Received: 17 July 2023 | Accepted: 14 December 2023

DOI: 10.1002/jpn3.12184

JPGN

CLINICAL TRIAL

Gastroenterology

Clinical trial: Randomized controlled trial of linaclotide in children aged 6–17 years with functional constipation

Carlo Di Lorenzo[1] | **Samuel Nurko**[2] | **Jeffrey S. Hyams**[3] | **Gerardo Rodriguez-Araujo**[4] | **Cristina Almansa**[5] | **Valentina Shakhnovich**[6] | **Miguel Saps**[7] | **Michael Simon**[8]

[1]Nationwide Children's Hospital, Columbus, Ohio, USA

[2]Boston Children's Hospital, Boston, Massachusetts, USA

[3]Connecticut Children's Medical Center, Hartford, Connecticut, USA

[4]AbbVie Inc., North Chicago, Illinois, USA

[5]Janssen Pharmaceutical Companies of Johnson and Johnson, Cambridge, Massachusetts, USA

[6]Ironwood Pharmaceuticals, Inc., Boston, Massachusetts, USA

[7]Miller School of Medicine, University of Miami, Miami, Florida, USA

[8]Department of Pediatrics, University of Kentucky, Lexington, Kentucky, USA

Correspondence

Carlo Di Lorenzo, Gastroenterology & Hepatology & Nutrition, Nationwide Children's Hospital, 700 Children's Dr., Columbus, OH 43205, USA.
Email: carlo.dilorenzo@nationwidechildrens.org

Funding information

AbbVie Inc.; Ironwood Pharmaceuticals, Inc.

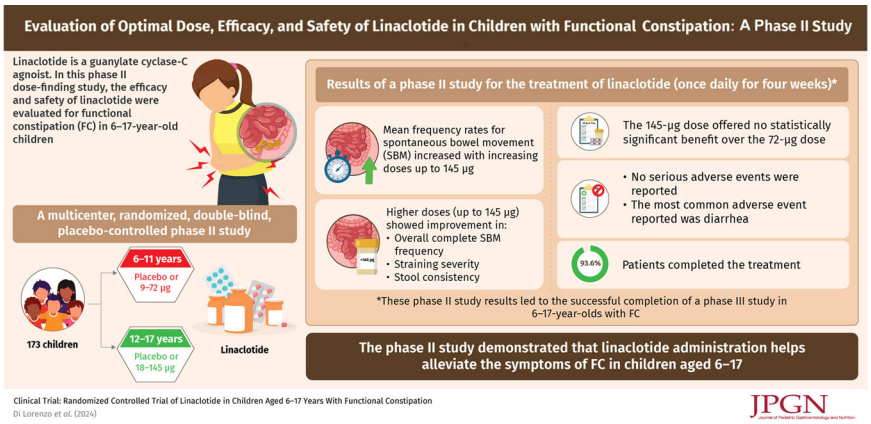
Abstract

Objectives: Linaclotide, a guanylate cyclase-C agonist, was recently approved in the United States for treatment of children 6–17 years old with functional constipation (FC). This study evaluated the safety and efficacy of several linaclotide doses in children 6–17 years old with FC.

Methods: In this multicenter, randomized, double-blind, placebo-controlled phase 2 study, 173 children with FC (based on Rome III criteria) were randomized to once-daily linaclotide (A: 9 or 18 µg, B: 18 or 36 µg, or C: 36 or 72 µg) or placebo in a 1:1:1:1 ratio for 6- to 11-year-olds (dosage determined by weight: 18 to <35 or ≥35 kg) and linaclotide (18, 36, 72, or 145 µg) or placebo in a 1:1:1:1:1 ratio for 12- to 17-year-olds. The primary efficacy endpoint was change from baseline in weekly spontaneous bowel movement (SBM) frequency throughout the 4-week treatment period. Adverse events (AE), clinical laboratory values, and electrocardiograms were monitored.

Results: Efficacy and safety were assessed in 173 patients (52.0% aged 6–11 years; 48.0% aged 12–17 years); 162 (93.6%) completed the treatment period. A numerical improvement in mean SBM frequency was observed with increasing linaclotide doses (1.90 in 6- to 11-year-olds [36 or 72 µg] and 2.86 in 12- to 17-year-olds [72 µg]). The most reported treatment-emergent AE was diarrhea, with most cases being mild; none were severe.

