclotide 145 mcg and 290 mcg groups increased from 0% in the baseline period to 43.4% and 53.2% in the DBTP (Table 21). The proportion of subjects with a mean stool frequency scores between 3 and 5 in the linaclotide 145 mcg and 290 mcg groups increased from 23.4% and 38.5% in the baseline period to 60.8% and 68.1% in the DBTP (Table 21).

Table 21: Binary Secondary Efficacy Endpoint Analyses (mITT Population, LIN-MD-64)

	Mean Weekly SBM Frequency ≥ 3	**Mean Weekly Stool Consistency Score between 3 and 5**

	Linaclotide 145 mcg N = 53	Linaclotide 290 mcg N = 47	Linaclotide 145 mcg N = 53	Linaclotide 290 mcg N = 47
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Baseline	0	0	11/47 (23.4)	15/39 (38.5)
12 Week DBTP	23/53 (43.4)	25/47 (53.2)	31/49 (63.3)	31/46 (67.4)
Week 1-2	23/53 (43.4)	22/47 (46.8)	27/47 (57.4)	23/44 (52.3)
Week 3-4	29/53 (54.7)	27/46 (58.7)	32/48 (66.7)	24/43 (55.8)
Week 5-6	29/53 (54.7)	26/44 (59.1)	26/47 (55.3)	21/40 (52.5)
Week 7-8	24/52 (46.2)	27/42 (64.3)	28/48 (58.3)	26/42 (61.9)
Week 9-10	21/50 (42.0)	23/42 (54.8)	30/44 (68.2)	28/38 (73.7)
Week 11-12	22/49 (44.9)	16/41 (39.0)	25/44 (56.8)	27/39 (69.2)

Source: Based on the response to Information Request dated July 29, 2025. Verified by reviewer using ADEFF.xpt.
Abbreviations: N=number of subjects in population treatment group; n=number of responders; SBM = spontaneous bowel movement

Efficacy Results – Exploratory endpoints

Results for key prespecified exploratory endpoints are summarized in Table 22 and provide additional support for treatment efficacy. Both linaclotide groups showed decreases in weekly abdominal pain scores during each period (i.e., daytime symptoms, nighttime symptoms), straining scores, and bloating scores during the 12-week treatment period, as compared to baseline. Moreover, 27.5% and 41.9% of subjects in the linaclotide 145 mcg and linaclotide 290 mcg groups, respectively, no longer fulfilled the Rome III criteria for IBS-C at the end of treatment. Finally, 15.1% and 10.6% of subjects in the linaclotide 145 mcg and linaclotide 290 mcg groups, respectively, fulfill a more stringent 9/12 weeks APS + 2 responder criteria.

Table 22: Exploratory Efficacy Endpoint Analyses (mITT Population , LIN-MD-64)

		Linaclotide 145 mcg N=53		Linaclotide 290 mcg N = 47
	Baseline	Change from baseline	Baseline	Change from baseline
12-week abdominal pain (daytime)				
Mean (SD)	2.13 (0.73)	-0.95 (0.92)	2.03 (0.84)	-0.83 (0.90)
Median	2	-1.01	1.71	-0.83
IQR	1.62, 2.67	-1.36, -0.60	1.27, 2.85	-1.38, -0.17
Min, Max	1.08, 4.00	-3.07, 2.46	1.00, 4.00	-3.12, 1.26
n[a]	53	53	47	47
12-week abdominal pain (nighttime)				
Mean (SD)	1.75 (0.86)	-0.72 (0.98)	1.75 (0.92)	-0.81 (0.92)

Median	1.64	-0.78	1.54	-0.69
IQR	1.07, 2.33	-1.36, -0.20	0.93, 2.47	-1.18, -0.17
Min, Max	0.42, 4.00	-2.74, 2.89	0.53, 4.00	-3.75, 0.61
n[a]	53	53	47	47
12-week straining				
Mean (SD)	2.53 (0.75)	-1.06 (1.23)	2.65 (0.87)	-1.26 (1.02)
Median	2.5	-0.92	2.75	-1.19
IQR	2.00, 3.00	-2.08, 0.07	2.00, 3.20	-1.92, -0.49
Min, Max	1.25, 4.00	-3.00, 1.27	1.00, 4.00	-3.88, 0.58
12-week bloating[b]				
Mean (SD)	1.81 (1.11)	-0.75 (0.90)	1.58 (0.97)	-0.73 (0.94)
Median	1.54	-0.54	1.43	-0.58
IQR	0.93, 2.73	-1.08, -0.28	0.70, 2.57	-1.00, -0.13
Min, Max	0.00, 4.00	-3.25, 0.90	0.00, 3.50	-3.35, 1.26
n[a]	53	53	47	47
		Responder Rate, n/N		**Responder Rate, n/N**
No longer fulfill Rome III criteria at Week 12		14/51 (27.5%)		18/43 (41.9%)
9/12 weeks APS + 2 responder		8/53 (15.1)		5/47 (10.6)

Source: Clinical Study Report Table 14.2-3.6 (page 171), Table 14.2-3.9.1 (page 175), and 14.2-3.11 (page 179). Verified by reviewer using ADEFF.xpt, ADEFFROM.xpt.

[a] Subjects with analysis values at both baseline and postbaseline during the specified time period.

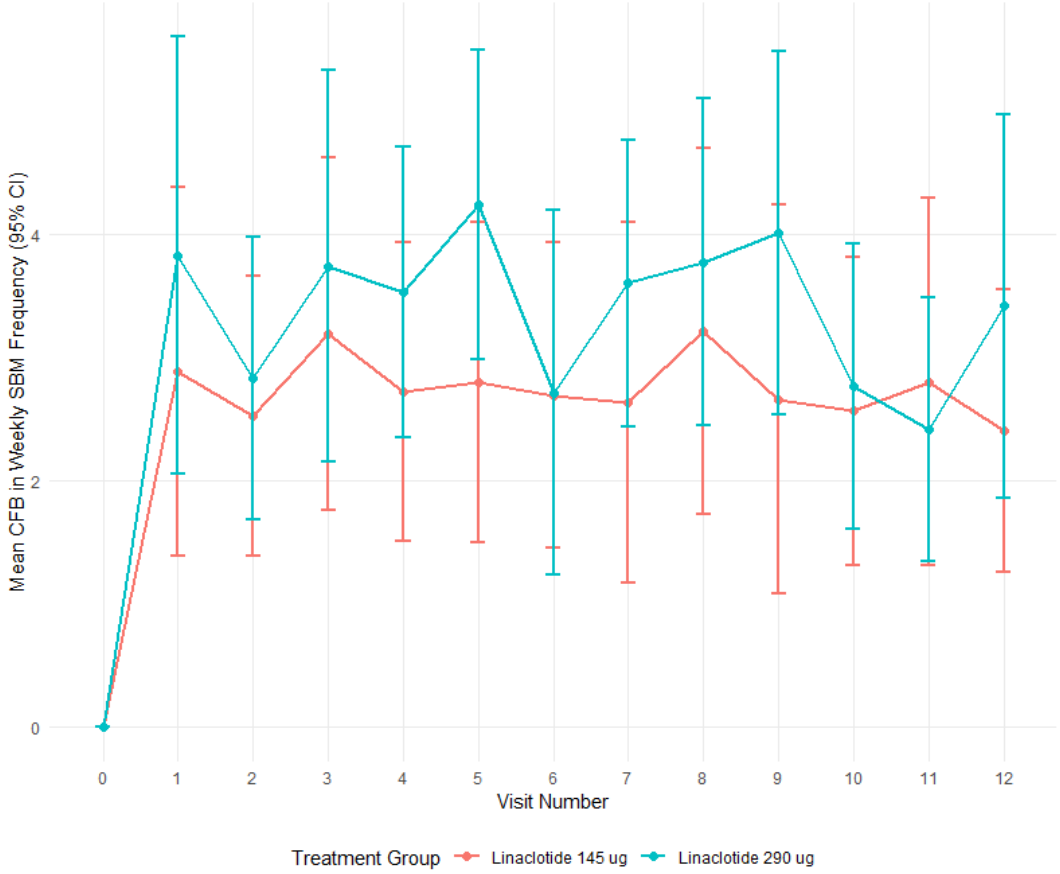
[b] Based on an average of morning and evening assessments.

Abbreviations: IQR = interquartile range; max=maximum; min=minimum; N=number of subjects in population treatment group; n=number of subjects in subgroups; SD=standard deviation.

