

Linzess (linaclotide)

NDA/BLA Multi-Disciplinary Review and Evaluation

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Established/Proper Name	Linaclotide
(Proposed) Trade Name	Linzess
Pharmacologic Class	Guanylate cyclase-C agonist
Applicant	AbbVie Inc.
Dosage form	capsules
Applicant proposed Dosing Regimen	72 µg orally once daily
Applicant Proposed Indication(s)/Population(s)	Treatment of functional constipation (FC) in (b) (4) 6 to 17 years of age
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	197118003 Constipation – functional (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of functional constipation (FC) in pediatric patients 6 to 17 years of age
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	197118003 Constipation – functional (disorder)
Recommended Dosing Regimen	72 µg orally once daily

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OPQ = Office of Pharmaceutical Quality

OPDP = Office of Prescription Drug Promotion

OSI = Office of Scientific Investigations

OSE = Office of Surveillance and Epidemiology

DMEPA = Division of Medication Error Prevention and Analysis

DPV = Division of Pharmacovigilance

DRISK = Division of Risk Management

DCOA = Division of Clinical Outcome Assessment

PFSS = Patient-Focused Statistical Support

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Glossary

AE	adverse event
ANCOVA	analysis of covariance
AR	adverse reaction
BLA	biologics license application
BM	bowel movement
CFB	change from baseline
CIC	chronic idiopathic constipation
COA	clinical outcome assessment
CSBM	complete spontaneous bowel movement
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DPV-I	Division of Pharmacovigilance I
eCDF	empirical cumulative distribution function
FAERS	FDA Adverse Event Reporting System
FC	functional constipation
FDA	Food and Drug Administration
GC-C	guanylate cyclase-C
IBS-C	irritable bowel syndrome with constipation
IND	Investigational New Drug
LAR	legally authorized representative
MAR	missing at random
mITT	modified intent to treat
MMRM	mixed model for repeated measures
NDA	new drug application
NMAR	not missing at random
p-BSFS	Pediatric Bristol Stool Form Scale
PFCSD	Pediatric Functional Constipation Symptom Diary
PK	pharmacokinetics
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PWR	pediatric written request
REMS	risk evaluation and mitigation strategy
RM	rescue medication
SAE	serious adverse event
SBM	spontaneous bowel movement
sNDA	supplemental new drug application
TEAE	treatment emergent adverse event
VRS	verbal rating scale
WR	written request

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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 µg, 145 µg, and 290 µg 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 a safety and efficacy study in pediatric patients with CIC.¹ In the years following the approval, the original PMR for pediatric CIC was released and eventually replaced with two PMRs for pediatric CIC studies in different age groups, and a Best Pharmaceuticals for Children Act Written Request (WR) was issued that described the designs of studies to be conducted. This efficacy supplement is intended to fulfill the following PMR and address the three studies listed below that are described in the pediatric WR (PWR):

- PMR 2161-3: Conduct a safety and efficacy study in pediatric patients with chronic idiopathic constipation ages 6 to 17 years treated with Linzess (linaclotide).
- PWR Study 01: Randomized, double-blind, placebo-controlled, parallel group, dose-ranging study for the treatment of chronic idiopathic constipation in children ages 6 to 17 years.
- PWR Study 03: Randomized, double-blind, placebo-controlled, parallel group confirmatory study for the treatment of chronic idiopathic constipation in children ages 6 to 17 years.
- PWR 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 04.²

¹ In clinical practice, chronic idiopathic constipation (CIC) and functional constipation 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.

² Study 02 is a randomized, double-blind, placebo-controlled, parallel group, dose-ranging study for the treatment of IBS-C in children ages 7 to 17 years. Study 04 is a randomized, double-blind, parallel group confirmatory safety and efficacy study for the treatment of IBS-C in children ages 7 to 17 years.

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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 functional constipation (FC) in pediatric patients 6 to 17 years of age.” To support this submission, the Applicant conducted Study LIN-MD-64, a phase 3 randomized, double-blind, controlled study of linaclotide 72 µg versus placebo in 328 subjects 6 to 17 years of age who met modified Rome III criteria for FC. The use of linaclotide in this pediatric population relies upon extrapolation of efficacy from adequate and well-controlled studies that supported approval of linaclotide in adults with CIC. In general, similar products are used to treat constipation in adults and pediatric patients, and the disease definition, clinical manifestations, and outcomes to measure response to treatment (e.g., stool frequency, stool consistency) are considered sufficiently similar between the adult and pediatric population with constipation; however, there are some knowledge gaps (e.g., there may be age-related factors that contribute to constipation) and information from controlled studies in pediatric patients are limited as there are no products approved for treating pediatric FC.

In Study LIN-MD-64, linaclotide demonstrated a statistically significant improvement over placebo on the primary endpoint of 12-week spontaneous bowel movement (SBM) frequency rate. The mean baseline SBM frequency rate was 1.16 SBMs/week for linaclotide and 1.28 SBMs/week for placebo. The least square mean change from baseline in 12-week SBM frequency rate was 2.58 for linaclotide and 1.33 for placebo, a treatment difference of 1.25 ($p < 0.0001$; 95% CI = 0.67, 1.83). Although the study achieved statistical significance on the multiplicity controlled secondary endpoint of change from baseline in stool consistency (using the pediatric Bristol Stool Form Scale [p-BSFS]), there was insufficient evidence to support that the observed treatment difference for linaclotide versus placebo was clinically meaningful. Exploratory analyses that assessed reductions in straining and use of rescue medication further supported a benefit for linaclotide over placebo. Additionally, the adult studies that supported approval of linaclotide in CIC assessed the same endpoints of change from baseline in SBM frequency, stool consistency, and straining with bowel movements; the results were generally consistent across the adult and pediatric studies.

The collective evidence from adult and pediatric studies established substantial evidence of effectiveness for linaclotide and supports expanding the indication to include the treatment of FC in patients 6 to 17 years of age.

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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 with constipation (IBS-C) and chronic idiopathic constipation (CIC) in adults. In this NDA supplement, the Applicant proposes the added indication of linaclotide 72 µg once daily for treatment of functional constipation (FC) in pediatric patients 6 to 17 years of age.

Functional constipation (FC), defined by the Rome diagnostic criteria, is a common condition experienced by children and adolescents. Contributing factors can include, but are not limited to, stool withholding behaviors (e.g., due to painful defecation), diet, and genetics. Untreated FC can negatively affect the child or adolescent's quality of life and lead to further problems such as anal fissures or cystitis. There are currently no FDA approved therapies for treating pediatric patients with FC. Treatment typically includes dietary modification and off-label treatments such as nonprescription osmotic, stimulant, or lubricant laxatives, and stool softeners.

To support this submission, the Applicant conducted Study LIN-MD-64, a phase 3 randomized, double-blind, controlled study of linaclotide 72 µg versus placebo in 328 subjects 6 to 17 years of age who met modified Rome III criteria for functional constipation (FC). The data submitted from Study LIN-MD-64 support the safety and effectiveness for linaclotide 72 µg in treatment of FC in pediatric patients 6 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 CIC (Studies MCP-103-303, LIN-MD-01, and MCP-103-309). In general, similar products are used to treat constipation in adults and pediatric patients, and the disease definition, clinical manifestations, and objective outcomes to measure response (e.g., stool frequency, stool consistency) to treatment are considered sufficiently similar between the adult and pediatric population with constipation; however, there are some knowledge gaps (e.g., there may be age-related factors that contribute to constipation) and information from controlled studies in pediatric patients are limited as there are no products approved for treating pediatric FC.

Study LIN-MD-64 achieved statistical significance on the prespecified primary endpoint of change from baseline in 12-week spontaneous bowel movement (SBM) frequency rate (calculated as SBMs per week, over 12 weeks). The mean baseline SBM frequency rate was 1.16 SBMs/week for linaclotide and 1.28 SBMs/week for placebo. The least square mean change from baseline in 12-week SBM frequency rate was 2.58 for linaclotide and 1.33 for placebo, a treatment difference of 1.25 ($p < 0.0001$; 95% CI = 0.67, 1.83). Additionally, the results from the adult CIC study that also evaluated the 72 µg dose (MCP-103-309) showed generally similar treatment differences for 12-week SBM frequency rate.

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Study LIN-MD-64 also included a secondary endpoint of change from baseline in 12-week stool consistency using the pediatric Bristol Stool Form Scale (p-BSFS). The mean baseline stool consistency, using the p-BSFS scale from 1 (hard lumps of stool) to 7 (watery stool), was 2.37 for linaclotide and 2.40 for placebo. The least square mean change from baseline was 1.11 for linaclotide and 0.69 for placebo, a treatment difference of 0.42 ($p=0.0001$; 95% CI = 0.21, 0.64).

The Applicant conducted anchor-based analyses of patient- or caregiver-reported assessments of global severity and change in signs/symptoms to aid in determining whether the results represented clinically meaningful changes; however, the anchor-based methods for this study were not interpretable [REDACTED] (b) (4). While anchor-based methods remain the preferred approach to defining thresholds for clinically meaningful within-patient changes in COA scores, in this specific circumstance, an alternative approach for interpreting clinical meaningfulness was possible due to the nature of the data (the inherent observability of SBM frequency) and availability of established Rome criteria that define a diagnostic threshold for weekly bowel movement frequency, information regarding generally normal pediatric bowel habits, and supportive data from other secondary and exploratory endpoints (e.g., rescue medication use throughout the study).

Of the factors that contributed to the team's determination of the adequacy of an alternative approach, the observability of stool frequency was important because Study LIN-MD-64 included subjects from various stages of child and adolescent development (6 to 17 years) and offered the option for younger subjects to have their data reported by a caregiver, based on the caregiver interviewing the subject. Therefore, the review team considered measurement of observable signs (i.e., counting SBMs) to have greater interpretability across the range of respondents than unobservable symptoms (which only each individual patient could reliably report, using age-appropriate COAs). The review team confirmed interpretability of primary endpoint data by assessing results by COA administration method (i.e., subject self-report versus caregiver report), which showed that the treatment difference for linaclotide versus placebo on the primary endpoint was consistent across the two administration methods.

Given the lack of interpretable anchor-based analyses, the review team used an alternate approach to assess whether the statistically significant result for the primary endpoint (change from baseline in 12-week stool frequency rate) was clinically meaningful. The team evaluated the available data for observed post-baseline mean SBM frequency rates for linaclotide (3.41 SBMs/week) and placebo (2.29 SBMs/week) and considered available information regarding diagnostic criteria for pediatric FC and normal ranges for stool frequency in children age 6 years and older. The team noted that the post-baseline mean for linaclotide no longer met the stool frequency component of the Rome criteria for pediatric FC ("two or fewer defecations in the toilet per week") and corresponded to a stool frequency that can generally be considered normal in children and adolescents (3 BMs per week). In contrast, the post-baseline mean for placebo did not achieve the same thresholds.

The review team also considered the results of exploratory analyses of reductions in rescue medication use and straining to further inform characterization of potential clinical benefit. An exploratory analysis of rescue medication use showed notably lower weekly rates of use for

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linaclotide-treated subjects versus placebo. After Week 6, weekly rates of rescue medication use for linaclotide-treated subjects were approximately half the rates of the placebo group, and at Week 12, 10.7% of linaclotide-treated subjects used rescue medication versus 21.9% in the placebo group. Overall, fewer linaclotide-treated subjects (52.1%) used at least one dose of rescue medication over the 12-week treatment than placebo (60.4%). Additionally, an exploratory analysis of change from baseline in 12-week straining favored linaclotide over placebo (-1.19 versus -0.75, respectively, on a scale of 0 to 4), but clinical meaningfulness of changes in straining could not be determined due to lack of interpretable anchor-based analyses.

The review team acknowledged that improvement in stool consistency is a clinically relevant outcome for patients with FC; however, insufficient evidence was provided to demonstrate that the statistically significant observed treatment difference in stool consistency for linaclotide versus placebo was clinically meaningful. The observed post-baseline mean stool consistency results were 3.50 for linaclotide and 3.08 for placebo, which appeared to be similar based on the p-BSFS (an ordinal scale for which values of 3 or 4 represent stool types that are neither overly hard nor overly soft) and appeared to no longer meet relevant Rome criteria related to stool consistency (“painful or hard bowel movements”). Interpretability of the data were further limited by the analysis of secondary endpoint results by COA administration method, which showed inconsistent treatment differences across the two administration methods, in that caregiver-reported data showed an inconclusive treatment difference between linaclotide and placebo.

In light of the unmet need for approved treatments for pediatric FC, the review team concluded that the pediatric study data, supported by efficacy data from adequate and well-controlled studies in adults with CIC, provided evidence of meaningful clinical benefit for linaclotide in pediatric patients ages 6 to 17 years with FC.

The safety of linaclotide was characterized through data obtained from the 4-week phase 2, randomized, double-blind, placebo-controlled (Study LIN-MD-62) and the 12-week phase 3 Study LIN-MD-64. Additionally, interim data from the ongoing open-label extension Study LIN-MD-66 were submitted, which provided longer term safety data for mean and median exposures of approximately 23 and 24 weeks, respectively, at the time of submission. In the Study LIN-MD-64, diarrhea was the most common treatment-emergent adverse event (TEAE) occurring in a greater proportion of subjects for linaclotide than placebo (4.3% versus 1.8%, respectively). Diarrhea-related dehydration was an adverse event of special interest (AESI) and occurred in one subject receiving linaclotide, resulting in permanent discontinuation. Serious adverse events (SAEs) and AE-related discontinuations were rare overall, and no deaths were reported. Additionally, the Division of Pharmacovigilance-I (DPV-I) was also consulted to conduct a search of postmarketing safety reports using the FDA Adverse Event Reporting System (FAERS). In the postmarketing safety review, DPV-I did not identify any new safety signals. 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 adult studies.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	<ul style="list-style-type: none"> FC is a common condition experienced by children and adolescents. There is no known underlying organic cause and etiology is usually multifactorial. Contributing factors can include, but are not limited to, withholding behaviors (e.g., due to painful defecation), diet, and genetics. Untreated FC can negatively affect the child or adolescent’s quality of life and lead to further problems such as anal fissures or cystitis. 	<ul style="list-style-type: none"> FC can have clinically significant impacts on the health and well-being of children and adolescents.
<u>Current Treatment Options</u>	<ul style="list-style-type: none"> No FDA-approved treatment options exist for pediatric patients with FC. Nonprescription osmotic laxatives (e.g., polyethylene glycol, lactulose, magnesium citrate), stimulant laxatives (e.g., senna, bisacodyl), lubricant laxatives (e.g., mineral oil), and stool softeners (e.g., docusate, mineral oil) are commonly used off-label for treatment of chronic constipation in pediatric patients. 	<ul style="list-style-type: none"> There is an unmet medical need for safe and effective therapies for treatment of pediatric FC.

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<p><u>Benefit</u></p>	<ul style="list-style-type: none"> • The Applicant conducted a phase 3 randomized, double-blind, controlled study of linaclotide 72 µg once daily versus placebo for 12 weeks in subjects 6 to 17 years of age meeting modified Rome III criteria for FC (study LIN-MD-64). • Linaclotide demonstrated statistically significant improvements over placebo for SBM frequency rate (primary endpoint) and stool consistency (secondary endpoint). • For the primary endpoint, the observed change from baseline in 12-week SBM frequency rate was 2.22 SBMs/week for linaclotide and 1.05 SBMs/week for placebo (p<0.0001), resulting in observed post-baseline means of 3.41 SBMs/week for linaclotide and 2.29 SBMs/week for placebo. Treatment differences were consistent across COA administration methods (subject self-report vs. caregiver-report). • For the secondary endpoint, the observed change from baseline in 12-week stool consistency (using the p-BSFS ordinal scale of 1 to 7) was 1.11 for linaclotide and 0.69 for placebo (p=0.0001), resulting in observed post-baseline means of 3.50 for linaclotide and 3.08 for placebo. • An exploratory analysis of rescue medication use showed fewer linaclotide subjects used rescue medication than placebo subjects (52.1% versus 60.4% used at least one dose of rescue medication over the 12-week treatment period). • An exploratory analysis of change from baseline in 12-week straining favored linaclotide over placebo (-1.19 versus -0.75 on a scale of 0 to 4). • Anchor-based analyses of clinically meaningful within-patient change were uninterpretable (b) (4) 	<ul style="list-style-type: none"> • Linaclotide demonstrated statistically significant improvements over placebo for SBM frequency rate (primary endpoint) and stool consistency (secondary endpoint). • Clinical meaningfulness could not be informed using anchor-based methods (b) (4) however, an alternative approach was possible in this case. • The observed post-baseline mean SBM frequency rates (3.41 SBMs/week for linaclotide vs 2.29 SBMs/week for placebo) no longer met the threshold for the weekly bowel movement frequency component of the Rome diagnostic criteria for FC (≤2 defecations in the toilet per week), and corresponded to a stool frequency that can generally be considered normal for the intended patient population. • Observed post-baseline mean stool consistency results, using the p-BSFS, for linaclotide (3.50) and placebo (3.08) achieved a mean stool type that was neither overly hard nor overly soft, and no longer met relevant Rome criteria related to stool consistency (“painful or hard bowel movements”). Additionally, treatment differences were not consistent across COA administration methods. • Exploratory analyses of reduction in straining favored linaclotide over placebo, although clinical meaningfulness could not be determined using anchor-based methods. • Exploratory analyses of reductions in use of rescue medication revealed lower rates of rescue medication use in the linaclotide group vs placebo over the 12-week treatment period. • 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 age 6 to 17 with FC.
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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><u>Risk and Risk Management</u></p>	<ul style="list-style-type: none"> • Diarrhea was the most common treatment emergent adverse event (TEAE) occurring at greater frequency in linaclotide versus placebo (4.3% versus 1.8%, respectively, in Study LIN-MD-64). • Dehydration related to diarrhea can have potentially serious outcomes in pediatric patients. 	<ul style="list-style-type: none"> • Diarrhea is a known risk of linaclotide use. Diarrhea was the most commonly reported TEAE. Only 1 subject reported severe diarrhea and diarrhea-related dehydration in the submitted datasets. • 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 adult studies.

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1.4. Patient Experience Data

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

<input checked="" type="checkbox"/>	The patient experience data that were submitted as part of the application include:	Section of review where discussed, if applicable
<input checked="" type="checkbox"/>	Clinical outcome assessment (COA) data, such as	
<input checked="" type="checkbox"/>	Patient reported outcome (PRO)	15.5, 15.6, 15.7
<input type="checkbox"/>	Observer reported outcome (ObsRO)	
<input type="checkbox"/>	Clinician reported outcome (ClinRO)	
<input type="checkbox"/>	Performance outcome (PerfO)	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies (e.g., submitted studies or scientific publications)	
<input type="checkbox"/>	Other: (Please specify):	
<input type="checkbox"/>	Patient experience data that were not submitted in the application, but were considered in this review:	
<input type="checkbox"/>	Input informed from participation in meetings with patient stakeholders	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Other: (Please specify):	
<input type="checkbox"/>	Patient experience data was not submitted as part of this application.	

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2. Therapeutic Context

2.1. Analysis of Condition

Functional constipation (FC) is a common condition experienced by approximately 14% of children and adolescents in the US (Robin et al. 2018). There is no known underlying organic cause and etiology is usually multifactorial. Contributing factors can include, but are not limited to, stool withholding behaviors (e.g., due to painful defecation), diet, and genetics. Untreated FC can negatively affect the child or adolescent's quality of life and lead to further problems such as anal fissures or cystitis.