Conclusions: Linaclotide was well tolerated in this pediatric population, with a trend toward efficacy in the higher doses, warranting further evaluation.



© 2024 European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition.

KEYWORDS
constipation, functional GI diseases, pediatric gastroenterology, small intestine

1 | INTRODUCTION

Functional constipation (FC), characterized by hard stool consistency and few and/or painful defecations,[1] is one of the most common disorders of gut–brain interaction in individuals <18 years of age.[2] If left untreated, constipation may cause fecal impaction, fecal incontinence, abdominal pain and distension, rectal bleeding, and anorexia.[1,3] The clinical diagnosis of FC is currently based on the updated pediatric diagnostic Rome IV criteria. For children and adolescents, the duration of symptoms needed to fulfill the criteria for FC was decreased from 2 months in Rome III to 1 month in Rome IV, allowing for an earlier diagnosis.[3]

FC negatively impacts health-related quality of life of children and their parents.[4] Moreover, some cases of FC can persist into adulthood,[5] where reduced health-related quality of life and increased costs remain common.[4,6] Current treatment for childhood FC includes rectal or oral disimpaction and maintenance therapy[3,7] with over-the-counter or pharmacologic treatments. Until recently, there were no approved therapies to treat FC in children in the United States or European Union, and the current treatment of choice, polyethylene glycol, is used off label.[8,9]

Linaclotide, a guanylate cyclase-C (GC-C) agonist acting on the luminal surface of the intestinal epithelium, is approved in the United States for the treatment of adults with chronic idiopathic constipation and constipation-predominant irritable bowel syndrome (IBS).[10] Linaclotide has demonstrated sustained efficacy in trials in patients with chronic idiopathic constipation[11] and constipation-predominant IBS.[12,13] At the time this study was conducted, linaclotide was not approved for use in children. This study therefore aimed to evaluate the dose response, safety, and efficacy of 4 weeks of treatment with different linaclotide doses compared with placebo in pediatric patients aged 6–17 years with FC.

What Is Known

- Functional constipation (FC) is a common disorder in children that severely impacts quality of life; however, limited treatment options are available.
- At the time of this study, linaclotide, a guanylate cyclase-C agonist, was approved for the treatment of adults with chronic idiopathic constipation and constipation-predominant irritable bowel syndrome, but not for use in children.

What Is New

- This phase 2 dose-finding study evaluated the efficacy and safety of linaclotide in children with FC.
- Linaclotide treatment led to numerical improvements in mean spontaneous bowel movement frequency, with a trend toward efficacy at the higher doses tested.
- Linaclotide was well tolerated in this pediatric population.

2 | METHODS

2.1 | Trial design

This was a randomized, double-blind, placebo-controlled, parallel-group, dose-ranging phase 2 trial in the United States (NCT02559570). Enrolled patients were aged 6–17 years who fulfilled modified Rome III criteria for pediatric FC as outlined below. The modified Rome III criteria were used to mandate that the first criterion for stool frequency be met in addition to one of the other five criteria. For at least 2 months before the screening visit, the patient had to report 2 or fewer defecations (with each defecation occurring in the absence of any laxative, suppository, or enema use during the preceding 24 h) in the toilet per week. In addition, the patient had to meet one or more of the following at least once per week: (1) history of retentive posturing or excessive volitional stool retention; (2) history of painful or hard bowel movements (BMs); (3) presence of a large fecal mass in the rectum; (4) history of large diameter stools that may obstruct the toilet; and (5) at least one episode of fecal incontinence per week. Patients who met the conventional Rome III criteria were required to meet any two of the criteria listed.

Patients and caregivers were trained on using an e-diary, which they completed twice daily (morning/evening) to report on the trial's efficacy assessments and once weekly to report patient-/observer-completed global items. The participants were instructed to take the study treatment at approximately the same time each day, 30 min before their evening meal.