Persistence of Effect

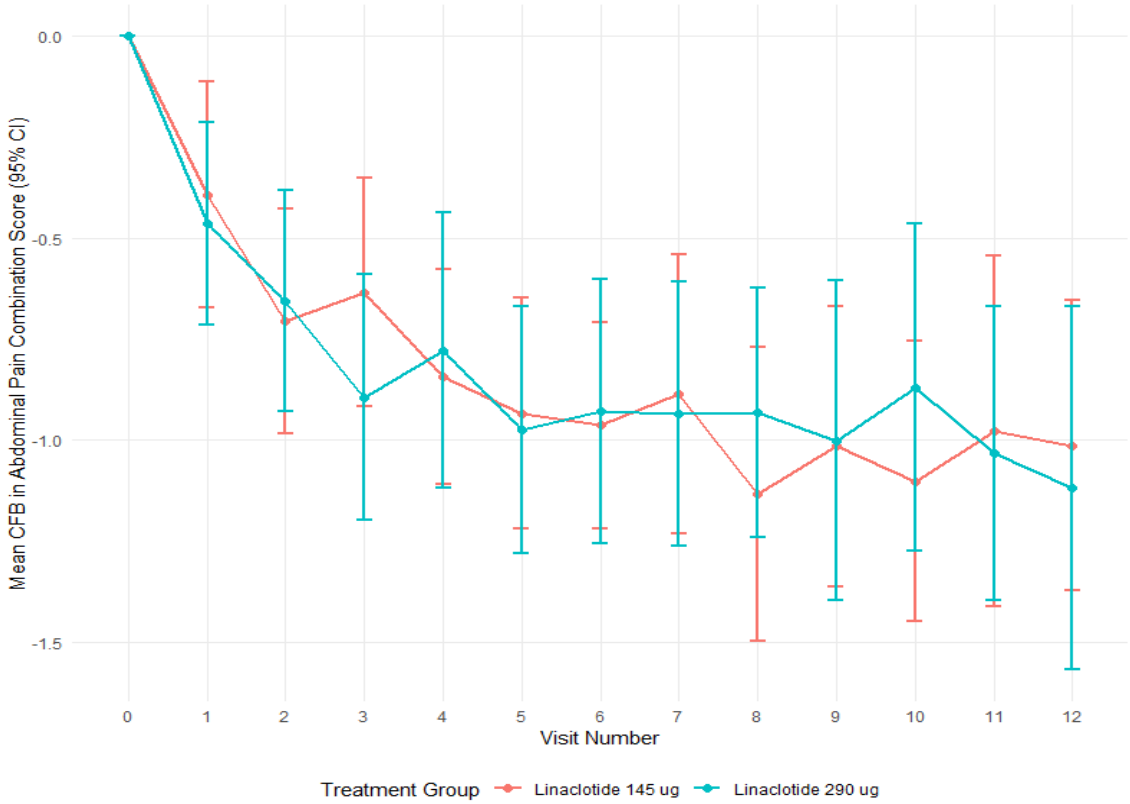
The mean CFB in the weekly SBM frequency and mean CFB in abdominal pain score are plotted by week in Figure 2 and Figure 3. The mean weekly SBM frequency increased during the first week and then remained relatively constant for the remainder of the DBTP. The mean abdominal pain score decreased steadily over the first half of the DBTP and then remained relatively constant.

Figure 2: Mean Change From Baseline (CFB) in Weekly SBM Frequency by Week



Source: Created by reviewer using ADEFF.xpt. Note, means are based only on subjects with ≥ 4 completed diary days.

Figure 3: Mean Change From Baseline (CFB) in Abdominal Pain Combination Score by Week



Source: Created by reviewer using ADEFF.xpt. Note, means are based only on subjects with ≥ 4 completed diary days.

8.1.3. Pediatric Irritable Bowel Syndrome with Constipation Symptom Diary (PIBSCSD)

The PIBSCSD is a PRO measure that was used to support the efficacy endpoints in the phase 3 trial (LIN-MD-64). The PIBSCSD is designed to measure abdominal symptoms (pain, bloating) and bowel movement characteristics (frequency, consistency, straining, and complete evacuation). The PIBSCSD was administered twice daily, in the morning when the subject woke up (i.e., nighttime symptoms) and in the evening before bedtime (i.e., daytime symptoms) using an eDiary. Both self-administered and interviewer-administered formats were adopted. The self-administered PIBSCSD was completed by all subjects (i.e., patients with IBS-C aged 7-17 years) without any involvement or interpretation by a caregiver or clinician. For subjects aged 7 to 11 years and had difficulty reading or understanding the PIBSCSD without assistance, an interviewer-administered version was completed. The interviewer (i.e., a parent, guardian, legally authorized representative, or caregiver) was instructed to read the questions and response choices verbatim as they appeared on the screen and recorded the subject's responses, while refraining from influencing or changing the answer chosen by the subject.

Several factors limited the interpretability of the quantitative anchor-based analyses for the evaluation of clinically meaningful within-subject change in the PIBSCSD scores (e.g., abdominal pain, spontaneous bowel movement frequency). As such, the clinical meaningfulness of the PIBSCSD-based endpoint results from the phase 3 trial (LIN-MD-64) cannot be determined based on the anchor-based analyses. The limitations include the following:

- The Applicant's anchor-based analyses relied on phase 2 results (LIN-MD-63) due to high missing data rates (86%-87% at Week 12) in the global anchor scales (i.e., patient global impression of severity [PGI-S] and patient global impression of change [PGI-C]) administered in the phase 3 trial.
- Given the difference in the study assessment duration (i.e., 4 weeks for phase 2 and 12 weeks for phase 3) and limitations of the anchor scales in phase 2 (e.g., data collection error in the PGI-S and PGI-C), the anchor-based analysis results using phase 2 data may not be interpretable and generalizable to phase 3 study results.

8.1.4. Assessment of Efficacy Across Trials

Prior to initiating their phase 3 study, the Applicant conducted a randomized, *placebo-controlled* phase 2 dose-finding study, LIN-MD-63 (see Section 15.4). The population and study design of LIN-MD-63 was generally similar to the design of LIN-MD-64, except that the DBTP was only 4 weeks. The doses regimen for LIN-MD-63 are described in Figure 4. For "Dose C", subjects 7-11 years old ≥ 35 kg and all subjects 12 – 17 years old received 145 mcg. Table 23 shows the results for the change from baseline in abdominal pain score over the first four weeks of LIN-MD-63 and LIN-MD-64. Table 24 shows the results for the change from baseline in weekly SBM frequency during the first four weeks of each trial. The mean change from baseline for each of these two key endpoints were generally similar across the higher-dose linaclotide groups in the two trials and were numerically larger than changes observed in the LIN-MD-63 placebo group.

Table 23. Mean Change from Baseline in Abdominal Pain Symptoms in LIN-MD-63 and LIN-MD-64 During the First Four Weeks of the Double-Blind Treatment Period (mITT populations)

	LIN-MD-63			LIN-MD-64	
	Placebo N=19	**Linaclotide Dose C[a] N=23**	**Linaclotide 290 ug N=8**	**Linaclotide 145 mcg N = 53**	**Linaclotide 290 mcg N = 47**
Abdominal pain	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)
Baseline	2.28 (0.69)	2.21 (0.85)	2.59 (1.18)	1.94 (0.80)	1.92 (0.84)
Change from Baseline[b]	-0.63 (0.93)	-0.61 (0.82)	-1.02 (0.95)	-0.63 (0.85)	-0.71 (0.82)

Source: Based on LIN-MD-63 Clinical Study Report Table 14.2-3.10 (page 163) and reviewer-generated results.
[a] Subjects 7-11 years < 35 kg received 72 mcg, subjects 7-11 ≥ 35 kg received 145 mcg, and subjects 12-17 years received 145 mcg.
[b] For LIN-MD-64, the change from baseline during the first four weeks of the DBTP was the average of the four weekly values.

Table 24. Mean Change from Baseline in Weekly SBM Frequency in LIN-MD-63 and LIN-MD-64 During the First Four Weeks of the Double-Blind Treatment Period (mITT populations)

	LIN-MD-63			LIN-MD-64	
	Placebo N=19	Linaclotide Dose C[a] N=23	Linaclotide 290 ug N=8	Linaclotide 145 mcg N = 53	Linaclotide 290 mcg N = 47
SBM/Week	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)
Baseline	0.97 (0.53)	1.41 (0.68)	1.21 (0.82)	1.34 (0.84)	1.26 (0.90)
Change from Baseline[b]	1.45 (1.38)	2.68 (2.77)	3.22 (2.19)	2.53 (3.73)	2.89 (3.49)

Source: Based on LIN-MD-63 Clinical Study Report Table 11-1 (page 35) and reviewer-generated results.
[a] Subjects 7-11 years < 35 kg received 72 mcg, subjects 7-11 ≥ 35 kg received 145 mcg, and subjects 12-17 years received 145 mcg.
[b] For LIN-MD-64, the change from baseline during the first four weeks of the DBTP was the average of the four weekly values.

Although the size of each treatment arm in LIN-MD-63 was relatively small, the similarity of effects across studies and the greater improvements in the linaclotide groups, as compared to the placebo group provide further support for the efficacy treatment.

8.1.5. Integrated Assessment of Effectiveness

This efficacy supplement included one phase 3 clinical study to demonstrate efficacy and the phase 2 study dose ranging study, LIN-MD-63, utilized a different design. Therefore, an integrated assessment of efficacy across studies was not performed. Refer to Section 15.4 for additional information on LIN-MD-63.

8.2. Review of Safety

8.2.1. Safety Review Approach

Review of safety focused on data from the 12-week double-blind, placebo-controlled phase 3 study LIN-MD-64. Interim data from the long-term extension study LIN-MD-66, which enrolled subjects that completed LIN-MD-63 or LIN-MD-64, were also assessed. Data from the phase 2 study LIN-MD-63 were also reviewed (see Section 15.4), but the phase 2 data did not contribute considerably to the safety review due to a relatively small sample size for subjects receiving linaclotide 145 mcg and a short treatment duration of 4 weeks.