Diagnosis of FC 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 functional constipation as follows (Hyams et al. 2016):

Table 1. Rome IV Diagnostic Criteria for Functional Constipation in Children/Adolescents

Must include two or more of the following occurring at least once per week for a minimum of 1 month with insufficient criteria for a diagnosis of IBS:

- Two or fewer defecations in the toilet per week in a child of a developmental age of at least 4 years
- At least one episode of fecal incontinence per week
- History of retentive posturing or excessive volitional stool retention
- History of painful or hard bowel movements
- Presence of a large fecal mass in the rectum
- History of large diameter stools which can obstruct the toilet
- 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 criteria³ were used in the clinical studies supporting this NDA supplement. However, the definition of FC is similar in Rome IV and Rome III, with the only difference being that Rome IV uses a 1-month duration of signs/symptoms to fulfill criteria for diagnosis whereas Rome III uses a 2-month duration (Russo et al. 2019).

2.2. Analysis of Current Treatment Options

No FDA-approved treatment options currently exist for pediatric FC. Treatment typically includes dietary modification and commonly used off-label treatments for chronic constipation in pediatric patients include nonprescription osmotic laxatives (e.g., polyethylene glycol, lactulose, magnesium citrate), stimulant laxatives (e.g., senna, bisacodyl), lubricant laxatives (e.g., mineral

³ The “modified” Rome III criteria used in LIN-MD-64 required all enrolled subjects to meet the criterion of “2 or fewer defecations[...] in the toilet per week,” plus at least one additional criterion from Rome III (retentive posturing or excessive volitional stool retention; painful or hard BMs; large diameter stools; large fecal mass; fecal incontinence). The original, unmodified Rome III criteria did not assign priority to “2 or fewer defecations[...] in the toilet per week,” but rather required patients to experience “two or more” of any listed criteria.

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oil), and stool softeners (e.g., docusate, mineral oil).

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing 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 under NDA 202811. The approved dosage for the treatment of IBS-C is 290 µg capsule taken orally once daily. The approved dosages for the treatment of chronic idiopathic constipation (CIC) are either 145 µg or 72 µg capsule taken orally once daily. The safety and efficacy of the 72-µg dose was established for CIC in supplement 10, approved on January 25, 2017.

This NDA is subject to multiple post-marketing requirements (PMRs) under the Pediatric Research Equity Act (PREA). At the time of original approval, PMR 1915-2 (“a safety and efficacy study in pediatric patients with chronic idiopathic constipation ages seven months up to 17 years treated with Linzess [linaclotide]”) was issued. This PMR was released on July 16, 2014 and replaced with PMR 2161-1 (“a safety and efficacy study in pediatric patients with chronic idiopathic constipation ages 2 to 17 years treated with Linzess [linaclotide]”), which was also released on April 30, 2015 and replaced with two PMRs: PMR 2161-2 (“a safety and efficacy study in pediatric patients with chronic idiopathic constipation ages 2 to 5 years treated with Linzess [linaclotide]”) and PMR 2161-3 (“a safety and efficacy study in pediatric patients with chronic idiopathic constipation ages 6 to 17 years treated with Linzess [linaclotide]”).

The NDA is also subject to 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]”). A phase 3 pediatric IBS-C study is currently ongoing, using a master protocol shared with the phase 3 pediatric FC study.

Under the Best Pharmaceuticals for Children Act, FDA issued a Written Request (WR) on March 11, 2016 to investigate the use of linaclotide for the treatment of IBS-C and FC in pediatric patients in response to the Applicant’s Proposed Pediatric Study Request submitted on August 3, 2015. An amended WR was issued on June 10, 2021 to reflect agreements on study designs of PMR studies.

This submission is intended to fulfill PREA PMR 2161-3 and address Studies 01 (“randomized, double-blind, placebo-controlled, parallel group, dose-ranging study for the treatment of chronic idiopathic constipation in children ages 6-17 years”), 03 (“randomized, double-blind, placebo-controlled, parallel group confirmatory study for the treatment of chronic idiopathic constipation in children ages 6-17 years”), and 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.

This product was co-developed by Allergan Sales, LLC and Ironwood Pharmaceuticals, Inc. The sNDA was originally submitted by Allergan Sales, LLC, and the Applicant name was formally changed to AbbVie Inc. on February 8, 2023 as a result of an acquisition of Allergan by AbbVie.

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3.2. Summary of Presubmission/Submission Regulatory Activity

Table 2. Summary of Regulatory History for Pediatric Functional Constipation Program

Date	Activity	Description
January 26, 2010	Type C meeting	Discussion centered around a proposed pediatric development plan for linaclotide in IBS-C and FC, including the overall approach to developing PRO and ObsRO measures to assess symptoms of FC and IBS-C in pediatric patients. FDA recommended that observer reports should only include events or behaviors that can be observed for patients who cannot respond for themselves.
March 22, 2011	Type B pre-NDA meeting (for adult populations)	FDA conveyed that appropriate PRO instruments for use in children in different age ranges were needed to pursue the proposed pediatric development plan.
August 30, 2012	Issuance of PREA PMRs	FDA issued PMR 1915-2 at the time of NDA approval for linaclotide in adults with IBS-C and CIC.
April 16, 2013	Type C meeting	Discussion centered around the interim PRO dossier for development of diaries proposed to evaluate symptoms of IBS-C and FC the pediatric population. FDA conveyed concern with ability to differentiate target populations of IBS-C versus FC in children and that content validity of the instruments cannot be determine if target patient populations are not well-defined. 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 by parents to young children.
February 5, 2014	Advice/Information Request	FDA advised narrowing the scope of items in the proposed PRO instruments to minimize risk of missing data due to responder burden and suggested evaluating responder burden, completion rates, and item reduction in a stand-alone validation study prior to use in clinical study.
July 16, 2014	PREA PMR Release and Reissue	FDA released Applicant from PMR 1912-2 and issued PMR 2161-1.
November 4, 2014	Type C meeting	Discussion centered around the pediatric development plan to fulfill PREA PMRs and plans for a future PPSR submission. FDA advised that the safety and efficacy of linaclotide should be studied in IBS-C and FC separately and that the population for the FC study be based on the Rome III criteria. FDA recommended that the safety and efficacy in children 6 to 17 years should be established prior to initiating studies in children 2 to 5 years old. FDA conveyed that, as an alternative to a stand-alone validation study, performing psychometric validation of the PRO instrument in the phase 2 study was acceptable with the understanding that the validation data obtained from the phase 2 study would be used to inform the finalized scoring algorithm used in confirmatory studies.
December 8, 2014	Teleconference (follow-up from November 4, 2014, type C meeting)	Follow-up to provide for clarifications of the PRO aspects of the pediatric development plan. Agreement on using the proposed Applicant-modified version of the BSFS instead of the published mBSFS-C.
March 17, 2015	Deferral extension granted	Deferral extension granted for PMR 2161-1 due to safety concerns in patients 2 to 5 years of age.

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Date	Activity	Description
April 30, 2015	PREA PMR Release and Reissue	FDA released Applicant from PMR 2161-1, reissued as PMRs 2161-2 and 2161-3 to allow for establishing safety and efficacy in children 6 to 17 years prior to initiating studies in children 2 to 5 years old.
March 11, 2016	Written Request	FDA issued WR to investigate use of linaclotide for the treatment of IBS-C and FC in pediatric patients.
February 19, 2019	Type B EOP2 meeting	Discussion centered around the proposed phase 3 confirmatory study (LIN-MD-64) and open label long-term safety study (LIN-MD-66). Agreement on proposal to use a change from baseline in 12-week SBM frequency rate for the primary efficacy endpoint in Study LIN-MD-64. FDA expressed concern with anchor items to inform meaningful change, and the Applicant agreed to submit a confirmatory psychometric analysis of the interim phase 3 data from Study LIN-MD-64 prior to unblinding.
April 30, 2020	Type C meeting	Discussion centered around the pediatric development program. Agreement that both patients with FC and IBS-C who received linaclotide, completed the lead-in study (LIN-MD-64), and enrolled in Study LIN-MD-66 within 28 days from last study intervention, may be considered to have continuous exposure when assessing the overall long-term safety. FDA advised that the actual duration during which patients received treatment with the study drug should be specific in the clinical study report and for safety analyses to be conducted separately in FC and IBS-C.
June 10, 2021	Written Request	FDA issued amended WR to reflect agreements on study designs of pediatric studies.
April 19, 2022	Type B pre-sNDA meeting	Discussion centered around the content and format of the planned sNDA submission for linaclotide for the treatment of pediatric patients 6 to 17 years with FC. FDA conveyed that an ISS should be submitted and agreed with the proposal to present data from each of the pediatric studies separately as part of the Summary of Clinical Efficacy in lieu of an ISE. FDA also agreed with the proposal to pool select safety data from Studies LIN-MD-62 and LIN-MD-64 for the ISS, and that it is reasonable not to pool that data with the data from Study LIN-MD-66.
September 28, 2022	Advice/Information Request	In response to a final confirmatory psychometric analysis report, FDA conveyed that it was premature to comment on the confirmatory psychometric analysis plan and that determination of what constitutes a meaningful within-patient change would be assessed during the sNDA review. FDA requested that results of psychometric analyses, including anchor-based analyses to evaluate meaningful within-patient change from baseline to Week 12 in primary and secondary efficacy endpoint scores using all patients in Study LIN-MD-64, be submitted with the sNDA submission.

Source: Reviewer's table, created from information in file for IND 063290 and NDA 202811

Abbreviations: BSFS, Bristol Stool Form Scale; CIC, chronic idiopathic constipation; EOP2, end of phase 2; FC, functional constipation; IBS-C, irritable bowel syndrome with constipation; ISE, integrated summary of effectiveness; ISS, integrated summary of safety; mBSFS-C, modified Bristol Stool Form Scale for Children; ObsRO, observed reported outcome; PMR, postmarketing request; PPSR, Proposed Pediatric Study Request; PREA, Pediatric Research Equity Act; PRO, patient reported outcome; SBM, spontaneous bowel movement; sNDA, supplemental new drug application; WR, written request

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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#10002 (Dr. Austina Cho) and 10015 (Dr. Louse Thurman) 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 May 1, 2023, by Glenn Mannheim, for full details.

4.2. Product Quality

The request for Categorical Exclusion from the requirement of preparing and submitting an Environmental Assessment under 21 CFR 25.31(b) is acceptable from the chemistry, manufacturing, and controls standpoint.

There are no changes to the quality information for the drug product (the proposed dosage for the new indication and patient population is one 72 µg capsule orally once daily). There are no changes to the quality-related portions of the United States Prescribing Information (sections 3, 11, and 16).

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 6 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.

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6. Clinical Pharmacology

6.1. Executive Summary

Linzess (linaclotide capsules) is a first-in-class, 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. The approved dosage is 290 µg once daily for IBS-C and 145 µg or 72 µg once daily for CIC.

In this supplement, the Applicant is seeking approval of Linzess for the treatment of FC in children and adolescents 6 to 17 years of age. To support the dose selection for the phase 3 study, a phase 2, dose-ranging, safety and efficacy study (Study LIN-MD-62) was conducted. In Study LIN-MD-62, in three dose cohorts, the doses were given based on age as well as the body weight for younger subjects 6 to 11 years of age:

- Subjects 6 to 11 years of age who weighed 18 to <35 kg received 9, 18 or 36 µg of linaclotide;
- Subjects 12 to 17 years of age who weighed \geq 35 kg received 18, 36 or 72 µg of linaclotide;
- Subjects 12 to 17 years of age received 18, 36, 72 or 145 µg (for exploratory purposes only) of linaclotide.

Based on efficacy results from this study, the Applicant concluded that linaclotide dose lower than 72 µg does not likely provide clinically meaningful outcomes in pediatric subjects 6 to 17 years of age and that an increase in dose above 72 µg (i.e., 145 µg) appeared to provide no additional benefit (Refer to Section 6.2.3 and Table 10). Together with the favorable safety profile of the 72-µg dose in pediatric subjects, the 72-µg dose was chosen for the phase 3 pivotal study.

Sparse pharmacokinetic (PK) samples were collected in Study LIN-MD-62 to determine the plasma concentrations of linaclotide and its active metabolites MM-419447. The concentrations of linaclotide and MM-419447 were below the limit of quantification 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.

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6.2. Clinical Pharmacology Assessment

6.2.1. Overall Study Design

Study LIN-MD-62 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 145 µg (only in subjects 12 to 17 years of age) with placebo in pediatrics 6 to 17 years of age with a diagnosis of FC (Table 3). The objective was to evaluate the dose response, safety, and efficacy of 4-week treatment with three linaclotide dose levels compared with placebo. The addition of the 145-µg dose level in subjects 12 to 17 years of age was for safety and exploratory efficacy evaluation only.

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 daytime abdominal pain
- 4-week stool consistency
- 4-week severity of straining
- 4-week daytime abdominal bloating
- 4-week overall complete spontaneous bowel movement (CSBM) frequency rate (CSBMs/week) during the Treatment Period
- 4-week daytime fecal incontinence

Dosing Regimen

Subjects 6 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 3). Assigned treatment was administered orally as a single daily dose and was taken 30 minutes before the evening meal on a consistent, ongoing basis. The treatment duration was 4 weeks.

Table 3. Linaclotide Doses Evaluated in Study LIN-MD-62

Age Group	Weight	Low Dose A	Medium Dose B	High Dose C	Approved Adult Dose
Subjects 6 to 11 years of age ^[a]	18 to <35 kg	9 µg placebo	18 µg placebo	36 µg placebo	— —
	≥35 kg	18 µg placebo	36 µg placebo	72 µg placebo	— —
Subjects 12 to 17 years of age ^[b]		18 µg placebo	36 µg placebo	72 µg placebo	145 µg ^[c] placebo

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

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

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

^[c] Approved dose was for safety and exploratory efficacy only.

The mean study treatment compliance during the 4-week treatment period was across all of the treatment group was >96%. The compliance was similar across the groups as summarized in Table 4.

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Table 4. Treatment Compliance in Study LIN-MD-62

Statistics	Placebo N=41	LIN Dose A N=36	LIN Dose B N=41	LIN Dose C N=39	LIN 145 µg N=16 ^[a]
Mean (SD)	98.54 (4.13)	97.55 (9.44)	98.65 (3.17)	96.46 (9.27)	97.42 (4.86)
Median	100.00	100.00	100.00	100.00	100.00
Min, max	79.3, 100.0	51.7, 113.3	86.2, 100.0	52.9, 100.0	83.3, 100.0
n ^[b]	40	36	41	39	16

Source: Adapted from the Applicant's Clinical Study Report, Table 10-8

% compliance = 100 × number of units/quantity taken / number of units/quantity prescribed (expected) during the visit interval

^[a] Linaclotide 145 µg was assigned only in 12 to 17 years old age group.

^[b] Subjects on study treatment within the compliance period.

Abbreviations: LIN, linaclotide

Study Subjects

A total of 173 subjects were randomized to receive either one of the linaclotide doses or placebo. Among them, 162 (93.6%) subjects completed the treatment period. The most frequent reason for discontinuation was withdrawal of consent. Three subjects (1.7%) discontinued due to adverse events (AEs) (diarrhea, suicidal ideation, and dyspnea in 1 subject each).

The demographic and baseline characteristics of the randomized subjects are summarized in Table 5 for the 6 to 11 years of age group and Table 6 for 12 to 17 years of age group.

Table 5. Summary of Demographics and Baseline Characteristics (6 to 11 Years of Age Group)

Characteristics	Placebo N=23	LIN Dose A N=21	LIN Dose B N=26	LIN Dose C N=20	Total N=90
Age (years)					
Mean (SD)	7.8 (1.9)	8.7 (1.5)	8.9 (1.7)	8.2 (1.7)	8.4 (1.7)
Median	7.0	9.0	9.0	8.0	8.0
Min, max	6, 11	6, 11	6, 11	6, 11	6, 11
Age group, n (%)					
6 to 8 years	15 (65.2)	10 (47.6)	11 (42.3)	12 (60.0)	48 (53.3)
9 to 11 years	8 (34.8)	11 (52.4)	15 (57.7)	8 (40.0)	42 (46.7)
Sex, n(%)					
Female	12 (52.2)	11 (52.4)	15 (57.7)	13 (65.0)	51 (56.7)
Male	11 (47.8)	10 (47.6)	11 (42.3)	7 (35.0)	39 (43.3)
Weight (kg)					
Mean (SD)	32.49 (10.93)	39.05 (14.39)	38.63 (18.40)	37.96 (14.28)	37.01 (14.90)
Median	29.60	34.00	35.50	33.35	33.35
Min, max	21.1, 66.8	21.7, 74.2	21.0, 101.1	18.4, 69.4	18.4, 101.1
Weight group, n (%)					
≥18 to <35 kg	16 (69.6)	11 (52.4)	13 (50.0)	12 (60.0)	52 (57.8)
≥35 kg	7 (30.4)	10 (47.6)	13 (50.0)	8 (40.0)	38 (42.2)
Body mass index (kg/m ²)					
Mean (SD)	19.15 (3.77)	20.34 (5.16)	19.85 (6.19)	20.97 (4.87)	20.03 (5.07)
Median	17.97	18.55	17.79	19.75	18.47
Min, max	15.2, 31.0	14.8, 32.5	14.6, 38.1	14.6, 32.0	14.6, 38.1

Source: Adapted from the Applicant's Clinical Study Report, Table 10-6

Abbreviations: LIN, linaclotide

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Table 6. Summary of Demographics and Baseline Characteristics (12 to 17 Years of Age Group)

Characteristics	Placebo N=18	LIN Dose A N=15	LIN Dose B N=15	LIN Dose C N=19	LIN 145 µg N=16	Total N=83
Age (years)						
Mean (SD)	14.4 (2.0)	14.0 (1.6)	14.5 (1.7)	14.7 (1.7)	14.7 (1.8)	14.5 (1.7)
Median	14.5	14.0	14.0	15.0	15.0	15.0
Min, max	12, 17	12, 16	12, 17	12, 17	12, 17	12, 17
Age group, n (%)						
12 to 14 years	9 (50.0)	9 (60.0)	8 (53.3)	8 (42.1)	6 (37.5)	40 (48.2)
15 to 17 years	9 (50.0)	6 (40.0)	7 (46.7)	11 (57.9)	10 (62.5)	43 (51.8)
Sex, n (%)						
Female	8 (44.4)	6 (40.0)	10 (66.7)	10 (52.6)	8 (50.0)	42 (50.6)
Male	10 (55.6)	9 (60.0)	5 (33.3)	9 (47.4)	8 (50.0)	41 (49.4)
Weight (kg)						
Mean (SD)	67.06 (26.48)	72.33 (23.42)	68.72 (24.01)	65.62 (14.18)	72.20 (20.82)	68.97 (21.64)
Median	61.85	62.30	62.40	68.00	67.05	63.10
Min, max	34.0, 136.5	43.3, 126.8	38.8, 132.0	42.7, 84.9	50.8, 136.8	34.0, 136.8
Body mass index (kg/m ²)						
Mean (SD)	24.94 (8.47)	27.05 (8.07)	25.39 (7.19)	25.16 (4.01)	26.80 (5.46)	25.81 (6.68)
Median	22.65	22.68	22.34	24.92	25.18	24.57
Min, max	14.6, 43.8	18.4, 45.8	16.4, 43.6	17.8, 32.5	21.2, 43.9	14.6, 45.8

Source: Adapted from the Applicant's Clinical Study Report, Table 10-7

Abbreviations: LIN, linaclotide

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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 7. 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 7. PK Sampling Schedule

Sample Collection Day	Time Postdose
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 4 subjects in the 6 to 11 years of age group had quantifiable plasma concentrations of linaclotide and/or MM-419447 as summarized in Table 8.