For the 4-week treatment period, patients aged 6–11 years were randomized 1:1:1:1 to linaclotide doses A (9 or 18 μg), B (18 or 36 μg), or C (36 or 72 μg), or placebo, and patients aged 12–17 years were randomized 1:1:1:1:1 to linaclotide doses A, B, C, or 145 μg, or placebo. Dosage was determined by weight

15364801, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jpn3.12184 by Osu Central Accounts Payable, Wiley Online Library on [02/04/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

for patients aged 6–11 years (18 to <35 or ≥35 kg) (Supporting Information S1: Figure 1, Supporting Information Digital Content 1, which shows an overview of the trial design). The drug was provided as either a capsule or a liquid oral solution of linaclotide or placebo. They were packaged in bottles by the sponsor and were provided as identically appearing bottles containing linaclotide or matching placebo capsules/solution.

The trial design was based on the US Food & Drug Administration Guidance for Industry E11 Clinical Investigation of Medicinal Products in the Pediatric Population and conducted in accordance with the International Council for Harmonisation E6 Guideline for Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by an institutional review board at each site. Patients provided assent and their legal guardians, or legally authorized representatives or caregivers, provided voluntary and written informed consent.

More detailed methods and the trial design can be found in Sections 2.1–2.4 of Supporting Information Digital Content 2.

2.2 | Patient population

Eligible patients had to have recorded an average of <3 spontaneous BMs (SBMs) per week during the pretreatment period. Full inclusion and exclusion criteria are provided in Supporting Information Digital Content 3.

2.3 | Efficacy and safety endpoints

The primary efficacy endpoint for this dose-finding study was the change from baseline in weekly SBM frequency rate (SBMs per week). An SBM was defined as a BM that occurred in the absence of laxative, suppository, or enema use on the calendar day of, or the calendar day before, the BM. Secondary efficacy endpoints included change from baseline in the following: daytime fecal incontinence, daytime abdominal pain, daytime abdominal bloating, severity of straining, stool consistency, and overall complete SBM (CSBM) frequency rate (CSBMs per week). Complete evacuation was defined as the feeling of fully evacuating the stool after SBM, without the residual sensation of the child still feeling like they had to poop. All efficacy endpoints were measured over the 4-week treatment period. Additional efficacy endpoints are described in Supporting Information Results of Supporting Information Digital Content 4. Safety assessments included recording of adverse events (AEs), clinical laboratory tests, vital sign measurements, weight, electrocardiograms, physical examinations, and exposure to treatment.

2.4 | Statistical analysis

Details on the determination of sample size are available in Section 2.6 of Supporting Information Digital Content 2, which shows more detailed methods. The safety population included all patients in the randomized population who received at least one dose of treatment, and the intention-to-treat (ITT) population included all patients in the safety population who had at least one postbaseline entry on BM characteristic assessments that determined occurrences of SBMs.

Comparisons between each linaclotide dose and placebo were performed using an analysis of covariance model, with treatment, age group, and treatment-by-age interaction as factors and the baseline value of each endpoint as a covariate. Least squares mean for each treatment group, differences in least squares means between each linaclotide treatment group (doses A, B, and C) versus placebo, associated two-sided 95% confidence intervals for these differences, and the corresponding p values were calculated, as well as for an exploratory treatment-by-age group interaction analysis.

3 | RESULTS

3.1 | Patient disposition

Of 471 patients screened, 173 (36.7%) were randomized to receive linaclotide or placebo: 90 (52.0%) were aged 6–11 years and 83 (48.0%) were aged 12–17 years. Full details on patient dispositions are shown in Supporting Information S1: Figure 2 of Supporting Information Digital Content 5. Demographics and other baseline characteristics were similar across the treatment groups in the overall safety population and within age groups (Supporting Information S1: Table 1, Supporting Information Digital Content 6). The most common medical histories that occurred in ≥5% of patients are provided in Supporting Information S1: Table 2 in Supporting Information Digital Content 7.