8.2.2. Review of the Safety Database

Overall Exposure

Study LIN-MD-64 included 108 subjects, with 55 receiving linaclotide 145 mcg and 53 receiving 290 mcg (mean exposure durations were 85.3 and 80.2 days, respectively) (see Table 25).

Table 25: Duration of Exposure in LIN-MD-64 (Safety Population)

Parameter	Linaclotide 145 mcg N=55	Linaclotide 290 mcg N=53
Duration of exposure (days), n (%)		
>1 dose	55 (100)	53 (100)
>14 days	55 (100)	51 (96.3)
>28 days	54 (98.1)	51 (96.3)
>56 days	54 (98.1)	48 (90.6)
>96 days	2 (3.6)	0 (0.0)
Mean (SD)	85.3 (9.5)	80.2 (17.9)
Median	86.0	85.0

Source: Adapted from Applicant's LIN-MD-64 Study Report Table 14.3.1
Abbreviations: SD, standard deviation

In study LIN-MD-63, 82 subjects were exposed to at least one dose of linaclotide, with a mean exposure duration of 27.5 to 29.0 days across treatment groups. The specific doses administered (18, 36, 72, and 145 mcg) were based on the subject's age and, for the youngest group, body weight. Twenty-two subjects received the TBM dose of linaclotide (145 mcg). The long-term safety study LIN-MD-66 included 98 subjects, 22 on 145 mcg and 76 on 290 mcg (mean exposure durations of 47.1 and 42.7 weeks, respectively). Of these, 67 subjects were exposed to linaclotide for at least 52 weeks. Specifically, 19 subjects were exposed to the TBM dose of linaclotide (145 mcg) for at least 36 weeks, of whom 10 were exposed for at least 52 weeks (see Table 26). Additionally, 56 subjects were exposed to the 290 mcg dose for at least 36 weeks (of whom 40 were exposed for at least 52 weeks), contributing to the overall evaluation of linaclotide's safety profile.

Table 26. Duration of Exposure in LIN-MD-66 (Safety Population)

Parameter	Linaclotide 145 mcg N=22	Linaclotide 290 mcg N=76
Duration of exposure (weeks), n (%)		
≤4 weeks	0 (0.0)	1 (1.3)
>4 weeks	22 (100)	75 (98.6)
>12 weeks	21 (95.5)	72 (94.7)
>20 weeks	21 (95.5)	67 (88.1)
>36 weeks	19 (86.4)	56 (73.6)
>52 weeks	10 (45.5)	40 (52.6)
Mean (SD)	47.1 (12.13)	42.7 (14.51)
Median	52.0	52.1

Source: Adapted from Applicant's LIN-MD-66 Clinical Study Report Table 14.3-1.1
Abbreviations: SD, standard deviation

Adequacy of the safety database:

The Applicant's safety database contained safety data from 108 subjects from the phase 3 study LIN-MD-64. This included 55 subjects who received linaclotide 145 mcg and 53 subjects who received linaclotide 290 mcg. A total of 98 subjects completed the 12-week intervention period for the study (52 [94.5%] for linaclotide 145 mcg and 46 [86.8%] for linaclotide 290 mcg).

The review team considered the limitations of interpreting non-placebo-controlled and open-label safety data because such data can be challenging to interpret and do not necessarily replace the need for controlled, blinded data to determine whether adverse events are related to the drug or other factors. However, given the recruitment challenges the Applicant reported during the phase 2 study LIN-MD-63, the Agency agreed to the removal of the placebo arm from the phase 3 study LIN-MD-64, among other modifications to the study design, to facilitate enrollment (see Section 3).

Because pediatric IBS-C is sufficiently similar to adult IBS-C and CIC, as well as pediatric FC, with respect to pathophysiology, clinical presentation, and expected response to treatment, the available pediatric safety data in the current submission can be evaluated in light of regulatory and clinical experience with linaclotide since its initial approval for these indications in 2012 and 2023, respectively.

As described in the approved product label, exposure in clinical development included: approximately 2,570, 2,040, and 1,220 adult patients with either IBS-C or CIC who were treated with Linzess for 6 months or longer, 1 year or longer, and 18 months or longer, respectively (not mutually exclusive); and approximately 209, 189, and 51 pediatric patients with FC who were treated with Linzess for 4 weeks or longer, 24 weeks or longer, and 36 weeks or longer, respectively (also not mutually exclusive). Therefore, in addition to the safety data submitted from the pediatric studies supporting this NDA supplement, the review team considered the comprehensive body of pre- and post-marketing safety data that has been collected and analyzed for linaclotide.

The review team concluded that, based on the ability to leverage existing regulatory and clinical experience with linaclotide, and the available safety data collected from the pediatric clinical studies, the Applicant's safety database was adequate to characterize the safety profile in pediatric patients 7 to 17 years of age with IBS-C.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No issues identified.

Categorization of Adverse Events

Overall, the Applicant's definitions for treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESIs), categorization of adverse

events (AEs), and classifications of AE severity were appropriate.

Adverse events were identified based on open-ended questioning of the subject (or caregiver, if applicable) at each study visit. AEs were considered treatment-emergent adverse events (TEAEs) if the AE began on or after the date of the first dose of study drug, or if the AE was present before the date of the first dose of study drug but increased in severity or became serious on or after the date of the first dose of study drug. AEs that occurred more than 30 days after the last dose of study drug were not counted as TEAEs, establishing clear temporal boundaries for classification.

AEs presented in the clinical study reports for studies LIN-MD-64 and LIN-MD-66 were coded by the Applicant using the Medical Dictionary for Regulatory Activities (MedDRA) Version 27.0. AEs presented in the clinical study report for study LIN-MD-63 were coded using MedDRA version 22.0. No issues were identified regarding the Applicant's coding of AEs.

Routine Clinical Tests

Vital signs, physical findings, clinical laboratory evaluations, and ECG parameters were assessed across all studies. Overall, no issues were identified regarding the routine clinical tests.

8.2.4. Safety Results

Deaths

No deaths were reported in LIN-MD-63, LIN-MD-64, or LIN-MD-66.

Serious Adverse Events

No treatment-emergent serious adverse events (SAEs) were reported in LIN-MD-64.

In LIN-MD-63, two SAEs considered not related to study drug were reported. One treatment emergent SAE was anaphylactic reaction, that was determined to be not related to study drug given the event occurred in the placebo arm and confounding factors (including the subject's unspecified food allergies). A second SAE (not treatment-emergent) of fecaloma was determined to be not related to the study drug as it was attributed to the patient's underlying constipation that occurred during the post-treatment period of the study.

In LIN-MD-66, two subjects in the linaclotide 290 mcg treatment group experienced treatment-emergent SAEs. These included adenoidal hypertrophy with post procedural hemorrhage after tonsillectomy and adenoidectomy in one subject, and mental status changes with migraine in a second subject; these were not considered related to the study drug based on mechanism of action as well as timing of presentation of these events.

Dropouts and/or Discontinuations Due to Adverse Effects

No dropouts and/or discontinuations due to adverse effects were reported in LIN-MD-64 or LIN-MD-66. In LIN-MD-63, there were two AEs that led to study discontinuation: one subject with moderate diarrhea (treatment-emergent, drug-related) and one subject with abdominal pain, anaphylactic reaction, and hematemesis (treatment-emergent, not drug-related).

Significant Adverse Events

No severe AEs were reported for study LIN-MD-64. One severe adverse event not related to the study drug was reports for LIN-MD-63 (anaphylactic reaction in the placebo treatment group). Two subjects experienced severe AEs in the 290 mcg treatment group of LIN-MD-66, including post-procedural hemorrhage, adenoidal hypertropy, nasal turbinate hypertrophy, and tonsillar hypertrophy (all serious, not study drug-related, reported in the same subject), and severe diarrhea (non-serious, drug-related) in a second subject.

Treatment Emergent Adverse Events and Adverse Reactions

Table 27 summarizes the numbers of subjects who experienced TEAEs, treatment-emergent SAEs, and TEAE-related discontinuations in LIN-MD-64.

Table 27. Treatment-Emergent Adverse Event Summary: Study LIN-MD-64

Event Type	Linaclotide 145 mcg N=55 n (%)	Linaclotide 290 mcg N=53 n (%)
Subjects with any TEAE	11 (20.0%)	8 (15.8%)
Subjects with any treatment-emergent SAE	0	0
Subjects with any TEAE leading to death	0	0
Subjects with any TEAE leading to permanent discontinuation	0	0

Source: Reviewer's table using adae.xpt dataset from Study LIN-MD-64
Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event

Table 28 summarizes the most common TEAEs reported in LIN-MD-64 subjects receiving linaclotide. The review team selected a threshold of >2% because any AE that occurred in a single subject corresponded to a proportion of 1% (specifically 1.8% or 1.9% for 145 mcg and 290 mcg treatment groups, respectively). The most common AE in LIN-MD-64 was diarrhea, which was reported by 4 subjects in both the linaclotide 145 mcg and 290 mcg treatment groups (7.3% and 7.5% of subjects, respectively). Diarrhea is a known risk associated with linaclotide and represents the most common AE in linaclotide-treated patients in the pediatric FC trials, as well as in the pooled IBS-C and CIC trials in adult populations. Across all three studies in this review, there were no cases of diarrhea-related dehydration (see Section 8.2.5 for additional details) and one case of severe diarrhea. The case of severe diarrhea occurred in the 290 mcg treatment arm of the long-term extension (LTE) study LIN-MD-66. This arm also had 10 subjects who experienced treatment-related TEAEs and two subjects with TESAEs that

were determined to be not drug-related. In contrast, no treatment-related TEAEs or TESAEs occurred in the 145 mcg treatment group.