Table 8. Summary of Quantified PK Samples

Subject ID	Dose Group	PK Sampling Time Point	Analyte	Concentration (ng/mL)
(b) (6)	LIN Dose B	13 hr postdose at Week 2	MM-419447	0.107
	LIN Dose A	1 hr postdose at Day 1	Linaclotide	300
			MM-419447	1.26
	LIN Dose C	1.27 hr postdose at Day 1	Linaclotide	0.308
	LIN Dose C	3 hr postdose at Day 1	Linaclotide	0.199

Source: Reviewer's table based on the Applicant's Clinical Study Report
Abbreviations: LIN, linaclotide; PK, pharmacokinetics; hr, hour

The Clinical Pharmacology review team noted that the PK sample collected from Subject (b) (6) had very high linaclotide and MM-419447 levels. The Applicant concluded that the sample appeared to have been contaminated as a linaclotide concentration of 300 ng/mL was theoretically impossible for a 9-year-old female subject with a body weight of 47 kg who received 18 µg linaclotide dose. Per the Applicant, even if linaclotide was administered as an intravenous bolus to this subject, the C_{max} could not have exceeded 4.79 ng/mL. The review team concurs with the Applicant's conclusion that this sample appeared to have been contaminated.

Among the four subjects whose PK samples had quantifiable linaclotide and/or MM-419447, only one subject, Subject (b) (6) experienced AEs which was diarrhea and gastroenteritis. Diarrhea was mild in intensity and was resolved on the same day. Two events of gastroenteritis were reported with the first event prior to the study intervention and the second with moderate

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severity was reported on Day 15. The Applicant concluded that neither AEs were considered related to study intervention.

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 and key secondary endpoints, none of the 3 linaclotide doses (A [low dose], B [medium dose], and C [high dose]) indicated clear improvement over placebo (Table 9). However, there was a numerical trend toward efficacy at the higher doses for the primary endpoint of CFB in 4-week overall SMB frequency rate and the secondary endpoints of CFB in 4-week overall CSBM frequency rate, CFB in 4-week stool consistency, and CFB in 4-week severity of straining.

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Table 9. Key Efficacy Results From Study LIN-MD-62

Parameter	Timepoint	Statistic	Placebo N=41	LIN Dose A (Low) N=36	LIN Dose B (Medium) N=41	LIN Dose C (High) N=39
<i>Primary: CFB in 4-week overall SBM frequency rate^[a]</i>						
		n	41	36	41	39
Baseline		Mean (SD)	1.248 (0.850)	1.462 (0.852)	1.307 (0.734)	1.324 (0.789)
		Median	1.448	1.448	1.448	1.448
		Min, max	0.00, 2.90	0.00, 2.90	0.00, 2.90	0.00, 2.90
Change from baseline		Mean (SD)	2.048 (3.273)	1.317 (1.813)	1.816 (2.359)	2.367 (2.469)
		Median	0.917	0.724	1.207	2.517
		Min, max	-1.74, 14.32	-1.93, 6.75	-2.41, 7.78	-2.41, 7.61
<i>Secondary: CFB in 4-week stool consistency (adult derivation)^[b]</i>						
		n	34	32	34	34
Baseline		Mean (SD)	2.900 (1.089)	2.446 (0.847)	2.463 (1.064)	2.431 (1.103)
		Median	3.000	2.333	2.000	2.225
		Min, max	1.00, 5.50	1.00, 4.00	1.00, 5.00	1.00, 5.00
Change from baseline		Mean (SD)	0.397 (1.509)	0.736 (1.039)	0.727 (1.181)	1.155 (1.510)
		Median	0.292	0.472	0.606	1.165
		Min, max	-3.33, 5.17	-1.00, 3.19	-2.14, 3.34	-2.50, 4.00
<i>Secondary: CFB in 4-week stool consistency (based on observed weighted average)^[c]</i>						
		n	34	32	34	34
Baseline		Mean (SD)	2.887 (1.071)	2.433 (0.834)	2.463 (1.063)	2.429 (1.111)
		Median	3.000	2.333	2.000	2.225
		Min, max	1.00, 5.50	1.00, 4.00	1.00, 5.00	1.00, 5.00
Change from baseline		Mean (SD)	0.383 (1.458)	0.706 (0.974)	0.663 (1.182)	1.034 (1.463)
		Median	0.188	0.386	0.476	0.854
		Min, max	-3.33, 5.11	-1.00, 3.04	-2.14, 3.29	-2.50, 4.23

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Parameter	Timepoint	Statistic	Placebo N=41	LIN Dose A (Low) N=36	LIN Dose B (Medium) N=41	LIN Dose C (High) N=39
<i>Secondary: CFB in 4-week overall CSBM frequency rate^[d]</i>						
		n	41	36	41	39
Baseline		Mean (SD)	0.553 (0.737)	0.764 (0.889)	0.742 (0.764)	0.706 (0.725)
		Median	0.000	0.241	0.483	0.483
		Min, max	0.00, 2.41	0.00, 2.90	0.00, 2.41	0.00, 1.93
Change from baseline		Mean (SD)	1.305 (2.365)	0.813 (1.804)	1.025 (1.667)	1.318 (1.955)
		Median	0.241	0.302	0.500	0.724
		Min, max	-0.91, 10.30	-1.93, 7.23	-1.48, 5.00	-1.93, 7.31
<i>Secondary: CFB in 4-week daytime abdominal pain^[e]</i>						
		n	41	36	41	39
Baseline		Mean (SD)	1.362 (1.257)	0.903 (1.061)	1.047 (1.074)	0.935 (1.118)
		Median	1.000	0.439	0.636	0.357
		Min, max	0.00, 4.00	0.00, 3.85	0.00, 3.38	0.00, 4.00
Change from baseline		Mean (SD)	-0.434 (0.847)	-0.278 (0.663)	-0.310 (0.848)	-0.115 (0.879)
		Median	-0.154	-0.050	-0.154	0.000
		Min, max	-3.12, 1.32	-2.50, 0.74	-2.73, 1.40	-3.41, 1.36

Source: Applicant's Clinical Study Report, Table 11-1

^[a] 4-week overall SBM frequency rate = SBM rate (SBMs/week) during the 4-week Treatment Period

^[b] 4-week stool consistency (adult derivation) = mean of subject's nonmissing, SBM-associated p-BSFS scores during the 4-week Treatment Period

^[c] 4-week stool consistency = Observed weighted average of daily p-BSFS scores during the treatment period. Daily p-BSFS score is the average of non-missing p-BSFS scores of corresponding SBMs reported in morning and/or evening diaries in that specific day.

^[d] 4-week overall CSBM frequency rate = ([total number of CSBMs in the analysis period/number of days in the analysis period] x 7)

^[e] 4-week daytime abdominal pain = average of nonmissing scores in evening eDiary during the Treatment Period (based on scores: no and 4-point scales for tummy hurt; higher value indicating greater symptom severity)

Baseline derived from values collected during the Pretreatment Period (14 days before randomization and up to time of randomization).

Abbreviations: BM, bowel movement; CFB, change from baseline; CSBM, complete spontaneous bowel movement; LIN, linaclotide; p-BSFS, Pediatric Bristol Stool Form Scale, assessed for each BM via 7-point ordinal scale; SBM, spontaneous bowel movement

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In the exploratory linaclotide 145 µg group (which only included subjects 12 to 17 years of age), the mean CFB in 4-week SBM frequency rate was similar to the mean CFB observed in the LIN Dose C (72 µg) group in subjects 12 to 17 years of age (Table 10).

Table 10. Change From Baseline in 4-Week Overall SBM Frequency Rate in Subjects 12 to 17 Years of Age

Statistics	Placebo (N=18)	LIN Dose A (N=15)	LIN Dose B (N=15)	LIN Dose C (N=19)	LIN 145 µg (N=16)
Mean (SD)	1.788 (2.891)	1.174 (2.030)	1.672 (2.253)	2.857 (3.010)	2.623 (4.108)
Median	0.272	0.522	1.569	2.534	1.677
Min, max	-1.66, 9.82	-0.80, 6.75	-2.41, 5.55	-2.41, 7.61	-4.83, 14.44

Source: Adapted from the Applicant's Clinical Study Report, Table 14.2-1.1.B

Abbreviations: LIN, linaclotide; SBM, sudden bowel movement

Overall, linaclotide was well tolerated across all doses and both age groups. The most commonly reported AE was diarrhea and the majority of the treatment-emergent adverse events (TEAEs) of diarrhea were mild and none were severe. In subjects 6 to 11 years of age, no serious adverse events (SAEs) or AEs leading to discontinuation were reported. In subjects 12 to 17 years of age, 2 SAEs were reported, neither of which were considered related to study drug.

Based on efficacy results from this study, the Applicant concluded that linaclotide doses below 72 µg did not result in clinically meaningful improvements in pediatric subjects 6 to 17 years of age and that an increase in dose above 72 µg (i.e., 145 µg) appeared to provide no additional benefit (Table 10). Together with the favorable safety profile of the 72-µg dose in pediatric subjects, the 72-µg dose was chosen for the phase 3 pivotal study.

6.2.4. Formulations

In the dose-ranging study LIN-MD-62, formulations different from the to-be-marketed were used: oral solution (9 µg/mL and 36 µg/mL) and capsule (18 µg, 36 µg, 72 µg, and 145 µg) formulations. Subjects 6 to 11 years of age received oral solution and subjects 12 to 17 years of age received oral solution or oral capsules. The oral capsule formulation used on Study LIN-MD-62 is different from the to-be-marketed oral capsule formulation.

Although formulations used in Study LIN-MD-62 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).

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 11 below lists the clinical studies supporting review of efficacy and safety for NDA 202811/S-021.

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Table 11. Listing of Clinical Studies Relevant to This NDA

Study ID	Study Design	Dosing Regimen(s)	Endpoints	Duration	Sample Size	Study Population	Centers and Countries
<i>Controlled Studies</i>							
LIN-MD-62	R/DB/PC, dose-finding	LIN or PBO PO QD for 4 weeks Doses studied: <ul style="list-style-type: none"> • <u>6 to 11 yrs, 18 to <35 kg</u>: 9 µg; 18 µg; 36 µg; PBO • <u>6 to 11 yrs, ≥35 kg</u>: 18 µg; 36 µg; 72 µg; PBO • <u>12 to 17 yrs</u>: 18 µg; 36 µg; 72 µg; 145 µg; PBO 	<u>Primary</u> : Change from baseline in 4-week SBM frequency (SBM/week)	4 weeks	Total: 173 <ul style="list-style-type: none"> • LIN: 132 • PBO: 41 	Patients ages 6 to 17 years with FC per Rome III criteria	52 centers in US and CA
LIN-MD-64	R/DB/PC	LIN 72 µg or PBO PO QD for 12 weeks	<u>Primary</u> : Change from baseline in 12-week SBM frequency (SBM/week)	12 weeks	Total: 330 <ul style="list-style-type: none"> • LIN 72 µg: 166 • PBO: 164 	Patients ages 6 to 17 years with FC per Rome III criteria	64 centers in 7 countries (US, CA, IL, IT, NL, UA, EE)
<i>Uncontrolled Studies</i>							
LIN-MD-66	Open-label, long-term safety	LIN PO QD for 24 weeks Doses studied: <ul style="list-style-type: none"> • <u>6 to 11 yrs</u>: LIN 72 µg • <u>12 to 17 yrs</u>: LIN 72 µg or 145 µg 	Safety	24 weeks	Total: 283 <ul style="list-style-type: none"> • LIN 72 µg: 210 • LIN 145 µg: 73 	Subjects who completed LIN-MD-62 or LIN-MD-64	55 centers in 4 countries (US, CA, IL, NL)

Source: Reviewer's table

Abbreviations: CA, Canada; EE, Estonia; FC, functional constipation; IL, Israel; IT, Italy; LIN, linaclotide; NL, Netherlands; PBO, placebo; PO, by mouth; R/DB/PC, randomized, double-blind, placebo-controlled; QD, once daily; SBM, spontaneous bowel movement; UA, Ukraine; US, United States

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7.2. Review Strategy

Review of safety and efficacy focused on data from the phase 3 randomized, double-blind, placebo-controlled study LIN-MD-64. Review of safety additionally included assessment of interim data from the open-label extension study LIN-MD-66, which enrolled subjects who completed the phase 2 randomized, double-blind, placebo-controlled, dose-ranging study LIN-MD-62 or phase 3 study LIN-MD-64. Data from the phase 2 study, LIN-MD-62, were assessed as they informed selection of the proposed to-be-marketed dose, but these data did not contribute considerably to the review of safety and efficacy due to relatively small sample sizes and short treatment duration of 4 weeks.

The review team identified a substantive review issue that affected the team's approach to interpreting whether meaningful clinical benefit was demonstrated in LIN-MD-64. Although the review team intended to use anchor-based analyses to interpret whether changes in signs/symptoms were clinically meaningful, anchor-based analyses could not be interpreted

(b) (4)

Therefore, the team considered alternate methods for evaluating whether observed changes in signs/symptoms were clinically meaningful.

In addition to assessing safety and efficacy to support the proposed indication, the review team considered whether the submitted data fulfilled PMR 2161-3 and could address Studies 01, 03, and 05 described in the WR once all items of the WR are submitted in the future.

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8. Statistical and Clinical and Evaluation

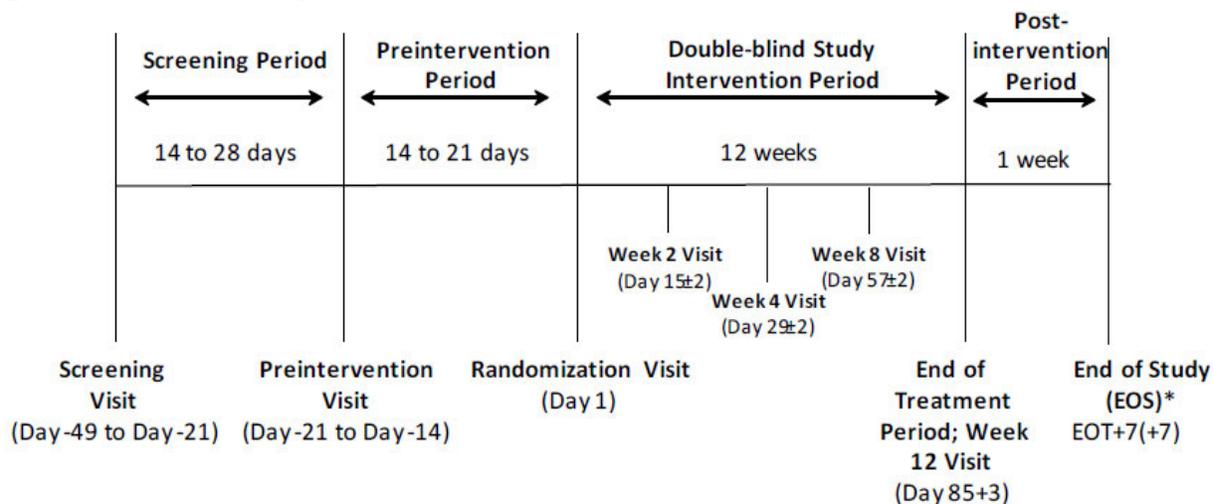
8.1. Review of Relevant Individual Studies Used to Support Efficacy

8.1.1. Phase 3 Study: LIN-MD-64

Study Design

LIN-MD-64 was a phase 3 randomized, double-blind, placebo-controlled, parallel-group study of linaclotide 72 µg versus placebo for 12 weeks. The study enrolled subjects ages 6 to 17 years who met modified Rome III criteria³ for functional constipation. The study design is illustrated in Figure 1 below.

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: Applicant's LIN-MD-64 Clinical Study Report

Study Population

Select eligibility criteria for LIN-MD-64 are summarized below. The complete list of inclusion and exclusion criteria are provided in Section 15.4.

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Inclusion Criteria:

- Male and female subjects ages 6 to 17 years
- Weight \geq 18 kg
- Meeting modified Rome III criteria for Child/Adolescent FC, defined as: for at least 2 months before the Screening Visit, the subject has had 2 or fewer defecations (with each defecation occurring in the absence of any laxative, suppository, or enema use during the preceding 24 hours) in the toilet per week. In addition, subject meets one or more of the following criteria at least once per week for at least 2 months before the screening visit:
 - History of retentive posturing or excessive volitional stool retention
 - History of painful or hard BMs
 - History of large diameter stools that may obstruct the toilet
 - Presence of a large fecal mass in the rectum
 - At least 1 episode of fecal incontinence per week

Exclusion Criteria:

- Meeting Rome III criteria for Child/Adolescent IBS, defined as: at least once per week for at least 2 months before the Screening Visit, the subject has 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
- Celiac disease, or positive serological test for celiac disease and the condition has not been ruled out by endoscopic biopsy

Study Endpoints

Primary Efficacy Endpoint:

- Change from baseline in 12-week spontaneous bowel movement (SBM) frequency rate (SBMs/week) during the Study Intervention Period. An SBM is defined as a bowel movement (BM) that occurs in the absence of laxative, enema, or suppository use on the calendar day of the BM or the calendar day before the BM.

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Secondary Efficacy Endpoint:

- Change from baseline in 12-week stool consistency during the Study Intervention Period. Consistency was measured using the Pediatric Bristol Stool Form Scale (p-BSFS).

Additional Efficacy Endpoints:

- Change from baseline in 12-week complete spontaneous bowel movement (CSBM) frequency rate (CSBMs/week) during the Study Intervention Period. A CSBM is an SBM that is associated with a sense of complete evacuation.
- Change from baseline in 12-week stool straining during the Study Intervention Period.

Statistical Analysis Plan

Analysis Populations

Efficacy analyses were based on the modified Intent-to-Treat (mITT) population, defined as all randomized subjects who received at least one dose of study drug during the double-blind treatment period. Subjects were analyzed according to randomized treatment group for efficacy analyses. All safety analyses were based on the safety population, defined as all randomized subjects who received at least 1 dose of study drug during the double-blind treatment period. Subjects were analyzed according to actual treatment received for safety analyses.

Estimand

The estimand was not explicitly specified in the protocol and statistical analysis plan. For the main analysis approach, the target population was subjects with FC, ages 6-17 years old, satisfying the inclusion and exclusion criteria as specified in LIN-MD-64 Inclusion/Exclusion criteria. The primary endpoint was the change from baseline in the subject's 12-week spontaneous bowel movement (SBM) frequency rate (SBMs/week) during the Study Intervention Period as derived from the twice daily eDiary (morning and evening). All BMs that occur on the day of or day after a subject took a laxative, enema, or suppository were not considered as SBMs for the analysis. Subjects who discontinue treatment prematurely prior to the completion of the double-blind Study Intervention Period had their eDiary data included up to the morning diary following the last dose date for primary endpoint. Subjects with any intermediate missing diary data during the 12-week Study Intervention Period had their data included as observed. The population-level summary for the primary endpoint was the difference in means between the linaclotide dose arm and placebo arm. The estimand for the secondary endpoint was similar to the primary endpoint as discussed in the main analysis approach.

Multiplicity Control

Hypothesis testing was performed for the primary and secondary endpoint, and the overall type I error rate for each endpoint was controlled at a 2-sided significance level of 0.05. Hypotheses were sequentially tested according to the prespecified hierarchical ordering. The primary endpoint of change from baseline in 12-week SBM frequency rate was tested first. If statistical significance was achieved for the primary endpoint, then testing could proceed to the secondary endpoint of change from baseline in 12-week stool consistency.

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Interim Analysis

Due to the poor recruitment experienced in phase 2, dose-ranging study LIN-MD-62 (N=172), a potential interim analysis to assess futility was added to the protocol and statistical analysis plan for this study. However, patient recruitment proceeded per plan and the interim analysis was not performed.