3.2 | Primary efficacy endpoint

In the entire ITT population ($n = 157$), there was a numerical trend toward higher SBM frequency (SBMs per week) at the higher doses of linaclotide (Figure 1A). This trend was also seen for doses up to 72 µg in both the younger (Figure 1B) and older (Figure 1C) age groups, when analyzed separately. In the linaclotide 145 µg group, administered only to children 12–17 years of age, the median change from baseline in overall SBM frequency was numerically higher (1.68 SBMs per week) compared with the placebo group aged 12–17 years (0.27 SBMs per

15364801, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jpn3.12184 by Osu Central Accounts Payable, Wiley Online Library on [02/04/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

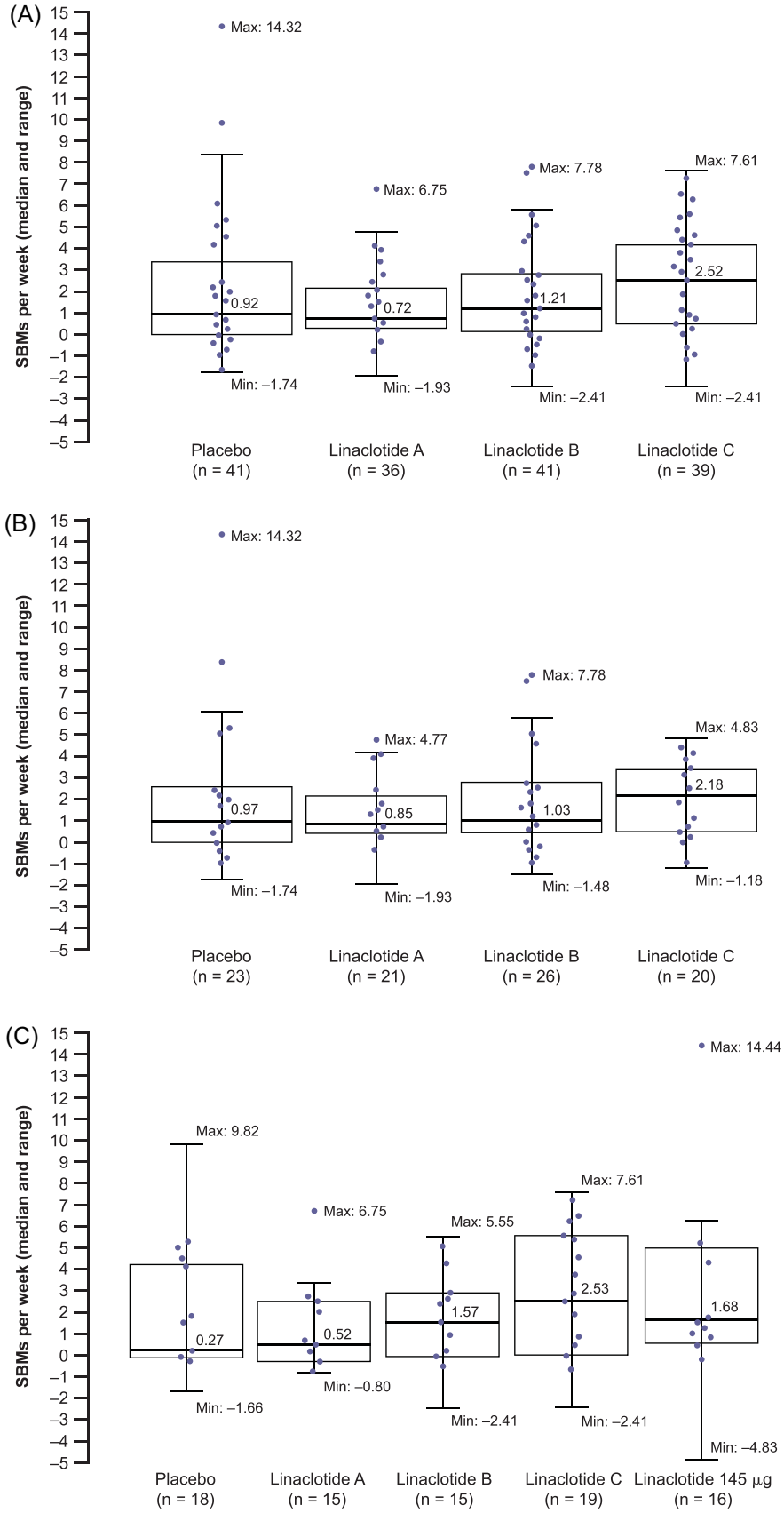


FIGURE 1 CFB 4-week overall SBM frequency (SBMs per week) for the (A) ITT population,* (B) 6- to 11-years age group, and (C) 12- to 17-years age group. An SBM was defined as a BM that occurred in the absence of laxative, suppository, or enema use on the day of, or the day before, the BM. Central box plot lines show median CFB value for each treatment group, with whiskers showing maximum and minimum values. *The ITT population ($n = 157$) does not include the patients treated with the linaclotide 145 μg dose. BM, bowel movement; CFB, change from baseline; SBM, spontaneous bowel movement; ITT, intention-to-treat.