Given the safety profile of linaclotide in pediatric IBS-C was similar to the safety profiles from trials in adults with IBS-C and CIC, and in pediatric patients with FC, the review team recommends including an overall comparative safety profile summary in the linaclotide labeling. In addition, the review team recommends listing diarrhea as an AE in the labeling and describing the single case of severe diarrhea that occurred in a subject receiving the 290 mcg dosage within the Warnings and Precautions section of the labeling (see Section 11).

Table 28. TEAEs Occurring in >2% Linaclotide-Treated Subjects (LIN-MD-64)

Adverse Event	Linaclotide 145 ug (N=55)	Linaclotide 290 ug (N=53)
Diarrhoea	4 (7.3%)	4 (7.5%)
Abdominal pain	2 (3.6%)	0 (0.0%)
Constipation	2 (3.6%)	0 (0.0%)
Polycystic ovarian syndrome†	1 (3.2%)	0 (0.0%)

†Event specific to female; gender-specific percentages are calculated relative to the number of subjects with the corresponding gender.
Source: Reviewer's table using adae.xpt dataset from Study LIN-MD-64
Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event

Laboratory Findings

In Study LIN-MD-64, clinical laboratory parameters were assessed at baseline and Week 12. Overall, no clinically significant laboratory abnormalities were identified.

Vital Signs

In Study LIN-MD-64, vital signs were assessed at baseline and Weeks 2, 4, 8, and 12. Overall, no clinically significant vital sign abnormalities were identified.

Electrocardiograms (ECGs)

In Study LIN-MD-64, electrocardiograms were conducted at baseline and Week 12. No clinically significant electrocardiogram abnormalities were identified.

QT

Not applicable.

Immunogenicity

Not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

Risk of Diarrhea and Dehydration

Given that diarrhea is a known risk for linaclotide that may lead to dehydration, particularly in pediatric patients, diarrhea-related dehydration was an adverse event of special interest (AESI) for this review. No AESI, including sequelae of diarrhea (e.g., volume depletion, electrolyte abnormalities), were reported across all three studies.

AE reports, laboratory parameter data, and daily diary data were reviewed for signs of dehydration possibly related to diarrhea. The most frequently reported TEAE across all 3 studies was diarrhea, and rates of diarrhea were similar between treatment groups in Study LIN-MD-64. As described in the Serious Adverse Events subsection, one severe case of diarrhea was reported across all three studies, occurring in a subject in the 290 mcg treatment group of LIN-MD-66. This event occurred on study day 1, was non-serious, and resolved on study day 3 following dose reduction. Additionally, 2 subjects had cases of mild diarrhea and 3 subjects with moderate diarrhea, all in the 290 mcg treatment group.

Although the incidence of diarrhea-related dehydration was low in the pediatric studies, diarrhea is a known risk of linaclotide that can lead to dehydration, which can be serious. Pediatric patients and their caregivers should be aware of the risks of diarrhea and dehydration and seek care from a healthcare professional in a timely manner. The review team therefore recommends that product labeling describe diarrhea and dehydration as AEs reported in the pediatric studies.

8.2.6. Safety Analyses by Demographic Subgroups

Table 29 describes the proportion of subjects who experienced at least one TEAE in Study LIN-MD-64, by demographic subgroups of sex, age group, and race/ethnicity.

Table 29. Subjects With Any TEAE by Demographic Subgroup (LIN-MD-64)

Parameter	Linaclotide 145 mcg N=55 (%)	Linaclotide 290 mcg N=53 (%)
Sex		
Female	7/31 (22.6)	4/34 (11.8)
Male	4/24 (16.7)	4/19 (21.1)
Age group		
7 to 11 years	6/22 (27.3)	2/21 (9.5)
12 to 17 years	5/33 (15.2)	6/32 (18.8)

Parameter	Linaclotide 145 mcg N=55 (%)	Linaclotide 290 mcg N=53 (%)
Race		
White	11/40 (27.5)	6/35 (17.1)
Black or African American	0/13 (0.0)	0/14 (0.0)
Asian	0/2 (0.0)	0/1 (0.0)
Native Hawaiian or other Pacific Islander	0/0 (0.0)	0/0 (0.0)
American Indian or Alaska Native	0/0 (0.0)	0/0 (0.0)
Multiple	0/0 (0.0)	1/1 (100.0)
Missing	0/0 (0.0)	1/2 (50.0)

Source: Reviewer's table using adae.xpt and adsl.xpt datasets from Study LIN-MD-64
Abbreviations: TEAE, treatment-emergent adverse event

Within the linaclotide 145 mcg treatment group, rates of AEs were slightly higher in the female subgroup compared to the male subgroup, and also higher in the 7- to 11-year-old subgroup compared to the 12- to 17-year-old subgroup. When analyzed by race, rates of TEAEs were slightly higher in the White subgroup compared to the overall TEAE rate (see Table 29), but sample sizes for the other racial subgroups were too small to assess. Overall, no clinically meaningful trends were identified by the subgroup analyses; however, the sample sizes for the subgroups were generally too small to permit meaningful comparisons.

8.2.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

As described in existing approved labeling for linaclotide, in 2-year carcinogenicity studies, linaclotide was not tumorigenic in rats at doses up to 3500 mcg/kg/day or in mice at doses up to 6000 mcg/kg/day. The maximum recommended human dose is approximately 5 mcg/kg/day based on a 60-kg body weight

Human Reproduction and Pregnancy

As described in existing approved labeling for linaclotide, linaclotide had no effect on fertility or reproductive function in male and female rats at oral doses of up to 100,000 mcg/kg/day.

Pediatrics and Assessment of Effects on Growth

No formal analyses of growth were conducted in the pediatric studies. In LIN-MD-64, subject weight was assessed at screening and at Weeks 2, 4, 8, and 12 (the end-of-treatment visit). Subject height was only assessed at screening and at the Week 12 visit. Meaningful changes in growth are unlikely to be observed over a short 12-week duration, and there were no unexpected changes of clinical relevance.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

At the time of data cutoff, there were no reports of overdose across the three studies. As described in the clinical review supporting the original 2012 approval of Linzess, single doses of linaclotide up to 2897 mcg were given to healthy volunteers and tolerated well with no consequences other than diarrhea (see NDA 202811 Clinical Review dated August 2, 2012; DARRTS ID: 3167659). Doses up to 966 mcg were given per protocol for up to 7 days in adult phase 2 studies. There were no known instances of intentional overdose and cases of purposeful drug abuse. Additionally, data from a 4-week randomized-withdrawal study of linaclotide 145 mcg and 290 mcg, designed to assess withdrawal and rebound potential of linaclotide, showed no evidence of withdrawal effects or a rebound worsening of constipation symptoms relative to baseline.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Division of Pharmacovigilance (DPV-I) conducted a comprehensive search of the FDA Adverse Event Reporting System (FAERS) database to identify all adverse events associated with linaclotide that were coded with serious outcomes across all age groups. The search encompassed the period from May 10, 2020 (the data-lock date of the prior DPV-I review of all adverse events with linaclotide) through June 10, 2025. This FAERS search yielded 1,215 reports, all of which underwent manual review by the clinical team.

The majority of retrieved AE reports were coded with Preferred Terms for labeled gastrointestinal events or were directly related to the drug's indication for use, which was consistent with linaclotide's known safety profile. To supplement the FAERS database review, DPV-I conducted a systematic search of the published medical literature for relevant case reports; however, this literature search did not retrieve any additional cases of clinical interest beyond those already identified in the FAERS database.

Based on the review conducted by DPV-I in response to this NDA supplement, the review team does not recommend any additional changes to the description of postmarketing safety in labeling.

Expectations on Safety in the Postmarket Setting

No new safety signals were identified during the review of this application or available postmarket safety data. Therefore, the review team expects that routine pharmacovigilance will be adequate to ensure safe use of linaclotide in patients aged 7 to 17 years.

8.2.10. Integrated Assessment of Safety

This efficacy supplement included one clinical study; therefore, an integrated assessment of safety across studies was not performed.

The review team concluded that the safety profile of linaclotide in the studied pediatric population was similar to the known safety profile in the adult population, with diarrhea being the most common adverse event. No new safety signals were identified from the submitted pediatric study data nor from postmarketing safety reports, no deaths occurred in the pediatric studies, and SAEs were rare overall. The review team considers the available body of safety data for linaclotide to be adequate to support product approval and labeling for the 145 mcg dose. In light of the reports of diarrhea in subjects receiving the 290 mcg dose in the LTE study, and consistent with established clinical practice guidelines advocating for the minimum effective dose to reduce potential dose-related adverse events, the 145 mcg dose regimen is recommended.

8.3. Statistical Issues

The large amount of missing data due to eDiary non-compliance in LIN-MD-64 and the use of NRI raised concerns about the reliability of the results from the primary statistical analysis of the primary endpoint. Therefore, additional sensitivity analyses using alternative methods for defining and handling missing data were performed to evaluate the efficacy of treatment. No additional significant statistical issues were identified.