Primary Endpoint

The primary endpoint was the change from baseline in 12-week SBM frequency rate (SBMs/week) during the Study Intervention Period. The weekly SBM frequency rate was calculated as the total number of SBM in a week divided by the total number of days during that week and multiplied by 7. There were four scenarios in which a week might not exactly be equal to 7 days, but none of them were due to missing diary entries:

1. For Week -1 (Preintervention Period), the upper bound was up to the time of randomization (first dose) on Day 1. It was considered as a half day (0.5 day) on Day 1. Therefore, the duration of Week -1 was 7.5 days.
2. Week 1 started from the time of randomization (first dose) on Day 1 (considered as a half day) and ended on Day 7. Therefore, the duration was 6.5 days.
3. The length of Week 12 with an upper bound of last dose day + 1 might differ from 7 days. The morning diary that was filled out the day after the last dose was considered a half day for the double-blind Intervention Period. Therefore, the duration could be 7.5 days (or longer).
4. When a subject prematurely discontinued from treatment, the length for the last analysis week during the Intervention Period would depend on the last dose date.

Baseline values for SBM frequency rate related to daily eDiary responses were derived from the eDiary in the Preintervention Period, specifically the time period from 14 days before randomization up to the time of randomization. The baseline SBM weekly rates were derived based on the number of SBMs a patient had during the Preintervention Period. The null hypothesis was that there was no difference between linaclotide group and the placebo group in 12-week SBM frequency rate. The main analysis approach used an analysis of covariance (ANCOVA) model with study intervention, age group (6 to 11 years of age or 12 to 17 years of age) as fixed factors and baseline SBM frequency as a covariate. Points estimates, the 95% CI for the treatment difference, and the p-value were reported. Missing BM response and rescue medication (RM) response were not imputed for the primary analysis. If RM use question was missing for any missing diary (morning or evening), no RM usage was considered during that diary period (morning or evening diary), with the exception that the missing RM was considered “used” if the other available assessment during that diary period was “yes”. If BM frequency was missing in any assessment (morning or evening), BM frequency was considered as zero for that diary period (morning or evening diary).

To assess the robustness of main analysis approach, two prespecified sensitivity analyses were performed: mixed effect model for repeated measures (MMRM) missing at random (MAR) and MMRM not missing at random (NMAR). The first MMRM MAR analysis used a mixed effect model for repeated measures with study intervention, week, age group (6 to 11 years of age, 12 to 17 years of age), and study intervention-by-week interaction as fixed effects and baseline

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value as a covariate. Points estimates, the 95% CI for the treatment difference, and the p-value were reported from the MMRM model. An unstructured covariance matrix was used to model the covariance of within-subject results. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. In the second MMRM NMAR analysis, a missing postbaseline week was imputed using control-based imputation using a pattern-mixture model. Fifty imputed datasets were generated. The same MMRM analysis was repeated for each imputed dataset. The estimates for each imputed dataset were combined using standard multiple imputation analysis techniques to provide a single within group estimate and a single estimate of treatment difference and its associated 95% CI and p-value. For these sensitivity analysis, at least 4 non-missing diary days (both morning and evening diary must be completed on same day for a non-missing diary day) were needed in an analysis week in order to compute the weekly SBM frequency for that week.

FDA suggested two sensitivity analyses:

- 1) MMRM analysis with a different formula for the SBM frequency rate
- 2) MMRM analysis imputing missing rescue medication as used

The first MMRM analysis with a different formula for the SBM frequency rate assumed that the SBM frequency for non-missing diaries during the week were representative of the SBM frequency for missing diaries. For this analysis, at least eight non-missing diaries were needed in an analysis week in order to compute the weekly SBM frequency. The following formula was used to calculate weekly frequency rate for each specific period:

$$\text{Weekly Frequency Rate} = \frac{\text{Number of observed SBMs during the week}}{\text{Number of nonmissing diaries during the week}} \times 14.$$

The second MMRM analysis imputing missing rescue medication as used assumed rescue medication was used when a diary was missing. For this analysis, at least four non-missing diary days were needed in an analysis week in order to compute the weekly SBM frequency.

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Secondary Endpoint

The secondary endpoint was the change from baseline in 12-week stool consistency during the Study Intervention Period. Stool consistency was collected twice daily (morning and evening) in the eDiary and measured using the 7-point p-BSFS for each BM. Subjects also had the option of responding “I don’t know” to the question on stool consistency. The response of “I don’t know” was treated as missing in the analyses. Stool consistency was calculated as the average of the non-missing values from the SBMs reported by the patient during the specific period. A patient’s baseline stool consistency could not be assessed if the patient did not have at least one SBM during the Preintervention Period. 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. Patients with missing baseline stool consistency were excluded from stool consistency analyses that involved change from baseline. The primary and sensitivity analyses of the secondary endpoint were similar to the analyses of the primary endpoint with ANCOVA analysis used as the main analysis and prespecified MMRM MAR sensitivity analysis.

Other Endpoints

The other endpoints included the change from baseline in 12-week complete spontaneous bowel movement (CSBM) frequency rate (CSBMs/week) during the Study Intervention Period and the change from baseline in 12-week straining during the Study Intervention Period. A CSBM is an SBM that is associated with a sense of complete evacuation. The 12-week CSBM frequency rate was calculated using the same method as the 12-week SBM frequency rate.

Straining was collected twice daily (morning and evening) in the eDiary and measured using a 5-point scale for each BM (on a 0-4 scale, with 0 describing no straining and 4 describing the most intense straining). Straining was calculated as the average of the non-missing values from the SBMs reported by the patient during the specific period. Similar to stool consistency, a subject’s baseline straining could not be assessed if the subject did not have at least 1 SBM during the Preintervention Period. For subjects who reported no SBMs during a study period, the straining assessments would be considered missing for that study period in the analyses. Subjects with missing baseline straining were excluded from straining analyses that involved change from baseline. The analyses for other endpoints were similar to the ANCOVA analysis used for the primary endpoint.

Protocol Amendments

The European Union-specific Protocol Amendment EU-3 (dated August 2020) was the final version of protocol. It included a potential interim analysis to assess futility for FC subjects. The statistical analysis plan amendment #1 (dated June 13, 2022) was the last version of the statistical analysis plan. The definition of mITT population was changed from “all subjects in the Randomized Population who receive at least 1 dose of double-blind study intervention and who had at least 1 postbaseline entry on bowel movement (BM) characteristic assessments that determine occurrences of spontaneous bowel movements (SBMs) (i.e., BM frequency and rescue medication use)” to “all subjects in the Randomized Population who receive at least 1 dose of double-blind study intervention”. The reasons for premature discontinuation from the study in subject disposition was removed as there was no corresponding eCRF. TEAE definition was

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modified to include any AE that occurs within 30 days (instead of 1 day) after the last dose of study intervention. The imputation rule for missing RM use question was modified. Missing RM usage was considered as “used” for morning or evening diary if the other available assessment during that period indicated RM was taken.

8.1.2. Study Results

Compliance With Good Clinical Practices

The Applicant asserts that studies LIN-MD-62, LIN-MD-64, and LIN-MD-66 were conducted in compliance with Good Clinical Practices. 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-62, 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 all randomized subjects in LIN-MD-64 is shown in Table 12. A total of 330 subjects were randomized to receive either placebo or linaclotide 72 µg and 328 subjects were treated with either placebo or linaclotide 72 µg. The majority (88.8%) of subjects completed the double-blind study intervention period. The largest reason for study discontinuation was withdrawal by subject. A total of 12 subjects (3.6%) withdrew. The reasons for study discontinuation were generally similar between arms with the exceptions of lost to follow-up and non-compliance with study drug. A higher proportion of placebo subjects were lost to follow-up compared to linaclotide subjects (2.4% versus 0%), whereas there was a higher proportion of subjects in the linaclotide arm who discontinued due to non-compliance with study drug compared to the placebo arm (2.4% versus 0%).

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Table 12. Disposition of Subjects (All Randomized Subjects)

	Number (%) of Subjects		
	Placebo N = 164	Linaclotide 72 µg N = 166	Total N = 330
Number of subjects treated	164 (100.0)	164 (98.8)	328 (99.4)
Double-Blind Study Intervention Period			
Number of subjects completed Double-Blind Intervention Period	145 (88.4)	148 (89.2)	293 (88.8)
Number of subjects discontinued from Double-Blind Intervention Period	19 (11.6)	18 (10.8)	37 (11.2)
Reasons for Discontinuation from Double-Blind Intervention Period			
Adverse event	2 (1.2)	2 (1.2)	4 (1.2)
Lack of efficacy	1 (0.6)	2 (1.2)	3 (0.9)
Withdrawal by subject	7 (4.3)	5 (3.0)	12 (3.6)
Lost to follow-up	4 (2.4)	0 (0.0)	4 (1.2)
Physician decision	1 (0.6)	1 (0.6)	2 (0.6)
Protocol deviation	0 (0.0)	1 (0.6)	1 (0.3)
Non-compliance with study treatment	0 (0.0)	4 (2.4)	4 (1.2)
Other	4 (2.4)	3 (1.8)	7 (2.1)
Related to COVID-19	6 (3.7)	1 (0.6)	7 (2.1)
Number of subjects signed informed consent for extension Study LIN-MD-66	131 (79.9)	127 (76.5)	258 (78.2)
Number of subjects completed study	144 (87.8)	144 (86.7)	288 (87.3)
Number of subjects discontinued from study	20 (12.2)	22 (13.3)	42 (12.7)

Source: Applicant's NDA 202811 S-021 submission, CSR Table 3; verified by the FDA review team.

Protocol Violations/Deviations

Table 13 below shows significant protocol deviations reported by the Applicant for LIN-MD-64. The Applicant asserts that the deviations were assessed for their impact on analyses and data integrity or subject safety, and that none of the deviations were considered to have affected the study outcome or interpretation of study results or conclusions. Given the low proportion of deviations and similarity across the linaclotide and placebo arms, the review team determined that these deviations/violations were unlikely to significantly impact the results of the analyses or overall conclusions of the study.

Table 13. Number (%) of Subjects With Significant Protocol Deviations, Randomized Population

Protocol Deviation Category	Placebo	Linaclotide 72 µg	Total
	N = 164 n (%)	N = 166 n (%)	N = 330 n (%)
Overall	6 (3.7)	9 (5.4)	15 (4.5)
Dosed with wrong study intervention (ICH)	1 (0.6)	1 (0.6)	2 (0.6)
Exclusion criteria met (ICH)	1 (0.6)	3 (1.8)	4 (1.2)
Inappropriate use of rescue medication	1 (0.6)	1 (0.6)	2 (0.6)

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Inclusion criteria not met (ICH)	1 (0.6)	2 (1.2)	3 (0.9)
Initial informed consent not signed (ICH)	1 (0.6)	0 (0.0)	1 (0.3)
Prohibited concomitant medication taken (ICH)	2 (1.2)	1 (0.6)	3 (0.9)
Withdrawal due to protocol deviation	0 (0.0)	1 (0.6)	1 (0.3)

Source: Applicant's LIN-MD-64 **Clinical Study Report, Table 4; verified by the FDA review team.**

Abbreviations: **ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use**

Table of Demographic Characteristics

Study demographics are summarized for the mITT Population in Table 14. Demographics were similar between the treatment groups. A total of 328 subjects received treatment with linaclotide 72 µg or placebo and were evaluated for efficacy. One-hundred and eighty-one subjects were 6 to 11 years and 147 subjects were 12 to 17 years. The overall mean age was 11.1 years. 55.2% of subjects were female and 44.8% of patients were male. 69.8% of patients were White and 26.2% of patients were either Black or African American patients. Hispanic or Latino ethnicity was reported by 45.1% of patients.

Table 14. Demographic Characteristics of the Primary Efficacy Analysis, mITT Population

Demographic Parameters	Placebo N=164 n (%)	Linaclotide 72 µg N=164 n (%)	Total N=328 n (%)
Sex			
Male	78 (47.6)	69 (42.1)	147 (44.8)
Female	86 (52.4)	95 (57.9)	181 (55.2)
Age			
Mean years (SD)	11.1 (2.96)	11.1 (3.33)	11.1 (3.14)
Median (years)	11.0	11.0	11.0
Min, max (years)	6, 17	6, 17	6, 17
Age group			
6 to 11 years of age	91 (55.5)	90 (54.9)	181 (55.2)
12 to 17 years of age	73 (44.5)	74 (45.1)	147 (44.8)
Race			
White	114 (69.5)	115 (70.1)	229 (69.8)
Black or African American	45 (27.4)	41 (25.0)	86 (26.2)
Asian	2 (1.2)	3 (1.8)	5 (1.5)
American Indian or Alaska Native	1 (0.6)	0 (0.0)	1 (0.3)
Native Hawaiian or Other Pacific Islander	1 (0.6)	3 (1.8)	4 (1.2)
Multiple ¹	1 (0.6)	2 (1.2)	3 (0.9)
Ethnicity			
Hispanic or Latino	77 (47.0)	71 (43.3)	148 (45.1)
Not Hispanic or Latino	87 (53.0)	93 (56.7)	180 (54.9)
Region			
United States	155 (94.5)	151 (92.1)	306 (93.3)
Canada	2 (1.2)	3 (1.8)	5 (1.5)
Europe ²	6 (3.6)	7 (4.3)	13 (4.0)
Middle East ³	1 (0.6)	3 (1.8)	4 (1.2)

Source: CSR Table 6 and Review team's analysis created from ADSL.xpt

¹ Subjects who reported multiple races are only included in the multiple category.

² Europe includes Estonia, Italy, Netherlands, and Ukraine.

³ Middle East includes Israel.

Abbreviations: mITT, modified intent-to-treat

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Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Baseline disease characteristics were generally balanced between treatment groups (Table 15). The mean SBM frequency rate was 1.22 SBMs/week and the mean CSBM frequency rate was 0.57 SBMs/week for the entire population. Forty-eight subjects did not have a SBM during the baseline period. Stool consistency and straining were based on SBMs and the baseline scores were not calculated if the subject did not have an SBM. In addition, four subjects had responses of “I don’t know” to stool consistency during the baseline period. These responses were treated as missing in the analysis, leading to no baseline stool consistency values for these four subjects. The mean stool consistency score was 2.37 (on the 7-point p-BSFS) and the mean straining score was 2.50 (on a 0 to 4 scale) for the entire population.

Table 15. Baseline Disease Characteristics

Efficacy Parameter	Placebo N=164		Linaclotide 72 ug N=164		Total N=328	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
SBM frequency	164	1.28 (0.87)	164	1.16 (0.83)	328	1.22 (0.85)
CSBM frequency	164	0.58 (0.75)	164	0.55 (0.75)	328	0.57 (0.74)
Stool consistency	138	2.39 (0.92)	138	2.35 (0.95)	276	2.37 (0.93)
Straining	141	2.58 (1.04)	139	2.42 (1.09)	280	2.50 (1.07)

Source: Adapted from Applicant's NDA 202811 S-021 submission, CSR Table 14.1-4.2.

Abbreviations: CSBM, complete spontaneous bowel movement; SBM, spontaneous bowel movement

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The frequency of rescue medication usage was measured by the twice daily diary (i.e., the question “Was Rescue Medication Taken?”). In Table 16, the percentage of subjects who reported using rescue medication at least once decreased for both linaclotide group and placebo group across 12 weeks. A lower percentage of subjects reported using rescue medication in the linaclotide group compared to the placebo group for all 12 weeks.

Table 16. Rescue Medication Usage

Subjects With at Least One Time of RM Use	Placebo N=164		Linaclotide 72 µg N=164	
	N	n (%)	N	n (%)
Week 1	161	53 (32.9)	162	42 (25.9)
Week 2	162	50 (30.9)	160	34 (21.3)
Week 3	162	39 (24.1)	158	35 (22.2)
Week 4	158	39 (24.7)	154	29 (18.8)
Week 5	155	35 (22.6)	150	25 (16.7)
Week 6	152	35 (23.0)	149	21 (14.1)
Week 7	149	41 (27.5)	146	19 (13.0)
Week 8	149	37 (24.8)	144	16 (11.1)
Week 9	142	37 (26.1)	147	19 (12.9)
Week 10	140	29 (20.7)	147	16 (10.9)
Week 11	140	31 (22.1)	141	16 (11.3)
Week 12	137	30 (21.9)	140	15 (10.7)
Treatment period	164	99 (60.4)	163	85 (52.1)

Source: Adapted from Applicant's NDA 202811 S-021 submission, Table 2 in the IR response of March 07, 2023.

Abbreviations: RM, rescue medication

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Efficacy Results – Primary Endpoint

Results for the Applicant’s pre-specified main analysis of the primary endpoint are displayed in Table 17. The main analysis of 12-week SBM frequency rate demonstrated a statistically significant ($p \leq 0.0001$) increase in SBMs for the linaclotide group as compared to the placebo group. The least square mean difference between treatment groups for change from baseline in 12-week SBM frequency rate was 1.17 SBMs/week (95% CI = 0.65, 1.69).

Table 17. 12-Week SBM Frequency Rate Analysis Results: Prespecified Main ANCOVA Analysis

Parameter	Placebo N=164	Linaclotide 72 µg N=164
Baseline mean	1.28	1.16
Post-baseline mean	2.29	3.41
Least square mean (SE)	1.05 (0.19)	2.22 (0.19)
Difference versus placebo (95% CI)	-	1.17 (0.65, 1.69)
p-value	-	<0.0001

Source: Adapted from Applicant’s NDA 202811 S-021 submission, CSR Table 14.2-1.1.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; SBM, spontaneous bowel movement

The Applicant’s two prespecified sensitivity analyses and two FDA requested sensitivity analyses were also performed to assess the impact of missing data on the study conclusions. Results of all four sensitivity analyses supported the primary analysis result, indicating that results were generally robust to the missing data assumptions in the primary analysis. A comparison of least square means results for different approaches are displayed in Table 18. The results for the Applicant’s prespecified sensitivity analyses produced similar estimated treatment effects to that of the main ANCOVA analysis. The review team considers the results of the MMRM MAR analysis and the MMRM NMAR analysis to be more informative than the primary ANCOVA analysis. Unlike the ANCOVA analysis, these two analyses require a minimum of four non-missing diary days within a week, which ensures that the observed weekly scores are more representative of the entire week. This MMRM analysis assumes that missing weekly scores are missing at random conditional on other observed weekly scores for that subject. If a subject worsened prior to dropping out of the study, this would likely be reflected in that subject’s last observed weekly SBM frequency and the analysis would account for worsening efficacy prior to dropout. The MAR assumption effectively assumes that outcomes for missing weeks for subjects who dropout of the study are similar to outcomes for subjects who had similar covariates and outcomes prior to the time of dropout but remained in the study. The NMAR analysis instead assumes that subjects who dropped out of the study would have similar outcomes to placebo subjects who had similar covariates and outcomes prior to the time of dropout but remained in the study. Neither of these assumptions can be verified because the missing outcomes are unknown, but these assumptions appear more appropriate for targeting a treatment policy strategy with respect to the intercurrent event of treatment discontinuation (where the actual outcome during the 12-week treatment period is of interest regardless of whether subjects prematurely discontinued study drug) compared to the missing data assumptions for the ANCOVA analysis. The ANCOVA analysis may be more appropriate for a while on treatment strategy, but, given the expectation of chronic dosing for FC in pediatric subjects, a treatment policy strategy is likely more meaningful for informing long-term efficacy. Note that 10 subjects were excluded from the MMRM MAR analysis because they had less than 4 completed dairy days in any analysis week; however, the MMRM NMAR analysis includes all

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randomized subjects who received study drug because subjects with no postbaseline scores have their outcomes imputed. As requiring subjects to have observed postbaseline values in order to be included in the analysis would condition on a post-randomization outcome, which could be affected by treatment assignment. Analyses conditioning on post-randomization outcomes could be biased and are generally not recommended. Therefore, the MMRM NMAR analysis was considered to be the more appropriate analysis for assessing efficacy. Results from the MMRM NMAR analysis are proposed for inclusion in the label.