8.4. Conclusions and Recommendations

Based on a comprehensive review of the submitted efficacy supplement and pediatric study data, the review team has reached several key determinations regarding linaclotide for the treatment of IBS-C in the pediatric population. The safety profile of linaclotide in pediatric patients aged 7-17 years demonstrates consistency with the established adult safety profile, with diarrhea as the most frequently reported adverse event. No novel safety signals emerged from either the pediatric clinical studies or postmarketing surveillance data. The absence of deaths in the pediatric studies, combined with the overall low incidence of serious adverse events, further supports the acceptable safety profile of this therapeutic intervention.

The efficacy analysis revealed conflicting age-specific trends that warrant cautious interpretation. The 290 mcg dose showed numerically superior response rates in adolescents (12-17 years), while the 145 mcg dose performed better in younger children (7-11 years). These disparate findings must be interpreted cautiously given limited subgroup sample sizes and absence of formal statistical testing for between-dose comparisons. Additionally, extensive missing data due to eDiary non-compliance in study LIN-MD-64 and the use of non-responder imputation (NRI) raised concerns about the reliability of the results from the primary analysis. Therefore, sensitivity analyses using alternative methods for handling missing data were performed. No additional significant statistical issues were identified. Despite these limitations, the available safety and efficacy data are considered sufficient to support regulatory approval for the 145 mcg dose across the studied pediatric population.

Recommendations

The review team recommends approval of the 145 mcg dose for both pediatric age groups (7-11 years and 12-17 years) based on adequate safety, conflicting efficacy data that do not support higher dosing, and the regulatory principle of using the lowest effective dose.

9 Advisory Committee Meeting and Other External Consultations

Not applicable.

10 Pediatrics

This NDA supplement (022) for linaclotide in intended to fulfill the following PMR and address the studies below that are described in the PWR:

- PMR 1915-3: A safety and efficacy study in pediatric patients with irritable bowel syndrome with constipation ages seven years up to 17 years treated with Linzess (linaclotide).

- PWR Study 02: A randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study for the treatment of irritable bowel syndrome with constipation (IBS-C) in children ages 7 to 17 years.

- PWR Study 04: A randomized, double-blind, parallel-group confirmatory safety and efficacy study for the treatment of IBS-C in children and adolescents 7 to 17 years of age.

- PWR Study 05: A long-term safety study enrolling children and adolescents with chronic idiopathic constipation (CIC) or IBS-C who completed Studies 01, 02, 03 or 04

To fulfill PWR Study 02, the Applicant conducted Study LIN-MD-63, a phase 2 randomized, double-blind, placebo-controlled, dose-ranging study in subjects ages 7 to 17 years who met modified Rome III criteria for IBS-C. LIN-MD-63 is discussed in Section 15.4.

To fulfill PWR Study 04 and PMR 1915-3, the Applicant conducted Study LIN-MD-64, a phase 3 randomized, double-blind, parallel-group study of linaclotide 145 mcg and 290 mcg once daily in subjects ages 7 to 17 years who met modified Rome III criteria for FC. LIN-MD-64 is discussed in Sections 8.1 and 8.2 above.

To fulfill PWR Study 05, the Applicant is currently conducting Study LIN-MD-66, an open-label long-term extension safety study in subjects who completed LIN-MD-63 or LIN-MD-64. Interim data from LIN-MD-66 are discussed in Section 8.2 above.

The review team recommends fulfillment of PMR 1915-3 based on the Applicant's completion of LIN-MD-64. In addition, this efficacy supplement adequately addresses the final remaining requested clinical studies to completely meet the terms of the WR.

Pediatric Exclusivity Board convened on September 17, 2025, and concurred with the Division that the Applicant met all the terms of the WR. The Pediatric Review Committee (PeRC) meeting was held on October 7, 2025, and the committee concurred with the Division on the fulfillment of PMR 1915-3.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Table 30. Prescribing Information

Full Prescribing Information Sections[1]	High-Level Summary of the Review Team's Recommended Changes to the Applicant's Proposed Draft PI
1 INDICATIONS AND USAGE	The indication was expanded for the treatment of irritable bowel syndrome with constipation (IBS-C) to include pediatric patients 7 years of age and older, as proposed by the Applicant.
2 DOSAGE AND ADMINISTRATION	The recommended dosage is 145 mcg orally once daily for the treatment of pediatric patients 7 years of age and older with IBS-C, as proposed by the Applicant.
5 WARNINGS AND PRECAUTIONS	5.2 Diarrhea The reported rate of diarrhea and severe diarrhea reported in the double-blind parallel-group study of pediatric patients with IBS-C has been added, similar to information already presented on the incidence of diarrhea and severe diarrhea in the adult IBS-C, chronic idiopathic constipation (CIC) and pediatric functional constipation (FC) populations. A single case of severe diarrhea in a pediatric patient with IBS-C treated with the higher than recommended dosage for IBS-C (i.e., 290 mcg once daily) was added.
6 ADVERSE REACTIONS 6.1 Clinical Trials Experience	The existing summary of exposure information from clinical trials was removed given the duration of time linaclotide has been marketed. In the subsection on adverse reactions reported in the pediatric clinical study of IBS-C, the discussion was limited to safety information of the to-be-marketed dosage (i.e., 145 mcg once daily). The most common adverse reaction of diarrhea is described in the text along with a summary statement of overall comparative safety profile in pediatric patients with IBS-C highlighting the similarity to the other approved indications (e.g., adult IBS-C and CIC, and pediatric patients with FC).
8 USE IN SPECIFIC POPULATIONS 8.4 Pediatric Use	Within Section 8.4, subsections with corresponding titles were created: (b) (4) "Functional Constipation (FC)," and "Irritable Bowel Syndrome with Constipation (IBS-C)." In the previously approved paragraph describing the findings in the clinical GC-C ontogeny study, the results were removed ("no age dependent trend in GC-C intestinal expression in children 2 to less than 18 years of age") (b) (4) (b) (4) the information is also redundant to text already appropriately included in Section 5.1 *Risk of Serious Dehydration in Pediatric Patients Less Than 2 Years of Age*. The text in the "Irritable Bowel Syndrome with Constipation (IBS-C)" subsection was added to describe the basis for approval as described in the FDA guidance for industry *Pediatric Information Incorporated Into Human*

	Prescription Drug and Biological Product Labeling (March 2019). The following information was added: "The safety and effectiveness of LINZESS for the treatment of IBS-C have been established in pediatric patients 7 years of age and older. Use of LINZESS for this indication is supported by evidence from adequate and well-controlled studies in adults and pediatric patients 7 to 17 years of age. The safety of LINZESS in adult and pediatric patients in these clinical studies was similar *[see Adverse Reactions (6.1) and Clinical Studies (14.2)]*."
14 CLINICAL STUDIES	14.2 Irritable Bowel Syndrome with Constipation [IBS-C] in Pediatric Patients 7 Years of Age and Older The proposed description of the pediatric clinical study of IBS-C was revised to include baseline demographics and relevant enrollment criteria. The clinical study description eliminated the specifics (i.e., dosage, demographics) of the higher than recommended dosage group (i.e., 290 mcg once daily). A summary statement regarding the rationale for the approval of the 145 mcg once daily dosage is provided (i.e., the higher dosage did not demonstrate additional treatment benefit). The section describes only the result of the primary endpoint analysis (the proportion of patients who achieved at least a 30% reduction in abdominal pain and an increase of at least 2 spontaneous bowel movements [SBMs]/week from baseline for at least 6 out of 12 weeks [i.e., combined responder]). The efficacy results are limited to the recommended 145 mcg once daily dosage, and the reported results are based on the agreed-upon alternative analyses that only require subjects to have at least 4 completed evening eDiary entries in the analysis week to be considered a weekly responder. The primary endpoint (combined responder rate) as well as the components (abdominal pain responder and SBM responder) are provided in table format. The review team did not agree with the Applicant's proposal (b) (4) [redacted] The review team did not agree to include (b) (4) [redacted] The review team agreed to describe in text following the table that "Abdominal pain and SBM frequency improved during week 1 and improvement was maintained throughout the remainder of the 12-week treatment period." Of note, the clinical study supporting the new pediatric IBS-C indication was moved to Section 14.2 to keep the adult (Section 14.1) and pediatric IBS-C subsections in consecutive sequence. All subsequent subsections (14.3 through 14.4) supporting previously approved indications (i.e., "CIC in Adults" and "FC in Pediatric Patients 6 Years of Age and Older") have been renumbered accordingly.

Source: Applicant's proposed PI submitted May 6, 2025; FDA recommended revisions sent to the Applicant on September 30, 2025; revised version submitted by the Applicant on October 8, 2025; FDA recommended revisions sent to the Applicant on October 21, 2025; revised version submitted by the Applicant on October 23, 2025.
[1] Some sections may not be included because those sections may not have major issues (or changes).
[2] The finalized PI is the PI that will be approved or is close to being approved
Abbreviations: PI, prescribing information

12 Risk Evaluation and Mitigation Strategies (REMS)

No REMS are recommended as a result of this review.