Table 18. Comparison Main and Sensitivity Analysis Results for the Primary Endpoint

Parameter	Placebo N=164		Linaclotide 72 µg N=164		Treatment Difference (95% CI)
	N	LS Mean Change from Baseline (SE)	N	LS Mean Change from Baseline (SE)	
Main analysis approach: ANCOVA	164	1.05 (0.19)	164	2.22 (0.19)	1.17 (0.65, 1.69)
Sensitivity analysis 1: MMRM analysis (MAR)	159	1.33 (0.21)	159	2.62 (0.21)	1.29 (0.71, 1.87)
Sensitivity analysis 2: MMRM analysis (NMAR)	164	1.33 (0.21)	164	2.58 (0.21)	1.25 (0.67, 1.83)
FDA sensitivity analysis 1: MMRM analysis computing weekly score based on average of observed SBMs	162	1.68 (0.25)	161	3.36 (0.25)	1.68 (0.98, 2.38)
FDA sensitivity analysis 2: MMRM analysis with missing rescue medication imputed as used	159	0.57 (0.16)	159	1.39 (0.16)	0.83 (0.39, 1.26)

Source: Adapted from Applicant's NDA 202811 S-021 submission, Table 14.2-1.1 and 14.2-1.3 in the CSR, Table 2-2.1, 2-1.1 and 2-1.2 in the IR response of February 02, 2023.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; LS, least square; MAR, missing at random; MMRM, mixed model for repeated measures; NMAR, not missing at random; SBM, spontaneous bowel movement

To better evaluate the change in SBMs over time, an exploratory analysis looked at the least square mean and standard error for each treatment group and least square mean difference between treatment groups by study week for the prespecified MMRM MAR analysis (Sensitivity Analysis 1). The results are shown in Table 19. The treatment period in the last row represented the average change for the entire 12 weeks. The linaclotide group showed a nominally significant improvement in SBM frequency compared to placebo for all 12 weeks. SBM frequency improved during Week 1 and was maintained throughout the remainder of the 12-week treatment period. For the majority (56.7%) of subjects in the linaclotide group, the first SBM occurred within 48 hours after starting linaclotide, while 38.4% of subjects in the placebo group had their first SBM within 48 hours of receiving placebo; however, the review team did not consider the 48-hour time point following treatment initiation to be necessarily meaningful, as patients with chronic constipation can experience daily fluctuations in bowel movement frequency.

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Table 19. SBM Frequency Rate by Study Week Computed Using Prespecified MMRM MAR Analysis

SBM Frequency	Placebo N=164		Linaclotide 72 µg N=164		Treatment Difference (95% CI)
	N	LS Mean Change from Baseline (SE)	N	LS Mean Change from Baseline (SE)	
Week 1	126	1.19 (0.28)	125	2.71 (0.28)	1.52 (0.75, 2.30)
Week 2	138	1.33 (0.28)	132	2.59 (0.29)	1.26 (0.47, 2.05)
Week 3	128	1.23 (0.27)	126	2.66 (0.27)	1.43 (0.69, 2.18)
Week 4	127	1.22 (0.25)	116	2.56 (0.25)	1.34 (0.65, 2.03)
Week 5	115	1.26 (0.26)	108	2.20 (0.26)	0.94 (0.22, 1.65)
Week 6	117	1.29 (0.28)	117	2.84 (0.28)	1.55 (0.78, 2.33)
Week 7	111	1.30 (0.28)	106	2.84 (0.28)	1.54 (0.76, 2.32)
Week 8	115	1.45 (0.28)	109	2.69 (0.28)	1.24 (0.46, 2.01)
Week 9	104	1.50 (0.26)	108	2.75 (0.26)	1.25 (0.53, 1.97)
Week 10	105	1.58 (0.27)	97	2.75 (0.27)	1.17 (0.42, 1.92)
Week 11	100	1.39 (0.26)	92	2.41 (0.27)	1.02 (0.28, 1.75)
Week 12	109	1.21 (0.26)	105	2.46 (0.26)	1.25 (0.53, 1.97)
Treatment period	159	1.33 (0.21)	159	2.62 (0.21)	1.29 (0.71, 1.87)

Source: Adapted from Applicant's NDA 202811 S-021 submission, Table 2-2.1 in the IR response of February 02, 2023.
Abbreviations: CI, confidence interval; LS, least square; MAR, missing at random; MMRM, mixed models for repeated measures; SBM, spontaneous bowel movement

Data Quality and Integrity

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

Efficacy Results – Secondary and Other Relevant Endpoints

Study LIN-MD-64 had one multiplicity controlled secondary endpoint (change in 12-week stool consistency). The main analysis of 12-week stool consistency demonstrated a statistically significant ($p=0.0001$) improvement in stool consistency for the linaclotide group as compared to the placebo group, with a least square mean difference between treatment groups of 0.42 (95% CI = 0.21, 0.64) and mean post-baseline stool consistency results of 3.50 for linaclotide and 3.08 for placebo. Results from sensitivity analysis of MMRM MAR supported the main analysis approach. The least square mean difference between treatment groups for this sensitivity analysis was 0.38 (95% CI = 0.17, 0.59). Although this endpoint achieved statistical significance, the clinical meaningfulness of the treatment difference in stool consistency was unclear, as the post-baseline results for both groups represented similar Bristol stool types (as discussed below under *Overall Assessment of Effectiveness*).

The study also demonstrated a nominally significant ($p\leq 0.0001$) improvement for the linaclotide group, as compared to the placebo group, for the endpoints of 12-week CSBM frequency rate and 12-week straining. These two endpoints were not controlled for multiplicity. The least square mean difference between treatment groups for 12-week CSBM frequency rate was 0.96 CSBMs/week (95% CI = 0.51, 1.40). The least square mean difference between treatment groups for 12-week straining was -0.44 (95% CI = -0.65, -0.23). While these two endpoints were not multiplicity controlled, they were included in the label for adult chronic idiopathic constipation. Additional details of results for secondary and other efficacy endpoints are presented in Table 20.

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A total of 48 subjects with no baseline SBMs were excluded from the stool consistency and straining analyses. Additional subjects were excluded from the stool consistency and straining analyses due to missing post-baseline data, with 9 subjects who had no available post-baseline data for stool consistency and 7 subjects who had no post-baseline data for straining. In addition, four subjects were excluded from the stool consistency analysis due to missing baseline data.

Table 20. Main ANCOVA Analysis of Secondary and Other Relevant Efficacy Endpoints

Efficacy Parameter	Placebo N=164				Linaclotide 72 µg N=164				Treatment Difference (95% CI)
	N	Baseline	Post-baseline	LS Mean Change from Baseline (SE)	N	Baseline	Post-baseline	LS Mean Change from Baseline (SE)	
Stool consistency	132	2.40	3.08	0.69 (0.08)	135	2.37	3.50	1.11 (0.08)	0.42 (0.21, 0.64)
CSBM frequency	164	0.58	1.48	0.90 (0.16)	164	0.55	2.43	1.85 (0.16)	0.96 (0.51, 1.40)
Straining	136	2.59	1.77	-0.75 (0.08)	137	2.40	1.28	-1.19 (0.08)	-0.44 (-0.65, -0.23)

Source: Adapted from Applicant's NDA 202811 S-021 submission, CSR Table 14.2-2.1, 14.2-3.3 and 14.2-3.12. Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; CSBM, complete spontaneous bowel movement; LS, least square

Demographic Subgroups

The primary ANCOVA analysis for 12-week SBM frequency rate was repeated for the following subpopulations: age group (6 to 11 years group, 12 to 17 years group), region (North American, European Union, and other), race (white, non-white), and sex (male, female). Results from subgroup analyses were generally similar to those from the primary analysis in the entire population. The estimated increase in SBMs was higher in the linaclotide group compared to the placebo group for each subgroup. The treatment difference was nominally significant for every subgroup except for the non-white subgroup, region European Union subgroup, region other subgroup, and <35 kg weight subgroup. The lower bounds for the 95% confidence intervals for the non-white subgroup and <35 kg weight subgroup were just below 0 (-0.04 and -0.03, respectively). The two non-significant region subgroups had <10 subjects in each treatment group.

Table 21. 12-Week SBM Frequency Rate Analysis for Subgroups (Main ANCOVA Analysis)

Subgroups	Placebo N=164		Linaclotide 72 µg N=164		Treatment Difference (95% CI)
	N	LS Mean Change from Baseline (SE)	N	LS Mean Change from Baseline (SE)	
Age group					
6 to 11 years	91	0.89 (0.25)	90	2.27 (0.25)	1.38 (0.68, 2.08)
12 to 17 years	73	1.23 (0.28)	74	2.17 (0.28)	0.94 (0.15, 1.73)
Sex					
Male	78	0.85 (0.26)	69	2.04 (0.28)	1.19 (0.44, 1.94)
Female	86	1.20 (0.27)	95	2.36 (0.25)	1.15 (0.43, 1.88)
Race					
White	114	1.05 (0.21)	115	2.25 (0.21)	1.19 (0.62, 1.77)
Non-White	50	1.04 (0.40)	49	2.13 (0.41)	1.08 (-0.04, 2.20)

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Subgroups	Placebo N=164		Linaclotide 72 µg N=164		Treatment Difference (95% CI)
	LS Mean Change N from Baseline (SE)		LS Mean Change N from Baseline (SE)		
Region					
North American	157	1.08 (0.19)	154	2.28 (0.20)	1.20 (0.66, 1.74)
EU	6	1.02 (0.55)	7	1.34 (0.50)	0.32 (-1.39, 2.03)
Other	1	-0.71 (1.85)	3	1.72 (0.99)	2.43 (-25.66, 30.51)
Ethnicity					
Hispanic or Latino	77	1.30 (0.26)	71	2.30 (0.27)	1.00 (0.26, 1.74)
Not Hispanic or Latino	87	0.78 (0.27)	93	2.13 (0.26)	1.35 (0.61, 2.09)
Weight group					
<35 kg	52	1.45 (0.53)	47	2.28 (0.55)	0.83 (-0.03, 1.70)
≥35 kg	112	0.99 (0.24)	117	2.31 (0.23)	1.32 (0.67, 1.97)

Source: Adapted from Applicant's NDA 202811 S-021 submission, CSR Table 14.2-4.1 and IR response of March 28, 2023.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; EU, European Union; LS, least square; SBM, spontaneous bowel movement

Dose/Dose Response

The 72-µg dose was selected based on the results of Study LIN-MD-62, a phase 2 randomized, double-blind, placebo-controlled dose-ranging study in subjects 6 to 17 years of age with FC. The primary endpoint was change from baseline in 4-week overall SBM frequency rate (SBMs/week). Subjects were randomized according to age and weight to one of four linaclotide dose arms or placebo, as described in Table 22 below.

Table 22. Study LIN-MD-62: Doses Studied (Randomized Population)

Age Group	Weight	Dose A	Dose B	Dose C	Placebo	Exploratory Dose ^a
		N=36	N=41	N=39	N=41	N=16
6 to 11 years (N=90)	18 to <35 kg	9 µg	18 µg	36 µg	Placebo	—
	≥35 kg	18 µg	36 µg	72 µg	Placebo	—
12 to 17 years (N=83)		18 µg	36 µg	72 µg	Placebo	145 µg

Source: Reviewer's table adapted from Applicant's LIN-MD-62 Clinical Study Report

^a Linaclotide 145-µg dose included for safety and exploratory efficacy only, and studied only in the 12-to-17-year age group

For the primary endpoint of change from baseline in 4-week overall SBM frequency rate, none of the linaclotide dose groups (A, B, or C) achieved statistically significant improvement over placebo. However, numerical trends appeared to suggest that the 72-µg dose demonstrated greater efficacy than lower doses (<72 µg), while the higher dose (145 µg) appeared to demonstrate no additional benefit over the 72-µg dose. Therefore, the 72-µg dose was chosen for inclusion in the pivotal phase 3 study LIN-MD-64.

Durability of Response

In the open-label extension study LIN-MD-66, subjects were assessed by investigators at Screening and at Week 24 for fulfillment of Rome III criteria. In the investigator assessment, a response of "Yes" meant that a subject did not fulfill modified Rome III criteria. Enrollment in LIN-MD-66 was open to subjects who completed LIN-MD-62 or LIN-MD-64; inclusion was not dependent on whether a subject fulfilled Rome criteria at time of LIN-MD-66 screening.

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As shown in Table 23 below, the proportions of subjects with an assessment of “Yes” (i.e., not meeting diagnostic criteria for FC on the investigator assessment) increased from baseline to end of open-label study treatment (for linaclotide 72 µg, 17.1% at baseline to 63.4% at end of treatment).

Table 23. Subjects Not Fulfilling Modified Rome III Criteria (LIN-MD-66)

Parameter	Linaclotide 72 µg	Linaclotide 145 µg
	N=210 n/N1 (%)	N=73 n/N1 (%)
Screening		
Yes (Not fulfilling modified Rome III criteria)	14/82 (17.1)	4/25 (16.0)
No (Fulfilling modified Rome III criteria)	68/82 (82.9)	21/25 (84.0)
End of open-label study treatment		
Yes (Not fulfilling modified Rome III criteria)	52/82 (63.4)	16/25 (64.0)
No (Fulfilling modified Rome III criteria)	30/82 (36.6)	9/25 (36.0)

Source: Reviewer's table adapted from Table 1 of Applicant's response to FDA's information request, received April 19, 2023
N1 (percentage denominator) = subjects with modified Rome III assessments at both LIN-MD-66 screening and end of treatment

Several limitations affect interpretability of these data, including that the data were collected during an open-label, uncontrolled treatment period. Of note, a total of 176 subjects enrolled in LIN-MD-66 were not included in the analyses; 104 subjects were enrolled prior to implementation of the assessments in the study protocol, and an additional 72 subjects had missing data for other reasons. Therefore, while the available data suggest most subjects experienced clinical improvement during the 24-week open-label treatment period, the long-term efficacy of linaclotide in the pediatric population has not been fully characterized.

Persistence of Effect

The review team considered whether subjects who responded to linaclotide in LIN-MD-64 continued to respond to linaclotide in LIN-MD-66. The only efficacy variable implemented across both studies was the investigator assessment of “Not Fulfilling Modified Rome III Criteria.” However, of 283 subjects who completed LIN-MD-66, only 50 subjects who completed linaclotide treatment in LIN-MD-64 also had evaluable end of treatment data for LIN-MD-66. Of these 50 subjects, 9 subjects had an assessment of “Not Fulfilling Modified Rome III Criteria” at end of treatment in LIN-MD-64. All 9 subjects had an assessment of “Not Fulfilling Modified Rome III Criteria” at end of treatment in LIN-MD-66. The review team did not consider the data to be conclusive due to the limitations stated above under *Durability of Response*.

Overall Assessment of Effectiveness

Study LIN-MD-64 demonstrated statistical significance for linaclotide over placebo on the primary endpoint of change from baseline in 12-week SBM frequency rate and multiplicity controlled secondary endpoint of change from baseline in 12-week stool consistency. The review team also considered clinical meaningfulness of the efficacy results. Although Study LIN-MD-64 included weekly administration of patient- or caregiver-reported assessments of global severity and change in signs/symptoms, the anchor-based analyses were uninterpretable (b) (4)

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(b) (4) While anchor-based methods remain the review team's preferred approach to defining thresholds for clinically meaningful within-patient changes in COA scores, the review team considered alternate methods for interpreting whether efficacy results were clinically meaningful in the intended patient population with FC.

The team agreed that, in this specific circumstance, an alternative approach for interpreting clinical meaningfulness was possible due to the nature of the data (inherent observability of SBM frequency), availability of established Rome criteria that define a diagnostic threshold for weekly bowel movement frequency ("two or fewer defecations in the toilet per week in a child of a developmental age of at least 4 years") (Table 1), information regarding generally normal bowel habits in the intended population, and supportive data from other secondary and exploratory endpoints (e.g., rescue medication use throughout the study). Of note, the observability of stool frequency was an important factor because LIN-MD-64 included subjects from various stages of child and adolescent development (6 to 17 years) and offered the option for younger subjects to have their data reported by a caregiver, based on the caregiver interviewing the subject. Therefore, the review team considered measurement of observable signs (i.e., counting SBMs) to have greater interpretability across the range of respondents than unobservable symptoms (which only each individual patient could reliably report, using age-appropriate COAs).

Given the lack of interpretable anchor-based analyses, the review team used an alternative approach to assess whether the statistically significant result for the primary endpoint (change from baseline in 12-week stool frequency rate) was clinically meaningful. The 12-week SBM frequency rate results showed that the observed post-baseline mean SBM frequency rate for linaclotide (3.41 SBMs/week) no longer met the Rome criterion for weekly bowel movement frequency ("two or fewer defecations in the toilet per week"), whereas the post-baseline mean for placebo was 2.29 SBMs/week (Table 17). The review team also noted that a stool frequency of at least 3 bowel movements per week can generally be considered normal in children and adolescents (NASPGHAN 2006; Tabbers et al. 2010). In contrast, the post-baseline mean for placebo did not achieve the same thresholds. The review team confirmed interpretability of primary endpoint data by assessing results by COA administration method (i.e., subject self-report versus caregiver report), which showed that the treatment difference for linaclotide versus placebo on the primary endpoint was consistent across the two administration methods (Section 15.7).

For the multiplicity-controlled secondary endpoint, the observed post-baseline mean stool consistency results for linaclotide (3.50) and placebo (3.08) (Table 20) appeared to be similar, as both groups achieved a mean stool type that was neither too hard nor too soft, and no longer meet relevant Rome criteria for FC related to stool consistency (i.e., "painful or hard bowel movements"). These data were further limited since the analysis of change from baseline in 12-week stool consistency by COA administration method showed inconsistent treatment differences across the two administration methods, with caregiver-reported data showing an inconclusive difference between linaclotide and placebo (Section 15.7), Table 20 (i.e., soft and formed). Therefore, although improvement in stool consistency is a clinically relevant outcome for patients with FC, there was insufficient evidence to support that the observed treatment difference for linaclotide versus placebo was clinically meaningful.

The review team also considered the results of exploratory analyses to further inform

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characterization of potential clinical benefit. An exploratory analysis of rescue medication use showed that, after Week 6, weekly rates of rescue medication use for linaclotide-treated subjects were approximately half the rates for those on placebo; at Week 12, 10.7% of linaclotide-treated subjects used rescue medication versus 21.9% on placebo, and overall, fewer linaclotide subjects (52.1%) used at least one dose of rescue medication over the 12-week treatment period than placebo (60.4%) (Table 16). Additionally, an exploratory endpoint of change in mean straining scores favored linaclotide over placebo (-1.19 versus -0.75, respectively) (Table 20); however, clinical meaningfulness of the treatment difference could not be determined due to lack of interpretable anchor-based analyses.

The review team also considered exploratory analyses of fecal incontinence. At baseline, fecal incontinence was reported in 56 (34.1%) subjects randomized to linaclotide and 54 (32.9%) subjects randomized to placebo. Overall, fecal incontinence was reported by slightly more linaclotide-treated subjects than placebo, with 94 (57.7%) linaclotide subjects and 85 (51.8%) placebo subjects reporting at least 1 response of “yes” to a daily diary item regarding fecal incontinence over the 12-week treatment period. When analyzing each individual week in the 12-week intervention period, rates of fecal incontinence were similar for linaclotide and placebo groups at Weeks 8 (16.9% versus 16.9%), 10 (13.8% versus 15.8%), and 12 (20.6% versus 19.1%). When analyzing SBM frequency and stool consistency on days when fecal incontinence was reported versus days when it was not reported, days with fecal incontinence were associated with higher SBM frequency and/or higher (i.e., softer) stool consistency in both groups. Overall, the review team concluded that linaclotide did not improve fecal incontinence in this study, although the observed effects on fecal incontinence appear to be consistent with the known mechanism of action for linaclotide.

The observed improvements in SBM frequency rate, stool consistency, and reductions in rescue medication use and straining in Study LIN-MD-64 were considered collectively with the available efficacy data from adult studies (Section 8.1.3) to inform an overall characterization of potential clinical benefit.

8.1.3. Assessment of Efficacy Across Studies

In general, similar products are used to treat constipation in adults and pediatric patients, and the disease definition, pathophysiology, clinical presentation, and outcomes to measure response (e.g., stool frequency, stool consistency) to treatment are considered sufficiently similar between the adult and pediatric population with constipation.

Therefore, results from pediatric study LIN-MD-64 were compared to results from the phase 3 studies that supported approval for linaclotide (72 µg and 145 µg once daily) in adults with CIC (MCP-103-303, LIN-MD-01, and MCP-103-309). The pediatric and adult studies included similar efficacy endpoints. Results from Study MCP-103-309, which supported the approval of linaclotide 72 µg in adults with CIC, are displayed in Table 24.

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Table 24. Efficacy Endpoint Results for Adult Chronic Idiopathic Constipation Study

Efficacy Parameter Change From Baseline	LS Mean (SE)		LSMD (95% CI)	p-value
	Placebo N=401	Linaclotide 72 µg N=411		
12-week CSBM frequency	0.884 (0.142)	1.725 (0.139)	0.841 (0.505, 1.176)	<0.0001
12-week SBM frequency	1.329 (0.169)	2.366 (0.166)	1.037 (0.636, 1.438)	<0.0001
12-week stool consistency	1.065 (0.076)	1.693 (0.074)	0.628 (0.450, 0.806)	<0.0001
12-week straining	-0.789 (0.051)	-1.118 (0.050)	-0.329 (-0.449, -0.210)	<0.0001

Source: Table 7 in the FDA statistical review for NDA 202811 Supplement 10. Originally adapted from Applicant's submission, Study MCP-103-309 CSR.

Abbreviations: CSBM, complete spontaneous bowel movement; LS, least squares; LSMD, least squares mean difference; SBM, spontaneous bowel movement

While the primary endpoint of the adult study was a responder definition based on achieving at least 3 CSBMs and an increase of at least 1 CSBM from baseline in a given week for at least 9 weeks of the 12-week treatment period, the change from baseline in the CSBM frequency, SBM frequency, stool consistency, and straining endpoints evaluated in the pediatric study LIN-MD-64 were also statistically significant for the adult study MCP-103-309. The estimated difference in least square means were generally similar between the adult and pediatric studies. The similarities in clinical response support relying on extrapolation of efficacy from adult data.

In light of the unmet need for approved treatments for pediatric FC, the review team concluded that the pediatric study data from a placebo-controlled study in 328 subjects with FC, supported by efficacy data from multiple adequate and well-controlled studies in adults with CIC, provided evidence of effectiveness and meaningful clinical benefit for linaclotide in pediatric patients ages 6 to 17 years with FC.

8.1.4. Integrated Assessment of Effectiveness

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

8.2. Review of Safety

8.2.1. Safety Review Approach

Review of safety focused on placebo-controlled data from the 12-week double-blind, placebo-controlled phase 3 study LIN-MD-64. Interim data from the 24-week open-label extension study LIN-MD-66, which enrolled subjects who completed LIN-MD-62 or LIN-MD-64, were also assessed. Data from the phase 2 study LIN-MD-62 were also reviewed (as described in Section 6.2.3), but the phase 2 data did not contribute considerably to the safety review due to a relatively small sample size for subjects receiving linaclotide 72 µg and short treatment duration of 4 weeks.

8.2.2. Review of the Safety Database

Overall Exposure

In LIN-MD-64, 164 subjects were randomized to receive linaclotide and 164 subjects were randomized to receive placebo. Table 25 below describes durations of exposure in LIN-MD-64.

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

Parameter	Placebo N=164	Linaclotide 72 µg N=164
Duration of exposure (days), n (%)		
1 to ≤14 days	2 (1.2)	5 (3.0)
>14 to ≤28 days	3 (1.8)	5 (3.0)
>28 to ≤56 days	7 (4.3)	2 (1.2)
>56 to ≤96 days	147 (89.6)	150 (91.5)
>96 days	5 (3.0)	2 (1.2)
Mean (SD)	82.5 (16.2)	81.1 (18.1)
Median	86.0	85.0

Source: Adapted from Applicant's LIN-MD-64 Study Report Table 14.3-1.1
Abbreviations: SD, standard deviation

Additionally, interim data were submitted from the ongoing open-label extension study LIN-MD-66, which enrolled linaclotide- and placebo-treated subjects who completed LIN-MD-62 or LIN-MD-64. As shown in Table 26 below, 145 subjects received at least 24 weeks of open-label linaclotide 72 µg and 46 subjects received at least 24 weeks of open-label linaclotide 145 µg, with mean and median exposures of approximately 23 and 24 weeks in both dose groups.

Table 26. Duration of Exposure in LIN-MD-66 (Interim Analysis)

Parameter	Linaclotide 72 µg N=210	Linaclotide 145 µg N=73	Linaclotide Total N=283
Duration of exposure (weeks), n (%)			
≤4 weeks	3 (1.4)	0	3 (1.1)
>4 to ≤8 weeks	4 (1.9)	2 (2.7)	6 (2.1)
>8 to ≤12 weeks	5 (2.4)	2 (2.7)	7 (2.5)
>12 to ≤18 weeks	7 (3.3)	3 (4.1)	10 (3.5)
>18 to ≤24 weeks	46 (21.9)	20 (27.4)	66 (23.3)
>24 weeks	145 (69.0)	46 (63.0)	191 (67.5)
Mean (SD)	23.3 (4.67)	23.1 (4.31)	23.2 (4.57)
Median	24.1	24.1	24.1

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

Total exposures from the lead-in study (LIN-MD-62 or LIN-MD-64) plus LIN-MD-66 were also examined. As shown in Table 27 below, 189 subjects had at least 24 weeks of total exposure to linaclotide 72 µg and 51 subjects had at least 36 weeks of exposure.

Table 27. Duration of Total Exposure to Linaclotide (Lead-in Study Through LIN-MD-66; Interim Analysis)

Parameter	Linaclotide 72 µg N=210	Linaclotide 145 µg N=73	Linaclotide Total N=283
Duration of exposure (weeks), n (%)			
≥4 weeks	209 (99.5)	73 (100.0)	282 (99.6)
≥12 weeks	204 (97.1)	70 (95.9)	274 (96.8)
≥24 weeks	189 (90.0)	61 (83.6)	250 (88.3)
≥30 weeks	63 (30.0)	17 (23.3)	80 (28.3)
≥36 weeks	51 (24.3)	14 (19.2)	65 (23.0)
Mean (SD)	27.3 (6.9)	26.3 (7.0)	27.1 (6.9)
Median	24.6	24.6	24.6

Source: Applicant's Response to Information Request received April 20, 2023, Table 2

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Adequacy of the Safety Database

The Applicant's safety database contained placebo-controlled safety data from 328 subjects, of which 293 subjects (148 for linaclotide 72 µg and 145 for placebo) completed 12 weeks, as well as open-label safety data from 189 subjects who received linaclotide 72 µg and 46 subjects who received linaclotide 145 µg for at least 24 weeks.

The review team considered the limitations of interpreting open-label data, given that uncontrolled, open-label data can be challenging to interpret and do not necessarily replace the need for controlled, blinded data to inform whether adverse events are related to the drug or other factors. Pediatric FC is sufficiently similar to adult CIC with respect to pathophysiology, clinical presentation, and expected response to treatment to allow available pediatric safety data to be examined in light of regulatory and clinical experience with linaclotide since its initial approval for adult indications in 2012. As described in the approved product label, exposure in adult clinical development included approximately 2570, 2040, and 1220 adult patients with either IBS-C or CIC, treated with Linzess for 6 months or longer, 1 year or longer, and 18 months or longer, respectively (not mutually exclusive). Therefore, in addition to the safety data submitted from the pediatric studies supporting this NDA supplement, the review team considered the body of pre- and post-marketing safety data that has been collected and analyzed for linaclotide.

The review team concluded that, due to 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 age 6 years and older with FC.

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. No issues were identified regarding the Applicant's categorization of TEAEs.

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AEs presented in the Study LIN-MD-64 clinical study report and the Integrated Summary of Safety were coded by the Applicant using Medical Dictionary for Regulatory Activities version 25.0. AEs presented in the clinical study report for Study LIN-MD-62 were coded using Medical Dictionary for Regulatory Activities version 21.0. No issues were identified regarding the Applicant's coding of AEs.

Routine Clinical Tests

Vital signs were assessed at every visit, physical examinations were performed at Screening and Week 12 visits, and clinical laboratory tests were performed at Screening, Baseline, and Week 12 visits. Overall, no issues were identified regarding the routine clinical tests.

8.2.4. Safety Results

Deaths

No deaths were reported in LIN-MD-62, LIN-MD-64, or LIN-MD-66.

Serious Adverse Events

In LIN-MD-64, 2 subjects in the linaclotide 72 µg group and 2 subjects in the placebo group experienced a treatment-emergent SAE (Table 28). The SAE narratives are summarized as follows:

- A 17-year-old female taking linaclotide 72 µg was hospitalized for severe diarrhea and dehydration. The subject began experiencing 3 to 5 daily episodes of diarrhea on Day 1 of treatment, then began experiencing symptoms of dehydration on Day 3. The subject reported the diarrhea to her parent on Day 10, and subsequently presented to the emergency department for care. The subject was permanently discontinued from study drug and recovered with supportive care. The SAEs were determined by the investigator to be related to linaclotide. Diarrhea, including serious diarrhea, is a known risk of linaclotide; risk of diarrhea will be addressed in labeling for linaclotide.
- An 11-year-old male taking linaclotide 72 µg was hospitalized for fecaloma on Day 26 of treatment. The subject was permanently discontinued from study drug and recovered with supportive care. The SAE was determined by the investigator to not be related to linaclotide.
- Two subjects in the placebo group, a 12-year-old male and a 12-year-old female, were hospitalized for suicide attempts. Both subjects were discontinued from the study.

Dropouts and/or Discontinuations Due to Adverse Effects

In LIN-MD-64, 2 subjects in the linaclotide 72 µg group and 3 subjects in the placebo group discontinued treatment due to a TEAE (Table 28). Both linaclotide 72 µg subjects and two placebo subjects who discontinued Study LIN-MD-64 are described above under *Serious Adverse Events*. A third placebo subject discontinued Study LIN-MD-64 due to moderate COVID-19.

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Significant Adverse Events

In LIN-MD-64, severe TEAEs were reported for 3 subjects in the linaclotide 72 µg group and 2 subjects in the placebo group. In the linaclotide group, severe TEAEs included diarrhea, dehydration (with diarrhea and dehydration reported in the same subject), fecaloma, and pulmonary artery stenosis. The TEAEs of diarrhea, dehydration, and fecaloma were considered serious and are described above under *Serious Adverse Events*. The TEAE of pulmonary artery stenosis was graded as severe but not considered serious or related to treatment, and the subject did not discontinue dosing. In the placebo group, severe TEAEs included suicide attempt and suicidal ideation, which were both considered serious and are described above under *Serious Adverse Events*.

Treatment Emergent Adverse Events and Adverse Reactions

Table 28 summarizes the numbers of subjects who experienced TEAEs, treatment-emergent SAEs, and TEAE-related discontinuations in LIN-MD-64. Rates of treatment-emergent SAEs and TEAE-related discontinuations were similar between linaclotide and placebo groups.

Table 28. Treatment-Emergent Adverse Event Summary: Study LIN-MD-64

Event Type	Placebo	Linaclotide 72 µg
	N=164 n (%)	N=164 n (%)
Subjects with any TEAE	35 (21.3%)	28 (17.1%)
Subjects with any treatment-emergent SAE	2 (1.2%)	2 (1.2%)
Subjects with any TEAE leading to death	0	0
Subjects with any TEAE leading to permanent discontinuation	3 (1.8%)	2 (1.2%)

Source: Reviewer's table using adae.xpt dataset from Study LIN-MD-64

Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event

Table 29 below summarizes the TEAEs most commonly reported in LIN-MD-64 subjects receiving linaclotide 72 µg and at greater incidence than placebo. The review team selected a threshold of >1% because any AE that occurred in a single subject corresponded to a proportion of 1% (specifically, 0.6%). The most common AE in LIN-MD-64 was diarrhea, which was reported by 7 subjects (4.3%) receiving linaclotide 72 µg and 3 (1.8%) receiving placebo. The second most common AE was nausea, which was reported in 2 subjects (1.2%) receiving linaclotide 72 µg and no subjects receiving placebo.

Table 29. Adverse Event Summary (TEAEs Occurring in >1% Linaclotide-Treated Subjects and Greater Than Placebo): Study LIN-MD-64

Adverse Event	Placebo	Linaclotide 72 µg
	N=164 n (%)	N=164 n (%)
Diarrhea	3 (1.8%)	7 (4.3%)
Nausea	0	2 (1.2%)

Source: Reviewer's table using adae.xpt dataset from Study LIN-MD-64

Additionally, TEAEs of abdominal discomfort and dehydration were reported in one patient each (0.6%) for linaclotide and were determined by investigators to be treatment-related. No cases of abdominal discomfort or dehydration were reported for placebo.

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The review team recommends listing diarrhea, nausea, abdominal discomfort, and dehydration as AEs in labeling for linaclotide. Although nausea, abdominal discomfort, and dehydration occurred at generally low incidence rates (<2%), sample sizes in LIN-MD-64 were relatively small when compared to sample sizes of studies supporting the adult chronic idiopathic constipation indication (for which labeling reflects data from 1275 adult patients across two studies). The review team considers diarrhea, nausea, abdominal discomfort, and dehydration to be clinically relevant treatment-related AEs.

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, with the exception of low bicarbonate in one subject experiencing adverse events of severe diarrhea and dehydration (described above under *Serious Adverse Events*).

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

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 for this review. AE reports, laboratory parameter data, and daily diary data were reviewed for signs of dehydration possibly related to diarrhea. As described above under *Serious Adverse Events*, 1 subject receiving linaclotide 72 µg in LIN-MD-64 experienced severe diarrhea and diarrhea-related dehydration that resulted in hospitalization and permanent discontinuation of linaclotide. Additionally, 1 subject receiving open-label linaclotide 72 µg in LIN-MD-66 (after completing double-blind placebo in LIN-MD-64) experienced mild diarrhea and dehydration that resulted in permanent discontinuation of linaclotide.

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The review team examined laboratory and vital sign data from LIN-MD-64 for possible evidence of dehydration events that may not have been reported to investigators as AEs. The review team also explored whether subjects who reported p-BSFS Type 7 stools (“looks like a milkshake, watery”) using the stool consistency item in the daily diary had concurrent laboratory or vital sign abnormalities that may be associated with dehydration. From the laboratory, vital sign, and daily diary data, the review team did not identify any additional cases of diarrhea-related dehydration that were not already reported as AEs.

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. In the case of the SAE reported in LIN-MD-64, an adolescent subject experienced diarrhea for 10 days before reporting it to her parent and receiving emergency care for dehydration. The review team therefore recommends that product labeling describe diarrhea and dehydration as AEs reported in the pediatric studies.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Refer to Section 8.2.5 above regarding assessment of diarrhea using daily diary items.

8.2.7. Safety Analyses by Demographic Subgroups

Table 30 below describes the proportion of subjects who experienced at least one TEAE, by demographic subgroups of sex, age group, and race/ethnicity.

Table 30. Subjects With Any TEAE by Demographic Subgroup (LIN-MD-64)

Parameter	Placebo N=164 (%)	Linaclotide 72 µg N=164 (%)	Risk Difference (Linaclotide - Placebo)
Sex			
Male	12/78 (15.4)	13/69 (18.8)	3.5
Female	23/86 (26.7)	15/95 (15.8)	-11.0
Age group			
6 to 11 years	18/91 (19.8)	16/90 (17.8)	-2.0
12 to 17 years	17/73 (23.3)	12/74 (16.2)	-7.1
Race			
White	26/114 (22.8)	21/115 (18.3)	-4.5
Black or African American	8/45 (17.8)	5/41 (12.2)	-5.6
Asian	1/2 (50.0)	0/3 (0.0)	-50.0
Native Hawaiian or other Pacific Islander	0/1 (0.0)	2/3 (66.7)	66.7
American Indian or Alaska Native	0/1 (0.0)	0/0 (0.0)	0.0

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

For sex, rates of AEs were similar for placebo and linaclotide in males whereas rates of AEs were higher for placebo versus linaclotide in females.

For age group, rates of AEs were similar for placebo and linaclotide in 6- to 11-year-olds whereas rates of AEs were higher for placebo versus linaclotide in 12- to 17-year-olds.

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For race, rates of AEs were similar for White and Black or African American subgroups. Sample sizes for the remaining race and ethnicity subgroups were too small to assess.

Overall, no clinically meaningful trends were identified by the subgroup analyses; however, sample sizes for subgroups were generally too small to facilitate meaningful comparisons.

8.2.8. Specific Safety Studies/Clinical Studies

Not applicable.

8.2.9. 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 µg/kg/day or in mice at doses up to 6000 µg/kg/day. The maximum recommended human dose is approximately 5 µg/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 µg/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 baseline and weekly throughout the 12-week treatment period, whereas subject height was only assessed at baseline. Meaningful changes in growth are unlikely to be observed over a short 12-week duration. Linaclotide and placebo groups were similar regarding the proportion of subjects meeting weight decreases of $\geq 5\%$ from baseline (4.4% of linaclotide subjects versus 3.7% of placebo subjects) and weight increases of $\geq 5\%$ from baseline (23.1% of linaclotide subjects versus 25.3% of placebo subjects).

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

As described in the clinical review supporting the original 2012 approval of Linzess, single doses of linaclotide up to 2897 µg 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 µg 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 µg and 290 µg, 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.

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8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Division of Pharmacovigilance I (DPV-I) was consulted to conduct a postmarket safety review of linaclotide use in patients younger than 18 years of age who received treatment with linaclotide. DPV-I previously reviewed data from the FDA Adverse Event Reporting System (FAERS) from the initial date of linaclotide approval through October 21, 2020 (see IND 063290 Post-Market Safety Review dated November 13, 2020; DARRTS ID: 4701057); therefore, the present DPV-I review considered FAERS data from October 22, 2020 through December 26, 2022.

DPV-I did not identify any relevant cases of AEs associated with linaclotide use in pediatric patients from October 22, 2020 to December 26, 2022 (see NDA 202811 Post-Market Safety Review dated January 4, 2023; DARRTS ID: 5103945). The previous DPV-I review, examining FAERS cases through October 21, 2020 (Labeling Review dated August 23, 2021; DARRTS ID: 4845684), identified 7 relevant cases of AEs with a possible causal relationship to linaclotide use, all occurring in patients 16 or 17 years of age. Of the 7 cases, 2 were serious and 5 were nonserious. Of the serious cases, one had limited information for assessment and the other described a 17-year-old female who experienced hematochezia while taking linaclotide 145 µg daily and then severe diarrhea, abdominal pain, vomiting, and hot/cold flashes following a dose increase to linaclotide 290 µg daily. The case did not report whether the patient experienced complications of diarrhea or required treatment for the AEs. Hematochezia is reflected in linaclotide labeling as an adverse reaction identified during post-approval use of Linzess.