13 Postmarketing Requirements and Commitment

No postmarketing requirements or commitments are recommended as a result of this review.

14 Designated Signatory Authority – Division Director (Clinical) Comments

I concur with the recommendation of the review team to approve supplemental NDA 202811/S-022 for Linzess (linaclotide) to expand the indications to include pediatric patients 7 years of age and older with irritable bowel syndrome with constipation (IBS-C). Data submitted in this sNDA support the conclusion that the benefit of treatment with Linzess in the intended population outweigh the identified risks. Linzess will be the first product to be approved to treat pediatric patients with IBS-C. The recommended dosage is 145 mcg orally once daily.

The efficacy of Linzess for the treatment of IBS-C in pediatric patients 7 years of age and older is supported, in part, by extrapolation of efficacy from adequate and well-controlled trials in adults with IBS-C, relying upon the similarity between adult and pediatric patients in disease course and the expected response to treatment. As linaclotide is minimally absorbed and acts locally in the gut, it is difficult or impossible to rely upon correlation between systemic drug exposures and therapeutic response; therefore, assessment of dose-response relationship using clinical endpoint(s) is needed as part of the extrapolation framework to establish substantial evidence of effectiveness (SEE).

As part of the collective evidence to establish SEE, the Applicant also submitted results from a phase 3, multicenter, randomized, double-blind trial (LIN-MD-64) that assessed Linzess 145 mcg and 290 mcg once daily in 108 pediatric subjects 7 to 17 years of age. The primary endpoint was the proportion of subjects who achieved at least a 30% reduction in abdominal pain and an increase of at least 2 spontaneous bowel movements (SBMs) per week from baseline for at least 6 out of 12 weeks; this primary endpoint definition is closely related to that assessed in adult trials. Although the primary analysis failed to meet prespecified success criteria in LIN-MD-64, the high rates of missing data likely due to the burdensome twice-daily eDiary requirement (compared to the once-daily eDiary requirement in the adult trials) and the subsequent use of conservative missing data rules with non-responder imputation (NRI) raised concerns about the reliability of the results from the primary statistical analysis. The review team's sensitivity analyses that modified the criteria required for data to be non-missing (to align more closely with the approach in the adult trials), while maintaining conservative NRI for missing data, yielded nominally significant results. In addition, secondary and exploratory endpoints further supported the treatment effect.

I agree with the review team that the collective evidence from adequate and well-controlled trials in adults and the submitted pediatric trial data establish a meaningful benefit for Linzess in the treatment of IBS-C in pediatric patients 7 years of age and older.

The safety of Linzess in pediatric patients with IBS-C was similar to that seen in adults with IBS-C and in trials of other related indications; no new safety signals were identified. Diarrhea remains the most common adverse reaction in patients treated with Linzess and is reflected in the Prescribing Information (PI).

Although two dosages were studied, the higher dosage group (i.e., 290 mcg once daily) did not demonstrate clear treatment benefit beyond that demonstrated with the 145 mcg once daily dosage. In addition, there was a single case of severe diarrhea in a pediatric patient with IBS-C treated with 290 mcg once daily dosage, which was added to the Warnings and Precautions of the PI. Thus, I agree with the review team to approve the 145 mcg once daily dosage.

The final PI and Medication Guide (MG) incorporating pediatric information will be adequate to communicate the potential risks to healthcare providers and patients; a REM will not be required.

This sNDA submission fulfills PMR 1915-3 issued at the time of NDA approval for the adult IBS-C indication and addresses the following studies included in the Pediatric Written Request (PWR):

> PMR 1915-3: A safety and efficacy study in pediatric patients with irritable bowel syndrome with constipation ages seven years up to 17 years treated with Linzess (linaclotide).
>
> PWR Study 02: A randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study for the treatment of irritable bowel syndrome with constipation (IBS-C) in children ages 7 to 17 years.
>
> PWR Study 04: A randomized, double-blind, parallel-group confirmatory safety and efficacy study for the treatment of IBS-C in children and adolescents 7 to 17 years of age.
>
> PWR Study 05: A long-term safety study enrolling children and adolescents with chronic idiopathic constipation (CIC) or IBS-C who completed Studies 01, 02, 03 or 04

Pediatric Exclusivity Board convened on September 17, 2025, to discuss the studies conducted under the WR and concurred with the Division that the Applicant met all the terms of the WR; Pediatric Exclusivity was granted, effective October 15, 2025.

In addition, the Pediatric Review Committee (PeRC) convened on October 7, 2025, and concurred with the Division on the fulfillment of PMR 1915-3.

No additional post-marketing studies will be required.

15 Appendices

15.1. References

Literature

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Guidance for Industry

Guidance for Industry *Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling* (March 2019).

Guidance for Industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998).

Guidance for Industry *E11A Pediatric Extrapolation* (December 2024).

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): LIN-MD-63, LIN-MD-64, LIN-MD-66

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 823		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator:0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

Bioanalytical Method and Analysis for Linaclotide and MM-419447 Quantification

The PK samples obtained from Study LIN-MD-63 were analyzed using a validated liquid chromatography with tandem mass spectrometry method. The method was the same method that was previously validated and utilized for analysis of PK samples obtained from Study LIN-MD-62 under the sNDA for functional constipation in pediatrics (NDA 202811/ S-021). Refer to the Multidisciplinary Review for the previous supplement for the review of the method validation.

The bioanalysis performance of in-study sample analysis is summarized in Table 31. Incurred sample reanalysis (IRS) was not conducted per test site standard operating procedure, as there were only a few samples with concentrations greater than the lower limit of quantification. All samples were analyzed within the established stabilities for the method excluding one sample (Subject (b) (6)). This sample was analyzed for linaclotide outside the established long-term storage stability (31 days at -20°C, and 282 days at -80°C).

The review team found no issues from the bioanalytical method and bioanalysis that would affect the conclusion of the clinical pharmacology review.

Table 31. Summary of Bioanalysis Performance Results

Clinical Study ID	LIN-MD-63
Bioanalysis Report ID and Title	AB-0124-RB-DS-RPT-01, LC-MS/MS Analysis of Linaclotide and MM-419447 in Human Plasma (K_2EDTA) in Support of (b) (4) Study Number LIN-MD-63
Calibration range	0.100 to 5.00 ng/mL for both linaclotide and MM-419447
QC concentrations	0.300 ng/mL (QC-Low), 1.00 ng/mL (QC-Mid), 4.00 ng/mL (QC-High), and 250.0 ng/mL (QC-Dil)
Linaclotide: QC Low, Mid, High accuracy (% Bias)	3.0-4.8
Linaclotide: QC Low, Mid, High precision (% CV)	6.8-10.7
MM-419447: QC Low, Mid, High accuracy (% Bias)	-4.3-1.5
MM-419447: QC Low, Mid, High precision (% CV)	7.7-13.7
Sample storage temperature	-80°C upon receipt

Source: Based on Applicant's Bioanalysis Report, AB-0124-RB-DS-RPT-01

15.4. LIN-MD-63

Prior to initiating their phase 3 study, the Applicant conducted a randomized, placebo-controlled, phase 2 dose-finding study, LIN-MD-63. Although only a limited number of subjects received the linaclotide 145 mcg and 290 mcg doses in this study, the inclusion of a placebo group allows this study to directly compare pediatric subjects receiving linaclotide with pediatric subjects receiving placebo. Additionally, the population and study design of LIN-MD-63 and LIN-MD-64 were, except for the duration of the DBTP, generally similar. Therefore, the results (e.g., weekly SBM frequency) for the placebo group in Lin-MD-63 provide another benchmark for the results in LIN-MD-64.

Study Design

LIN-MD-63 was a phase 2 randomized, double-blind, placebo-controlled study of linaclotide in pediatric subjects 7 to 17 years of age with a diagnosis of IBS-C that included a 4-week DBTP. At the start of the DBTP, subjects 7-11 years were randomized in a 1:1:1:1 ratio to receive either Dose A, Dose B, Dose C, or Placebo and subjects 12-17 year olds were randomized 1:1:1:1:1 to receive either Dose A, Dose B, Dose C, the approved adult dose of 290 mcg, or placebo. Dosing regimens are defined in Figure 4. The primary endpoint was the CFB in 4-week SBM frequency rate during the DBTP and the secondary endpoints included CFB in 4-week averages of other IBS-C symptoms (e.g., abdominal pain score, stool consistency, straining, abdominal bloating). The final sample size in the randomized population was only 101 subjects. Although the study initially planned to enroll 260 subjects, challenges with recruitment resulted in the Applicant terminating the study early. See the Type C meeting minutes dated June 21, 2019, for additional discussion regarding the study's early termination.

Figure 4: Double-blind Dosing Regimen, LIN-MD-63

		4-Week Treatment Period			
Age Group	**Weight**	**Linaclotide Dose A**	**Linaclotide Dose B**	**Linaclotide Dose C**	**Approved Adult Dose**
Participants 7 -11 years[a]					
	18 to < 35 kg	18 µg	36 µg	72 µg	—
		placebo	placebo	placebo	—
	≥ 35 kg	36 µg	72 µg	145 µg	—
		placebo	placebo	placebo	—
Participants 12 -17 years[b]					
		36 µg	72 µg	145 µg	290 µg[c]
		placebo	placebo	placebo	placebo

[a] Participants 7 to 11 years of age received linaclotide or placebo in a liquid oral solution or solid oral capsules.
[b] Participants 12 to 17 years of age received linaclotide or placebo in a solid oral capsule.
[c] Approved adult dose of 290 µg was for safety and exploratory efficacy only.
Source: Clinical Study Report, Table 9.1.4-1 (page 15).