Based on the review by DPV-I conducted 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 review of this Application or of available postmarket safety data. Therefore, the review team expects that routine pharmacovigilance will be adequate to ensure safe use of linaclotide in patients 6 to 17 years of age.

8.2.11. Integrated Assessment of Safety

The Applicant submitted pooled safety data from the placebo controlled studies LIN-MD-62 and LIN-MD-64, but the pooled data were not the focus of the safety review due to significant study design differences between LIN-MD-62 and LIN-MD-64. Specifically, treatment durations were 4 weeks in LIN-MD-62 and 12 weeks in LIN-MD-64; only subjects weighing ≥ 35 kg were eligible to receive linaclotide 72 µg in LIN-MD-62, whereas all enrolled subjects (weight ≥ 18 kg) were eligible to receive linaclotide 72 µg in LIN-MD-64; and subjects ages 6 to 11 years received oral solution in LIN-MD-62, whereas all subjects ages 6 to 17 years received oral capsules in LIN-MD-64. Therefore, the safety data from the LIN-MD-62 and LIN-MD-64 were assessed separately and not as pooled analyses.

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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.

8.3. Statistical Issues

The Applicant's prespecified main analysis for SBM frequency did not require a minimum number of diaries in order to compute SBM frequency. Furthermore, when diaries were missing, this analysis assumed that no SBMs occurred and that rescue medication was not used. These assumptions cannot be verified. The review team examined a number of missing data sensitivity analyses to determine whether these assumptions had an impact on efficacy conclusions (See Section 8.1.2). The results from these sensitivity analyses were consistent with the primary analysis and the missing data assumptions were not considered to have impacted efficacy conclusions.

Consistent with FDA's guidance, the Applicant conducted quantitative anchor-based analyses to aid in the interpretation of the efficacy analysis results for the Pediatric Functional Constipation Symptom Diary (PFCSD)-based endpoints of SBM frequency rate and stool consistency. However, given the unsurmountable limitations of the anchor data and anchor-based analyses (see Section 15.6 for detailed discussion on the limitations), the review team concluded that the Applicant's quantitative anchor-based analysis results were uninterpretable. As such, the evaluation of the meaningfulness of the treatment benefit relied on established clinical criteria for FC (see *Overall Assessment of Effectiveness* in Section 8.1.2 for the discussion on meaningfulness evaluation from a clinical perspective).

9. Advisory Committee Meeting and Other External Consultations

There were no safety or efficacy concerns identified during the review of this sNDA that required an Advisory Committee Meeting or other external consultations.

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10. Pediatrics

This NDA supplement (021) for linaclotide is intended to fulfill the following Postmarketing Requirement (PMR) and address the studies below that are described in the Pediatric Written Request (PWR) studies:

- PMR 2161-3: Conduct a safety and efficacy study in pediatric patients with chronic idiopathic constipation ages 6 to 17 years treated with Linzess (linaclotide).
- PWR Study 01: Randomized, double-blind, placebo-controlled, parallel group, dose-ranging study for the treatment of chronic idiopathic constipation in children ages 6 to 17 years. (n= ~160 total stratified by age group [6 to 11 years and 12 to 17 years] with $\geq 40\%$ enrollment in each age group; randomized to placebo, low dose, medium dose, high dose, or approved adult dose [12 to 17 years])
- PWR Study 03: Randomized, double-blind, placebo-controlled, parallel group confirmatory study for the treatment of chronic idiopathic constipation in children ages 6 to 17 years. (n \geq ~120 total stratified by age group with $\geq 40\%$ enrollment in each age group)
- PWR 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. (n \geq ~120)

To fulfill PWR Study 01, the Applicant conducted Study LIN-MD-62, a phase 2 randomized, double-blind, placebo-controlled, dose-ranging study in subjects ages 6 to 17 years who met modified Rome III criteria for functional constipation (FC). LIN-MD-62 is discussed in Section 6.2 above.

To fulfill PWR Study 03 and PMR 2161-3, the Applicant conducted Study LIN-MD-64, a phase 3 randomized, double-blind, placebo-controlled study of linaclotide 72 μg once daily versus placebo in subjects ages 6 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-62 or LIN-MD-64. Subjects 6 to 11 years of age receive open-label linaclotide 72 μg once daily, and subjects 12 to 17 years are randomized 1:1 to receive open-label linaclotide 72 μg or 145 μg once daily. Interim data from LIN-MD-66 are discussed in Sections 8.1 and 8.2 above.

The review team recommends fulfillment of PMR 2161-3 based on the Applicant's completion of LIN-MD-64. Although PWR Studies 01 and 03 have been completed there are additional studies described in the PWR that remain to be completed, and thus it is premature to determine that the PWR has been fulfilled at this time.

Linzess (linaclotide)

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Table 31. Prescribing Information

Full Prescribing Information Sections ¹	High-Level Summary of the Major Issues With the Applicant's Proposed Draft PI and How Those Major Issues Were Addressed in the Finalized PI ²
1 INDICATIONS AND USAGE	The indication was added for the treatment of functional constipation (FC) in pediatric patients 6 to 17 years of age.
2 DOSAGE AND ADMINISTRATION	The recommended dosage is 72 µg orally once daily for the treatment of pediatric patients 6 to 17 years of age with FC.
5 WARNINGS AND PRECAUTIONS	<p data-bbox="529 632 1419 688"><u>5.1 Risk of Serious Dehydration in Pediatric Patient Less Than 2 Years of Age</u></p> <p data-bbox="529 688 1419 814">The following sentence was removed by the Applicant: (b) (4)</p> <p data-bbox="529 814 1419 968">The review team agreed with removal of this sentence in WARNINGS AND PRECAUTIONS (b) (4) LINZESS continues to be contraindicated in pediatric patients less than 2 years of age given the adverse findings in nonclinical data.</p>
6 ADVERSE REACTIONS 6.1 Clinical Trials Experience	<p data-bbox="529 999 1419 1178"><u>5.2 Diarrhea</u> The reported rate of diarrhea and severe diarrhea reported in the double-blind placebo-controlled study of pediatric patients with FC has been added, similar to information already presented on the incidence of diarrhea and severe diarrhea in the adult irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) populations.</p> <p data-bbox="529 1178 1419 1335">In the subsection on adverse reactions reported in the pediatric clinical study of FC, the adverse reaction of diarrhea is described in body text (instead of in table format, as proposed by the Applicant) along with other less common adverse reactions of nausea and abdominal discomfort and dehydration.</p>
8 USE IN SPECIFIC POPULATIONS 8.4 Pediatric Use	<p data-bbox="529 1341 1419 1457">The text in this subsection was revised according to the FDA guidance for industry <i>Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling</i> (March 2019). The following information was added:</p> <p data-bbox="529 1486 1419 1696">“The safety and effectiveness of LINZESS for the treatment of FC in pediatric patients 6 to 17 years of age have been established. Use of LINZESS for this indication is supported by evidence from adequate and well-controlled studies in adults and pediatric patients 6 years of age and older. The safety of LINZESS in adult and pediatric patients 6 to 17 years of age in clinical studies was similar [see <i>Adverse Reactions (6.1) and Clinical Studies (14.3)</i>].”</p> <p data-bbox="529 1726 1419 1812">The paragraph describing the findings in the clinical GC-C ontogeny study was reworded for transition of information from nonclinical (findings in neonatal mice) to clinical safety information within this subsection.</p>

Linzess (linaclotide)

14 CLINICAL STUDIES

14.3 Functional Constipation [FC] in Pediatric Patients 6 to 17 Years of Age

The proposed description of the clinical study of FC was revised to include baseline demographics and relevant enrollment criteria.

The section will describe only the result of the primary endpoint analysis (12-week change from baseline in spontaneous bowel movement [SBM] frequency rate).

The review team did not agree with the Applicant's proposal (b) (4)

Rather, describing improvements over a week and then communicating that the improvement observed was maintained is clinically meaningful information for prescribers and patients. Thus, the review team agreed to describe that "SBM frequency improved during week 1 and was maintained throughout the remainder of the 12-week treatment period."

The team did not agree to include the Applicant's (b) (4)

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.

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14. Division Signatory Authority Comments

I concur with the recommendation of the review team to approve supplemental NDA 202811/S-021 for Linzess (linaclotide) to expand the indications to include the treatment of functional constipation in pediatric patients 6 to 17 years of age. The Division recognizes the unmet medical need for therapies to treat pediatric functional constipation, and Linzess will be the first product approved for treating pediatric functional constipation.

The efficacy of linaclotide in pediatric patients 6 to 17 years of age with functional constipation relies on extrapolation of efficacy from adequate and well-controlled studies in adults with CIC (Studies MCP-103-303, LIN-MD-01, and MCP-103-309), and supplemented by efficacy data in pediatric patients with functional constipation 6 years and older. In general, similar products are used to treat constipation in adults and pediatric patients, and the disease definition, clinical manifestations, and outcomes to measure response (e.g., stool frequency, stool consistency) to treatment are considered sufficiently similar between the adult and pediatric population with constipation; however, there are some knowledge gaps (e.g., there may be age-related factors that contribute to constipation) and information from controlled studies in pediatric patients are limited as there are no products approved for treating pediatric FC. The efficacy endpoints assessed in the pediatric study (change from baseline in SBM frequency, stool consistency, and straining) were also evaluated in the adult studies and the results were generally consistent across the pediatric and adult studies.

To support the indication, the Applicant conducted Study LIN-MD-64, a phase 3 randomized, double-blind, controlled study of linaclotide 72 µg versus placebo in 328 subjects 6 to 17 years of age who met modified Rome III criteria for functional constipation. Study LIN-MD-64 achieved statistical significance on the primary endpoint of change from baseline in 12-week spontaneous bowel movement (SBM) frequency rate, and the multiplicity controlled secondary endpoint of change from baseline in 12-week stool consistency using the pediatric Bristol Stool Form Scale (p-BSFS). The Applicant collected qualitative data using anchor scales to aid interpretation of the change from baseline analyses for the efficacy endpoints of SBM frequency and stool consistency. The anchor-based methods for this study were not interpretable (b) (4) [REDACTED] (b) (4) In this specific circumstance, an alternative approach for interpreting clinical meaningfulness of the efficacy results was possible given the nature of the endpoints, available information to inform bowel habits that can generally be considered normal in the intended pediatric population, and reliance on extrapolation of efficacy from adult data using similar endpoints.

The observed post-baseline mean SBM frequency rates for linaclotide (3.41 SBMs/week, improved from 1.16 SBMs/week at baseline) compared to placebo (2.29 SBMs/week, improved from 1.28 SBMs/week at baseline) supported that the results of the primary endpoint analysis of change from baseline in SBM frequency likely reflected a meaningful benefit. Although bowel habit patterns can vary by age and other factors, the stool frequency for children and adolescents generally ranges from approximately once per day to at least three times per week when not experiencing constipation. The post-baseline mean SBM frequency rate for linaclotide no longer meets the stool frequency component of the Rome criteria for functional constipation and reflects an average weekly stool frequency that is generally considered normal for the intended patient

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population. Furthermore, the linaclotide group showed improvement in SBM frequency compared to placebo at each of the 12 weeks. Additionally, exploratory analyses that assessed reductions in straining and use of rescue medication further supported the benefit of linaclotide over placebo.

Although the secondary endpoint analysis of change from baseline in stool consistency achieved statistical significance, there was insufficient evidence to support that the observed treatment difference for linaclotide versus placebo was clinically meaningful. The p-BSFS is an ordinal scale for which values of 3 or 4 represent stool types that are neither overly hard nor overly soft. Both linaclotide and placebo groups achieved a stool type within this range, which suggested that the difference from placebo was not clinically meaningful. These data were further limited since the analysis of change from baseline in 12-week stool consistency by COA administration method showed inconsistent treatment differences across the two administration methods (i.e., subject self-report and caregiver-report), with caregiver-reported data showing an inconclusive difference between linaclotide and placebo. Of note, this discrepancy between the administration methods was not observed for the SBM frequency data.

I agree with the review team that the collective evidence from adequate and well controlled studies in adults and the phase 3 pediatric study, establishes a meaningful benefit for linaclotide in the treatment of pediatric patients with FC who are 6 to 17 years of age. Additional data from adequate and well controlled studies in pediatric patients with FC will help inform the design of future studies and address existing knowledge gaps.

The safety of linaclotide was characterized through data obtained from the 4-week phase 2, randomized, double-blind, placebo-controlled study, 12-week phase 3 study LIN-MD-64, and interim data from the ongoing open-label extension study LIN-MD-66, which provided longer term safety data for approximately 24 weeks, at the time of submission. Diarrhea was the most common TEAE occurring at greater frequency for linaclotide than placebo in Study LIN-MD-64. I agree with the review team's conclusion 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 adult studies in other related indications. The Prescribing Information and Medication Guide adequately inform prescribers and patients about the risks of Linzess use, notably diarrhea, which is monitorable and treatable. No new post-marketing requirements or commitments will be issued.

This efficacy supplement is adequate to fulfill the following PREA PMR:

- PMR 2161-3: Conduct a safety and efficacy study in pediatric patients with chronic idiopathic constipation ages 6 to 17 years treated with Linzess (linaclotide).

The data in this efficacy supplement are also intended to address the three studies listed below that are described in the pediatric written request (PWR). As there are additional studies described in the PWR that remain to be completed, it is premature to determine that the PWR has been fulfilled at this time.

- PWR Study 01: Randomized, double-blind, placebo-controlled, parallel group, dose-ranging study for the treatment of chronic idiopathic constipation in children ages 6 to 17 years.

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- PWR Study 03: Randomized, double-blind, placebo-controlled, parallel group confirmatory study for the treatment of chronic idiopathic constipation in children ages 6 to 17 years.
- PWR 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.

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15. Appendices

15.1. References

Literature

Hyams, JS, C Di Lorenzo, M Saps, RJ Shulman, A Staiano, and M van Tilburg, 2016, Functional Disorders: Children and Adolescents, *Gastroenterology*.

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), 2006, Evaluation and Treatment of Constipation in Infants and Children: Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, *J Pediatr Gastroenterol Nutr*, 43(3):e1-13.

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Russo, M, C Strisciuglio, E Scarpato, D Bruzzese, M Casertano, and A Staiano, 2019, Functional Chronic Constipation: Rome III Criteria Versus Rome IV Criteria, *J Neurogastroenterol Motil*, 25(1):123-128.

Tabbers, MM, N Boluyt, MY Berger, and MA Benninga, 2010, Constipation in Children, *BMJ Clin Evid*.

Guidances for Industry

Guidance for Industry *Bioanalytical Method Validation* (May 2018).

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

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15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): LIN-MD-62, LIN-MD-64, LIN-MD-66

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>1044</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
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: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (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-62 were analyzed using a validated liquid chromatography with tandem mass spectrometry method. The method validation results are summarized in Table 32. The bioanalysis performance results are summarized in Table 33.

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Table 32. Summary of LC-MS/MS Method Validation Results

Parameter	Results
Validation report ID and title	MNP-103-081-MVR-01, Validation of an LC-MS/MS method for the analysis of linaclotide and its metabolite, MM-419447, in human plasma (K ₂ EDTA)
Matrix	Human plasma
Anticoagulant	K ₂ EDTA
Extraction procedure	Solid phase (Oasis MAX 96-well plate, 10 mg)
Analysis	Electrospray ionization (positive-ion mode) Multiple-reaction-monitoring scan mode
Analytes	Linaclotide MM-419447
Internal standard (ISTD)	MM-420026
Calibration range	0.100 to 5.00 ng/mL for both analytes
<i>Linaclotide</i>	
Accuracy (% Bias)	
Intrabatch	-6.0-15.0
Interbatch	-3.2-9.0
Precision (%CV)	
Intrabatch	1.4-7.2
Interbatch	3.4-6.6
Dilution linearity	50.0 ng/mL (Dilution factor=20)
Stability in whole blood	2 hours at room temperature
Stability in plasma	20.5 hours at room temperature
Freeze/Thaw stability in plasma	3 cycles (-20°C/room temperature) 4 cycles (-80°C/room temperature)
Reinjection reproducibility	7 days at 10°C
Stock solution short-term stability	25 hours at room temperature
Spiking solution short-term stability	25 hours at room temperature
Long-term stability in stock solution	747 days at -20°C
Long-term stability in spiking solution	10 days at -20°C
Long-term stability in human plasma	31 days at -20°C 282 days at -80°C
<i>MM-419447</i>	
Accuracy (% Bias)	
Intrabatch	-7.8-16
Interbatch	-3.3-10
Precision (%CV)	
Intrabatch	2.2-9.5
Interbatch	4.1-8.4
Dilution linearity	50.0 ng/mL (Dilution factor=20)
Stability in whole blood	2 hours at room temperature
Stability in plasma	20.5 hours at room temperature
Freeze/Thaw stability in plasma	3 cycles (-20°C/room temperature) 4 cycles (-80°C/room temperature)
Reinjection reproducibility	7 days at 10°C
Stock solution short-term stability	25 hours at room temperature
Spiking solution short-term stability	25 hours at room temperature
Long-term stability in stock solution	747 days at -20°C
Long-term stability in spiking solution	10 days at -20°C
Long-term stability in human plasma	95 days at -20°C 282 days at -80°C

Source: Applicant's Method Validation Report, MNP-103-081-MVR-01
Abbreviations: CV, coefficient of variation; ID, identifier; K₂EDTA, dipotassium ethylenediaminetetraacetic acid; LC-MS/MS, liquid chromatography tandem mass spectrometry

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Table 33. Summary of Bioanalysis Performance Results

Parameter	Findings
Clinical study ID	LIN-MD-62
Bioanalysis report ID and title	AB-0099-RB-DS-RPT-01, LC-MS/MS Analysis of Linaclotide and MM-419447 in Human Plasma (K ₂ EDTA) in Support of Ironwood Pharmaceuticals Study Number LIN-MD-62
Calibration range	0.100 to 5.00 ng/mL
QC concentrations	0.300 ng/mL (QC-Low), 1.00 ng/mL (QC-Mid), and 4.00 ng/mL (QC-High)
Linaclotide	
QC accuracy (% Bias)	2.5-4.0
QC precision (% CV)	8.1-10.7
MM-419447	
QC accuracy (% Bias)	0.8-5.7
QC precision (% CV)	9.4-16.2
Sample storage temperature	-80°C

Source: Applicant's Bioanalysis Report, AB-0099-RB-DS-RPT-01

Abbreviations: CV, coefficient of variation; ID, identifier; K₂EDTA, dipotassium ethylenediaminetetraacetic acid; LC-MS/MS, liquid chromatography tandem mass spectrometry; QC, quality control

The bioanalytical method was adequately validated and met the acceptance criteria suggested in the guidance for industry: *Bioanalytical Method Validation* (May 2018). Incurred sample reanalysis was not conducted as there were only few samples with concentrations greater than the lower limit of quantification. All samples were analyzed within the established stabilities for the method, except one sample collected from Subject (b) (6). This sample was analyzed outside the established freeze/thaw stability (analyzed in 5 freeze/thaw cycles instead of within the established 4 cycles).