Study Results

Citing potential concerns with the robustness of statistical inference due to the reduced sample size, SAP amendment 1 (dated August 16, 2019, submitted February 28, 2020) modified the statistical analysis to indicate that only descriptive statistics would be provided for all efficacy endpoints. A brief presentation of the results is provided below.

Table 32 summarizes the demographic characteristics of subjects in LIN-MD-63. The majority of subjects were female (67.3%), White (65.3%), and between 12 and 17 years old (59.4%).

Table 32: Demographic Characteristics (Randomized Population, LIN-MD-63)

	Placebo N=19	Lin Dose A N=29	Lin Dose B N=21	Lin Dose C N=24	Lin 290 mcg N=8	Total N=101
Age, years						
Mean (SD)	11.9 (2.6)	11.9 (3.0)	12.7 (3.5)	12.4 (3.3)	13.5 (1.8)	12.3 (3.0)
Median	12.0	12.0	13.0	12.5	13.0	12.0
IQR	10.0, 13.0	10.0, 15.0	9.0, 16.0	10.0, 15.5	12.0, 14.5	10.0, 15.0
Min, Max	7, 16	7, 17	8, 17	7, 17	12, 17	7, 17
Age Group, n (%)						
7-11 Years	8 (42.1)	13 (44.8)	9 (42.9)	11 (45.8)	0	41 (40.6)
12-17 Years	11 (57.9)	16 (55.2)	12 (57.1)	13 (54.2)	8 (100.0)	60 (59.4)
Sex, n (%)						
Female	13 (68.4)	19 (65.5)	15 (71.4)	16 (66.7)	5 (62.5)	68 (67.3)
Male	6 (31.6)	10 (34.5)	6 (28.6)	8 (33.3)	3 (37.5)	33 (32.7)
Race, n (%)						
Black or African American	7 (36.8)	10 (34.5)	6 (28.6)	7 (29.2)	1 (12.5)	31 (30.7)
White	12 (63.2)	17 (58.6)	15 (71.4)	16 (66.7)	6 (75.0)	66 (65.3)
Multiple	0	2 (6.9)	0	1 (4.2)	1 (12.5)	4 (4.0)
Ethnicity, n (%)						
Hispanic or Latino	4 (21.1)	7 (24.1)	5 (23.8)	7 (29.2)	3 (37.5)	26 (25.7)
Not Hispanic or Latino	15 (78.9)	22 (75.9)	16 (76.2)	17 (70.8)	5 (62.5)	75 (74.3)
Country, n (%)						
Canada	0	0	1 (4.8)	0	0	1 (1.0)
USA	19 (100.0)	29 (100.0)	20 (95.2)	24 (100.0)	8 (100.0)	100 (99.0)
Weight group, n (%1)						
Overall						
≥ 18 to < 35 kg	1 (5.3)	5 (17.2)	4 (19.0)	2 (8.3)	1 (12.5)	13 (12.9)
≥ 35 kg	18 (94.7)	24 (82.8)	17 (81.0)	22 (91.7)	7 (87.5)	88 (87.1)
7-11 years						
≥ 18 to < 35 kg	1 (12.5)	5 (38.5)	4 (44.4)	2 (18.2)	--	12 (29.3)
≥ 35 kg	7 (87.5)	8 (61.5)	5 (55.6)	9 (81.8)	--	29 (70.7)
12-17 years						
≥ 18 to < 35 kg	0	0	0	0	1 (12.5)	1 (1.6)
≥ 35 kg	11 (100)	16 (61.5)	12 (55.6)	13 (81.8)	7 (87.5)	60 (98.4)

Source: Based on Clinical Study Report Table 10-4 (pages 29-30), Table 10-5 (pages 30-31), Table 10-6 (pages 32-33).
Verified by reviewer using ADSL.xpt
Abbreviations: IQR = interquartile range; max=maximum; min=minimum; N=number of subjects in population treatment

group; n=number of subjects in subgroups; SD=standard deviation.

Table 33 summarizes baseline disease characteristics of subjects in LIN-MD-63. At baseline, the average number of SBM per week was 1.3, the average abdominal pain score was 2.5, and the average stool consistency score was 2.2. Overall, the demographics and baseline disease characteristics in Study LIN-MD-63 were similar across arms, and similar to those characteristics in Study LIN-MD-64.

Table 33: Baseline Disease Characteristics (Randomized Population, LIN-MD-63)

	Placebo N=19	Lin Dose A N=29	Lin Dose B N=21	Lin Dose C N=24	Lin 290 mcg N=8	Total N=101
SBM weekly frequency						
Mean (SD)	1.0 (0.5)	1.3 (1.0)	1.4 (1.0)	1.4 (0.7)	1.2 (0.8)	1.3 (0.8)
Median	1.0	1.0	1.4	1.4	1.0	1.0
IQR	0.5, 1.4	0.5, 2.4	1.0, 2.4	1.0, 1.9	0.5, 1.9	0.5, 1.9
Min, Max	0, 2	0, 3	0, 3	0, 2	0, 2	0, 3
Abdominal pain[a]						
Mean (SD)	2.3 (0.7)	2.5 (0.8)	2.9 (0.8)	2.2 (0.8)	2.6 (1.2)	2.5 (0.8)
Median	2.3	2.6	2.7	2.1	2.4	2.5
IQR	1.8, 2.7	2.0, 2.9	2.4, 3.6	1.6, 2.7	1.7, 3.8	1.8, 3.0
Min, Max	1, 3	1, 4	2, 4	1, 4	1, 4	1, 4
Stool consistency						
Mean (SD)	2.4 (1.2)	2.1 (0.8)	2.3 (0.8)	1.9 (0.7)	2.4 (1.0)	2.2 (0.9)
Median	2.0	2.0	2.3	2.0	2.2	2.0
IQR	1.5, 2.8	1.7, 2.5	2.0, 2.8	1.4, 2.5	1.6, 3.1	1.6, 2.8
Min, Max	1, 6	1, 4	1, 4	1, 3	1, 4	1, 6
Missing	2	4	4	0	0	10
Abdominal bloating[b]						
Mean (SD)	1.9 (1.0)	2.3 (1.1)	2.6 (1.1)	2.3 (1.0)	2.3 (1.5)	2.3 (1.1)
Median	1.8	2.5	2.9	2.3	2.4	2.3
IQR	1.1, 2.8	1.6, 2.9	1.9, 3.3	1.3, 3.0	1.2, 3.5	1.5, 3.1
Min, Max	0, 4	0, 4	0, 4	0, 4	0, 4	0, 4

Source: Based on Clinical Study Report Table 14.1-5.1 (page 97-98). Verified by reviewer using ADEFF.xpt.
[a] Based on morning and evening assessments.
[b] Based on evening assessments
Abbreviations: IQR = interquartile range; max=maximum; min=minimum; N=number of subjects in population treatment group; n=number of subjects in subgroups; SBM = spontaneous bowel movement; SD=standard deviation.

Table 34 summarizes electronic diary compliance. Similar to LIN-MD-64, the overall compliance was relatively low. The percentage of days with complete entries was only 72.6%.

Table 34: Electronic Diary Compliance (ITT Population, LIN-MD-63)

	Placebo N=19	Lin Dose A N=29	Lin Dose B N=21	Lin Dose C N=23	Lin 290 mcg N=8	Total N=100

Percentage of complete days, DBTP						
Mean (SD)	68.0 (20.8)	67.9 (24.2)	72.7 (18.9)	77.4 (20.2)	86.5 (9.4)	72.6 (21.1)
Median	73.3	78.1	81.5	82.1	89.3	80.4
IQR	55.4, 85.7	56.5, 82.8	60.3, 85.3	70.7, 89.7	81.6, 93.0	63.7, 86.2
Min, Max	11, 90	1, 93	21, 93	1, 100	68, 97	1, 100

Source: Based on Clinical Study Report Table 14.2-4 (page 170). Verified by reviewer using ADEFF.xpt
Abbreviations: IQR = interquartile range; max=maximum; min=minimum; N=number of subjects in population treatment group; n=number of subjects in subgroups; SD=standard deviation.

Table 35 summarizes the results for the primary endpoint. The change from baseline in 4-week SBM frequency rate was nominally higher in each treatment group, as compared to the placebo group, and the numerical improvement in SBM frequency increased with increasing linaclotide dose.

Table 35: Primary Efficacy Analysis, Change from Baseline in 4-Week Overall SBM Frequency Rate (ITT Population, LIN-MD-63)

	Placebo N=19	Lin Dose A N=29	Lin Dose B N=21	Lin Dose C N=23	Lin 290 ug N=8
Change From Baseline					
Mean (SD)	1.45 (1.38)	1.99 (2.35)	2.30 (2.63)	2.68 (2.77)	3.22 (2.19)
Median	1.21	1.62	1.52	2.3	3.26
IQR	0.28, 2.53	0.53, 2.66	0.52, 2.94	0.72, 5.27	1.53, 4.55
Min, Max	-0, 5	-1, 10	-1, 8	-2, 7	0, 7

Source: Based on Clinical Study Report Table 11-1 (page 35). Verified by reviewer using ADEFF.xpt.
Abbreviations: IQR = Interquartile Range; N=number of subjects in population treatment group; n=number of responders; SBM = spontaneous bowel movement; SD = standard deviation

The results for the two abdominal pain endpoints are summarized in Table 36. The CFB in 4-week abdominal pain daytime symptoms in the 290 mcg linaclotide group was nominally larger than the CFB in the placebo group (-1.19 vs -0.65). However, the CFB in the other three linaclotide groups were generally similar to the CFB in the placebo group. Similar results were observed when using the post-hoc endpoint that averaged daytime and evening abdominal pain symptoms.

Table 36: Change from Baseline in 4-Week Abdominal Pain Symptoms, (ITT Population, LIN-MD-63)

	Placebo N=19	Lin Dose A N=29	Lin Dose B N=21	Lin Dose C N=23	Lin 290 mcg N=8
Abdominal pain daytime symtoms, mean (SD)	-0.65 (0.79)	-0.71 (0.98)	-0.56 (0.86)	-0.65 (0.95)	-1.19 (1.03)

Abdominal pain combined[a] symptoms, mean (SD)	-0.63 (0.93)	-0.68 (0.91)	-0.46 (0.90)	-0.61 (0.82)	-1.02 (0.95)

Source: Clinical Study Report Table 11.1 (page 35), Table 14.2-3.10 (page 163). Verified by reviewer using ADEFF.xpt.
[a]The change from baseline in 4-week abdominal pain based is based on the combined morning and evening assessment.
Abbreviations: CFB = Change from Baseline; N=number of subjects in population treatment group; SD = standard deviation

The results for other key secondary endpoints are summarized in Table 37. Across these endpoints, the improvements were generally larger in the linaclotide dose groups, as compared to the placebo group.

Table 37: Secondary Efficacy Endpoint Analyses (ITT Population, LIN-MD-63)

	Placebo N=19	Lin Dose A N=29	Lin Dose B N=21	Lin Dose C N=23	Lin 290 mcg N=8
CFB in stool consistency					
n	16	24	16	22	8
Mean (SD)	0.65 (0.95)	1.20 (1.07)	1.50 (1.27)	2.05 (1.35)	1.34 (0.81)
CFB in severity of straining					
n	17	24	16	22	8
Mean (SD)	-0.58 (0.91)	-0.78 (1.19)	-0.86 (0.99)	-1.22 (0.97)	-1.24 (1.04)
CFB in abdominal bloating[a]					
n	19	29	21	22	8
Mean (SD)	-0.44 (0.75)	-0.49 (0.97)	-0.51 (0.99)	-0.44 (0.82)	-0.60 (1.28)

Source: Clinical Study Report Table 11-1 (35). Verified by reviewer using ADEFF.xpt.
[a] Based on daytime assessment.
Abbreviations: CFB = Change from Baseline; N=number of subjects in population treatment group; n = number of subjects with non-missing values; SD = standard deviation

The linacolitde 290 mcg group only included 12-17 year old subjects. Therefore, differences in the age distributions between the placebo and linaclotide 290 mcg group could confound comparisons between these groups. However, analyses restricted to the 12-17 year old subgroup produced similar results (Table 38).

Table 38: Efficacy Endpoints in 12-17 year olds (ITT Population, LIN-MD-63)

	Placebo N=11	Lin Dose A N=16	Lin Dose B N=12	Lin Dose C N=13	Lin 290 ug N=8
CFB in SBM Frequency	0.67 (0.81)	2.09 (2.13)	2.92 (2.58)	2.97 (2.79)	3.22 (2.19)
CFB in combined	-0.54 (0.96)	-0.78 (1.04)	-0.43 (0.92)	-0.61 (0.91)	-1.02 (0.95)

abdominal pain					
CFB in stool consistency	0.45 (0.97)	1.64 (1.13)	1.60 (1.30)	2.42 (1.57)	1.34 (0.81)
CFB in severity of straining	-0.58 (1.09)	-1.19 (1.09)	-0.89 (1.05)	-1.23 (1.00)	-1.24 (1.04)
CFB in abdominal bloating[a]	-0.26 (0.86)	-0.55 (0.92)	-0.54 (1.11)	-0.30 (0.80)	-0.60 (1.28)

Source: Based Clinical Study Report Table 14.2-1.1.A (page 105), Table 14.2-2.1.A (p120), Table 14.2-2.3.A (p135) . Verified or created by reviewer using ADEFF.xpt.
[a] Based on daytime assessment
Abbreviations: CFB = Change from Baseline; N=number of subjects in population treatment group; n = number of subjects with non-missing values; SD = standard deviation

15.5. Assessment Tools

The Sponsors developed a novel PRO measure, the Pediatric IBS-C Symptom Diary (PIBSCSD), to assess 6 core symptoms of IBS-C (abdominal pain, abdominal bloating, stool frequency, stool consistency, incomplete evacuation, and straining), as described below:
5

Abdominal Pain - Daytime Question

For this parameter, participants will rate their abdominal pain during the daytime by responding to the following in the evening eDiary:

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

If "yes", then participant answers the following question:

- How much did your tummy hurt?

1 = a tiny bit

2 = a little

3 = some

4 = a lot

6

Abdominal Pain - Nighttime Question

For this parameter, participants will rate their abdominal pain during the nighttime by responding to the following in the morning eDiary:

- From bedtime last night until now, did your tummy hurt at all?
    - Yes
    - No

If "yes", then the participant answers the following question:

- How much did your tummy hurt?

    1 = a tiny bit

    2 = a little

    3 = some

    4 = a lot

7

Bowel Movement Frequency Questions

- Morning eDiary

  From bedtime last night until now, how many times did you poop (and poop came out)?
    - Enter number of times
- Evening eDiary

  From when you got up this morning until now, how many times did you poop (and poop came out)?
    - Enter number of times

  If response is > 0 BMs, then the participant answers the following question for each BM reported:

  When did you poop today?
    - In the morning (from when you woke up until lunch)
    - In the afternoon (from lunch until dinner)
    - In the evening (from dinner until bedtime)

8

Stool Consistency Question

"Use the card provided to choose the poop that is most like the poop you had."

Type 1 = looks like small hard lumps or balls, like pebbles

Type 2 = looks like fat sausage shape but lumpy and hard

Type 3 = looks like a sausage but with cracks on it

Type 4 = looks like a sausage or snake, smooth and soft

Type 5 = looks like chicken nuggets, soft smooth blobs

Type 6 = looks like oatmeal, fluffy mushy pieces

Type 7 = looks like a milkshake, watery

99 - I don't know

Rescue Medication Use Questions

- Morning eDiary

  From bedtime last night until now, did you take any medicine to help you poop, other than the study medicine?

  - Yes
  - No

- Evening eDiary

  From when you got up this morning until now, did you take any medicine to help you poop, other than the study medicine?

  - Yes
  - No

  If the response is 'yes", then the participant answers the following question:

  When did you take the medicine (NOT your study medicine) to help you poop?

  - In the morning (from when you woke up until lunch)
  - In the afternoon (from lunch until dinner)
  - In the evening (from dinner until bedtime)

Complete Spontaneous Bowel movement (CSBM)/Incomplete Evacuation

A CSBM is an SBM that is associated with a sense of complete evacuation. Participants will record their assessment of the sensation of incomplete evacuation for each BM by responding to the following in the morning and evening eDiaries:

- When you pooped, did it feel like there was more poop left inside that didn't come out?
    - Yes
    - No

10Straining With BM Question

For every BM, participants will assess the degree of straining by responding to the following in the morning and evening eDiaries:

- When you pooped, how hard did you push?

    0 = not hard at all

    1 = I pushed a tiny bit hard

    2 = I pushed a little hard

    3 = I pushed hard

    4 = I pushed very hard

11Abdominal Bloating - Daytime Question

For this parameter, participants will record their assessment of abdominal bloating during the day by responding to the following in the evening eDiary:

- From when you got up this morning until now, did your tummy FEEL big and full?
    - Yes
    - No

If "yes" then participant answers the following question:

- How big and full did your tummy FEEL?

    1 = a tiny bit

    2 = a little

    3 = medium

    4 = very

12Abdominal Bloating - Nighttime Question

For this parameter, participants will record their assessment of nighttime abdominal bloating by responding to the following in the morning eDiary:

- From bedtime last night until now, did your tummy FEEL big and full?
    - Yes
    - No

  If "yes", then the participant answers the following question:

- How big and full did your tummy FEEL?

  1 = a tiny bit

  2 = a little

  3 = medium

  4 = very

Source: Protocol, Amendment 1 (pages 53 - 57).

Unireview Signatures

DISCIPLINE AND TITLE OR ROLE	REVIEWER NAME	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/APPROVED
Regulatory	Kristina Luong	OND/ORO/DROII	3, 4.2 ☒ Authored ☐ Contributed ☐ Approved
Project Manager	**Signature:** KRISTINA N. LUONG -S Digitally signed by KRISTINA N. LUONG -S Date: 2025.10.27 15:04:31 -04'00'		

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/s/

SUNA C SEO
11/04/2025 02:28:51 PM

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