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

15.4. LIN-MD-64 Inclusion/Exclusion criteria

Inclusion Criteria:

- Male and female subjects must be ages 6 to 17 years at the time the subject provides assent for the study and parent/guardian/legally authorized representative (LAR) has provided signed consent
- Subject weighs ≥ 18 kg at the time the subject provides assent and the parent/guardian/LAR has provided signed consent
- Subjects who meet the modified Rome III criteria for Child/Adolescent FC. For at least 2 months before the Screening Visit, the subject has had 2 or fewer defecations (with each defecation occurring in the absence of any laxative, suppository, or enema use during the preceding 24 hours) in the toilet per week. In addition, subject meets one or more of the following criteria at least once per week for at least 2 months before the screening visit:
 - History of retentive posturing or excessive volitional stool retention
 - History of painful or hard BMs
 - History of large diameter stools that may obstruct the toilet
 - Presence of a large fecal mass in the rectum
 - At least 1 episode of fecal incontinence per week

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- Subject is willing to discontinue any laxatives used before the Preintervention Visit in favor of the protocol-permitted rescue medicine
- Subject has an average of fewer than 3 SBMs per week 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). An SBM is defined as a BM that occurs in the absence of laxative, enema, or suppository use on the calendar day of the BM or the calendar day before the BM
- Subject or parent/guardian/LAR or caregiver is compliant with eDiary requirements by completing both the morning and evening assessments for 10 out of the 14 days immediately preceding the Randomization Visit
- Female subjects of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at the Randomization Visit prior to dosing
- Female subjects who have had their first menstrual period and are sexually active must agree to use a reliable form of contraception
- Subject must provide written or verbal informed assent and the parent/guardian/LAR and caregiver must provide written informed consent before the initiation of any study-specific procedures
- Subject is able to read and/or understand the assessments in the eDiary device. If the subject is 6 to 11 years of age and does not meet this criterion, the interviewer-administered version of the eDiary must be used and the parent/guardian/LAR or caregiver who will be administering the interviewer-administered version of the eDiary must undergo training
- Subject must have acquired toilet training skills

Exclusion Criteria:

- Subject meets Rome III criteria for Child/Adolescent IBS: At least once per week for at least 2 months before the Screening Visit, the subject has 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
- Subject 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)
- Subject has a history of non-retentive fecal incontinence
- Subject has (a) fecal impaction at Visit 2 after failing outpatient clean-out during the Screening Period or (b) fecal impaction at Visit 3
- Subject has required manual disimpaction any time prior to randomization

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- Subject currently has both unexplained and clinically significant alarm symptoms (lower GI bleeding [rectal bleeding or heme-positive stool], iron-deficiency anemia, or any unexplained anemia, or weight loss) and systemic signs of infection or colitis, or any neoplastic process
- Subject has clinically significant findings on a physical examination, vital sign assessment, electrocardiogram, or clinical laboratory test as determined by the investigator based on consideration of whether the finding could represent a safety concern or a condition that would be exclusionary, could prevent the subject from performing any protocol assessments, or could confound study assessments
- Subject has a history of drug or alcohol abuse
- Subject has any of the following conditions:
 - Celiac disease, or positive serological test for celiac disease and the condition has not been ruled out by endoscopic biopsy
 - Cystic fibrosis
 - Hypothyroidism that is untreated or treated with thyroid hormone at a dose that has not been stable for at least 3 months prior to the Screening Visit
 - Down's syndrome or any other chromosomal disorder
 - Active anal fissure (Note: History of anal fissure is not an exclusion)
 - Anatomic malformations (e.g., imperforate anus, anal stenosis, anterior displaced anus)
 - Intestinal nerve or muscle disorders (e.g., Hirschprung disease, visceral myopathies, visceral neuropathies)
 - Neuropathic conditions (e.g., spinal cord abnormalities, neurofibromatosis, tethered cord, spinal cord trauma)
 - Lead toxicity, hypercalcemia
 - Neurodevelopmental disabilities (early-onset, chronic disorders that share the essential feature of a predominant disturbance in the acquisition of cognitive, motor, language, or social skills, which has a significant and continuing impact on the developmental progress of an individual) producing a cognitive delay that precludes comprehension and completion of the daily eDiary or other study-related questionnaires (Note: Subjects are excluded if the person who will be completing the daily eDiary or other study-related questionnaires meets this criterion.)
 - Inflammatory bowel disease
 - Childhood functional abdominal pain syndrome
 - Childhood functional abdominal pain
 - Poorly treated or poorly controlled psychiatric disorders that might influence his or her ability to participate in the study
 - Lactose intolerance that is associated with abdominal pain or discomfort and could confound the assessments in this study
 - History of cancer other than treated basal cell carcinoma of the skin. (Note: Subjects with a history of cancer are allowed provided that the malignancy has been in a complete remission for at least 5 years before the Randomization Visit. A complete remission is defined as the disappearance of all signs of cancer in response to treatment.)
 - History of diabetic neuropathy

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- Subject has an acute or chronic condition that, in the investigator's opinion, would limit the subjects' ability to complete or participate in this clinical study.
- Subject has a known or suspected mechanical bowel obstruction or pseudo-obstruction
- Subject has a known allergy or sensitivity to the study intervention or its components or other medications in the same drug class
- Subject has had surgery that meets any of the following criteria:
 - Bariatric surgery for treatment of obesity, or surgery to remove a segment of the GI tract at any time before the Screening Visit
 - Surgery of the abdomen, pelvis, or retroperitoneal structures during the 6 months before the Screening Visit
 - An appendectomy or cholecystectomy during the 60 days before the Screening Visit
 - Other major surgery during the 30 days before the Screening Visit
- Subject used a protocol-specified prohibited medicine before the start of the Preintervention Period or failed to meet the stable-dose requirements of certain medications
- Subject used rescue medication on the calendar day before the Randomization Visit and on the day of the Randomization Visit until randomized
- Subject received a study intervention during the 30 days before the Screening Visit or is planning to receive a study intervention (other than that administered during this study)
- Subject has been randomized into any clinical study in which linaclotide was a study intervention
- The subject has a condition or is in a situation which, in the investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study
- Subject who have positive urine drug screen results for cocaine, barbiturates, opiates, or cannabinoids will be excluded from study participation
- Female subjects who are currently pregnant or nursing, or plan to become pregnant or nurse during the clinical study
- Subject's parent/guardian/LAR or caregiver has been directly or indirectly involved in the conduct and administration of this study as an investigator, study coordinator, or other study staff member. In addition, any subject, parent/guardian/LAR, or caregiver who has a first-degree family member, significant other, or relative residing with him/her directly or indirectly who is involved in this study

15.5. Patient-Reported Outcome (PRO) Measures Proposed in Labeling

The Applicant proposed labeling claims describing the effect of linaclotide on symptoms of FC as assessed by the Pediatric Functional Constipation Symptom Diary (PFCSD), a novel COA measure assessing 7 signs/symptoms of FC (abdominal pain, abdominal bloating, complete evacuation, fecal incontinence, BM frequency, BM consistency, and straining with BMs) in children and adolescents aged 6 to 17 years. It is completed as a morning and evening diary, using the recall periods, "From bedtime last night until now" and "From when you got up this morning until now," respectively.

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Section 8.1.2 describes SBM frequency, CSBM frequency, Stool Consistency, and Straining scores as assessed by the PFCSD in study LIN-MD-64. Section 15.6 describes results of the analyses to explore clinically meaningful within-patient change in SBM frequency and stool consistency scores as assessed by the PFCSD.

15.6. Interpretation of Change From Baseline in 12-Week Endpoint Scores (SBM Frequency Rate and Stool Consistency), Study LIN-MD-64

The Applicant proposed a meaningful change threshold of 2-point improvement in SBM frequency rate and a range of (b) (4)-point improvement in stool consistency. To support these proposed thresholds for meaningful within-patient change in SBM frequency rate and stool consistency, the Applicant performed a triangulation of the following analyses using Study LIN-MD-64 data:

- 1) Anchor-based analyses supplemented with empirical Cumulative Distribution Function (eCDF) curves and Probability Density Function curves
- 2) Classification statistics (i.e., sensitivity, specificity, positive predictive value, negative predictive value)
- 3) Distribution-based analyses (i.e., one-half standard deviation, standard error of measurement)

Greater consideration was given to results of the anchor-based analyses, while results from other analyses were considered supportive by the Applicant.

The review team noted the following limitations of the anchor data:



Given these insurmountable limitations, the review team agreed that, in this specific circumstance, alternative methods could be used to guide interpretation of clinical meaningfulness of the efficacy analysis results for SBM frequency rate and stool consistency endpoints (see *Overall Assessment of Effectiveness* in Section 8.1.2 for the discussion on meaningfulness evaluation from a clinical perspective).

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15.6.1. Anchor Assessments in Study LIN-MD-64

Descriptions of the anchor assessments that were used in Study LIN-MD-64 to support clinically meaningful within-patient change scores are below.

Participant⁴-completed Global Severity scale

The participant-completed global severity scale is a 2-item PRO measure assessing severity of FC symptoms (“Pooping Problems” and “Tummy problems”) over the past 7 days using a 4-point verbal rating scale (VRS) (“I have not had [pooping problems/tummy problems],” “A little bad,” “Bad,” “Very bad”).

Participant-completed Global Change scale

The participant-completed global change scale is a 2-item PRO measure assessing change in FC symptoms (“Pooping Problems” and “Tummy problems”) over the past 7 days using a 5-point VRS (“A lot better,” “A little better,” “The same,” “A little worse,” “A lot worse”).

Observer-completed Global Severity scale

The observer-completed global severity scale is a single-item observer reported outcome measure assessing severity of the child’s constipation over the past 7 days using a 5-point VRS (“none,” “mild,” “moderate,” “severe,” and “very severe”).

Observer-completed Global Change scale

The observer-completed global change scale is a single-item observer reported outcome measure assessing change in the child’s constipation symptoms today compared to 7 days ago using a 7-point VRS (“completely relieved,” “considerably relieved,” “somewhat relieved,” “unchanged,” “somewhat worse,” “considerably worse,” “as bad as I can imagine”).

15.6.2. Review Issues for the Anchor Assessments

Review issues for the anchor assessments that limit their utility to interpret meaningful change in PFCSD scores (SBM frequency rate and stool consistency) are described below.



⁴ The term “participant” is used interchangeably with “subject” or “patient.”

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(b) (4)

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15.6.3. Review Issues of the Applicant's Anchor-Based Analyses

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(b) (4)

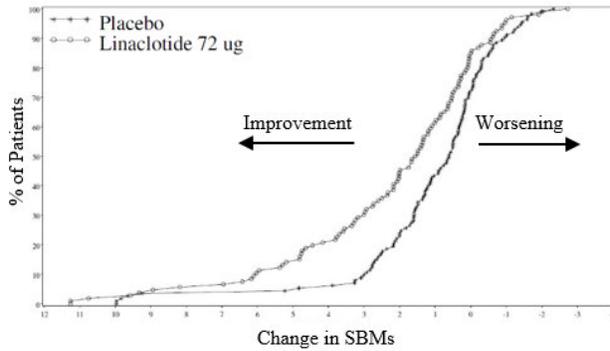


In summary, given all the limitations of the anchor assessments (see Section 15.6.2) and anchor-based analyses discussed above, the review team concluded that the quantitative anchor-based analysis results were uninterpretable.

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15.7. Empirical Cumulative Distribution Function Plots of Change From Baseline in 12-Week Endpoint Scores (SBM Frequency Rate and Stool Consistency) by Treatment Arm and Administration Method, Study LIN-MD-64

Figure 6. eCDF, Change From Baseline in 12-Week SBM Frequency Rate by Treatment Arm: Self-Administered Method



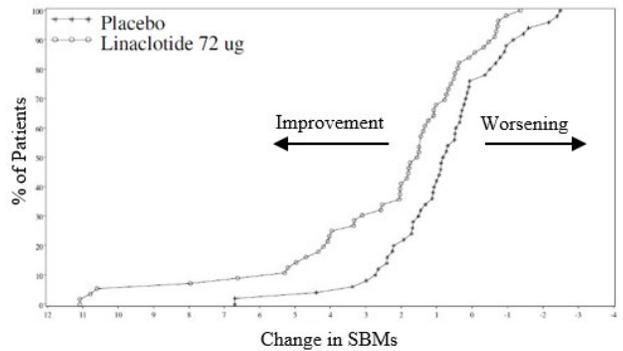
Source: Figure 1-1 of the Applicant's response to IR dated Feb 2, 2023. Analysis verified using Applicant submitted data adpsy.xpt and ADEFF.xpt.

Note: N=113 for Placebo; N=106 for Linaclotide.

SBM endpoint change scores were calculated as the average score over 12 weeks minus the score at baseline.

Abbreviations: eCDF, empirical Cumulative Distribution Function; SBM, spontaneous bowel movement

Figure 7. eCDF, Change From Baseline in 12-Week SBM Frequency Rate by Treatment Arm: Interviewer-Administered Method



Source: Figure 1-2 of the Applicant's response to IR dated Feb 2, 2023. Analysis verified using Applicant submitted data adpsy.xpt and ADEFF.xpt.

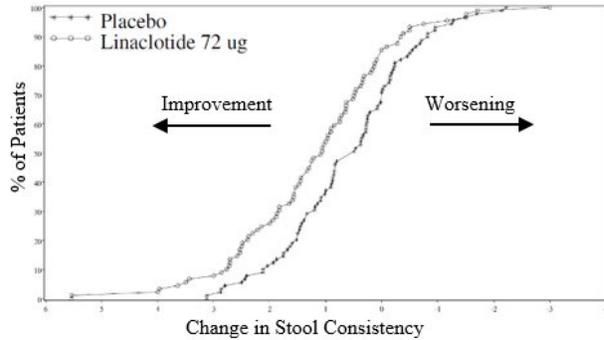
Note: N=50 for Placebo; N=56 for Linaclotide.

SBM endpoint change scores were calculated as the average score over 12 weeks minus the score at baseline.

Abbreviations: eCDF, empirical Cumulative Distribution Function; SBM, spontaneous bowel movement

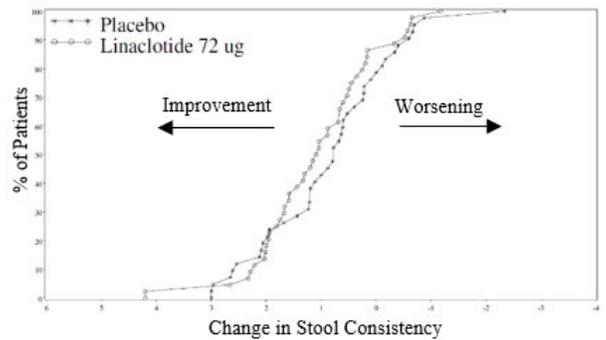
Linzess (linaclotide)

Figure 8. eCDF, Change From Baseline in 12-Week Stool Consistency by Treatment Arm: Self-Administered Method



Source: Figure 2-1 of the Applicant's response to IR dated Feb 2, 2023. Analysis verified using Applicant submitted data adpsy.xpt and ADEFF.xpt.
Note: N=89 for Placebo; N=89 for Linaclotide.
Stool consistency endpoint change scores were calculated as the average score over 12 weeks minus the score at baseline.
Abbreviations: eCDF, empirical Cumulative Distribution Function

Figure 9. eCDF, Change From Baseline in 12-Week Stool Consistency by Treatment Arm: Interviewer-Administered Method



Source: Figure 2-2 of the Applicant's response to IR dated Feb 2, 2023. Analysis verified using Applicant submitted data adpsy.xpt and ADEFF.xpt.
Note: N=42 for Placebo; N=44 for Linaclotide.
Stool consistency endpoint change scores were calculated as the average score over 12 weeks minus the score at baseline.
Abbreviations: eCDF, empirical Cumulative Distribution Function

NDA 202811/S-021 Linzess (linaclotide) Unireview Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Cross-Disciplinary Project Manager	Kristina Luong	OND/ORO/DROII	3	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
Signature: Kristina N. Luong -S  Digitally signed by Kristina N. Luong -S Date: 2023.06.02 12:48:11 -04'00'				

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Product Quality Reviewer	Le Zhang	OPQ/OLDP/DPMA1	4.2	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
Signature: Le Zhang -S  Digitally signed by Le Zhang -S Date: 2023.06.02 13:17:07 -04'00'				

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Product Quality Secondary Reviewer	David Lewis	OPQ/OLDP/DPMA1	4.2	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
Signature: David B. Lewis -S  Digitally signed by David B. Lewis -S Date: 2023.06.05 09:37:38 -04'00'				

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Sarah Morgan	OND/OII/DPTII	5	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
Signature: Sarah J. Morgan -S  Digitally signed by Sarah J. Morgan -S Date: 2023.06.02 12:57:52 -04'00'				

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Team Leader	Jackye Peretz	OND/OII/DPTII	5	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
Signature: Jackye R. Peretz -S Digitally signed by Jackye R. Peretz -S Date: 2023.06.09 09:11:44 -04'00'				

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Soo Hyeon Shin	OTS/OCP/DIIP	6, 15.3	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
Signature: Soo-hyeon Shin -S Digitally signed by Soo-hyeon Shin -S Date: 2023.06.02 19:04:07 -04'00'				

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Team Leader	Insook Kim	OTS/OCP/DIIP	6, 15.3	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
Signature: Insook Kim -S Digitally signed by Insook Kim -S Date: 2023.06.05 16:12:15 -04'00'				

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Reviewer	Xiaofeng (Tina) Wang	OTS/OB/DAI	8.1	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
Signature: Xiaofeng Wang -S Digitally signed by Xiaofeng Wang -S Date: 2023.06.05 10:02:40 -04'00'				

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Team Leader	Paul Imbriano	OTS/OB/DBIII	Authored 8.3 Approved 8.1	Select one: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: Paul M. Imbriano -S Digitally signed by Paul M. Imbriano -S Date: 2023.06.05 10:35:58 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Patient-Focused Statistical Scientists (PFSS) Reviewer	Xin Yuan	OTS/OB/DBIII	8.3, 15.6, 15.7	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	Signature: Xin Yuan -S Digitally signed by Xin Yuan -S Date: 2023.06.05 10:53:06 04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical PFSS Secondary Reviewer	Lili Garrard	OTS/OB/DBIII	8.3, 15.6, 15.7	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: Lili Garrard -S Digitally signed by Lili Garrard -S Date: 2023.06.05 11:13:33 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Outcome Assessment Reviewer	Susan Pretko	OND/ODES/DCOA	15.5, 15.6.1, 15.6.2	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	Signature: Susan M. Pretko -S Digitally signed by Susan M. Pretko -S Date: 2023.06.06 10:23:51 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Outcome Assessment	Onyekachukwu Illoh	OND/ODES/DCOA	15.5, 15.6.1, 15.6.2	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
Team Lead	Signature: Onyekachukwu A. Illoh -S Digitally signed by Onyekachukwu A. Illoh -S Date: 2023.06.06 10:44:55 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Outcome Assessment	David Reasner	OND/ODES/DCOA	15.5, 15.6.1, 15.6.2	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
Division Director	Signature: David Reasner -S Digitally signed by David Reasner -S Date: 2023.06.07 11:26:04 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Christopher St. Clair	OND/OII/DG	1, 2, 7, 8, 9, 10, 11, 12, 13, 15.1, 15.2, 15.4	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	Signature: Christopher O. Stclair -S Digitally signed by Christopher O. Stclair -S Date: 2023.06.07 12:01:30 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Cross-Disciplinary Team Lead	Suna Seo	OND/OII/DG	Authored 4.1, 4.3, 4.4 Approved All	Select one: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved All
	Signature: Suna Seo -S Digitally signed by Suna Seo -S Date: 2023.06.07 13:15:56 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Deputy Division Director	Juli Tomaino	OND/OII/DG	Authored Section 14 Approved All Sections	Select one: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved All Sections
Signature: Juli A. Tomaino -  Digitally signed by Juli A. Tomaino - Date: 2023.06.07 14:41:48 -04'00'				

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUNA C SEO
06/09/2023 04:17:14 PM

JULI A TOMAINO
06/12/2023 08:54:53 AM