15364801, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jpn3.12184 by Osu Central Accounts Payable, Wiley Online Library on [02/04/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

week) (Figure 1C). The increased dose appeared to have no additional efficacy benefit compared with the linaclotide 72 µg group (dose C) in this age group (2.53 SBMs per week) (Figure 1C; Supporting Information S1: Table 3, Supporting Information Digital Content 8, which shows the primary, secondary, and additional efficacy results for the 12- to 17-years age group). The treatment-by-age group interaction showed no statistically significant difference by age on the primary efficacy endpoint ($p = 0.73$).

No statistically significant differences were observed between linaclotide and placebo (minimum $p \geq 0.31$) (Table 1). An outlier in the placebo group resulted in a maximum change from baseline value of 14.32 SBMs per week, compared to 7.78 SBMs per week in the linaclotide groups (9–72 µg) (Table 1; Figure 1; Supporting Information S1: Figure 3, Supporting Information Digital Content 9, which shows a cumulative distribution plot of CFB in 4-week overall SBM frequency rate).

3.3 | Secondary efficacy endpoints

For the secondary efficacy endpoints in the ITT population ($n = 157$; excluding the linaclotide 145 µg group), numerical trends toward efficacy were observed for the change from baseline in overall CSBM frequency rate, straining severity, and stool consistency in the groups given dose C of linaclotide (Table 1). However, none of the three linaclotide groups showed clear improvement over the placebo group (minimum $p \geq 0.27$). The incidence of daytime fecal incontinence remained low throughout the trial (Supporting Information S1: Tables 3 and 4, Supporting Information Digital Content 8 and 10, respectively, which show primary, secondary, and additional efficacy results for each age group). The treatment-by-age group interaction showed a significant difference between age groups for straining ($p = 0.03$) and no statistically significant influence of age on the other secondary efficacy endpoints.

In the 12- to 17-years-of-age group, numerically greater efficacy was observed with the 145 µg linaclotide dose ($n = 16$) versus placebo ($n = 18$) for the change from baseline in straining severity and stool consistency. Although the linaclotide 145 µg dose seemed to have no additional efficacy benefit on straining severity, the increased dose ($n = 16$) showed numerical improvements over the linaclotide 72 µg dose (dose C; $n = 19$) in abdominal pain, stool consistency, CSBM frequency, and abdominal bloating in the 12- to 17-years-of-age group (Supporting Information S1: Table 3, Supporting Information Digital Content 8).

Additional efficacy endpoints have been summarized in Supporting Information Results of Supporting Information Digital Content 4.

3.4 | Safety

Of 173 patients across all treatment groups, 46 experienced treatment-emergent AEs (Table 2). There were no AEs of special interest or deaths. In patients aged 12–17 years, two experienced serious AEs (one of suicidal ideation in the linaclotide dose-A group and one of vomiting in the linaclotide 145 µg group), neither of which were related to the study drug. Two AEs in the linaclotide dose-A group (dyspnea [related] and suicidal ideation [not related]) and one (diarrhea [related]) in the linaclotide dose-C group led to discontinuation. In patients aged 6–11 years, no serious AEs or AEs led to discontinuation.

Treatment-emergent AEs occurring in ≥5% of patients are shown in Table 2. The most reported treatment-emergent AE was diarrhea; the majority of the treatment-emergent AEs of diarrhea among all patients across all doses were mild; none were severe.

4 | DISCUSSION

In this dose-finding phase 2 clinical trial of patients aged 6–17 years with FC, a trend of progressively greater numerical improvements with increasing linaclotide doses versus placebo was identified for the primary endpoint of SBM frequency rate. However, the improvements in SBM frequency did not achieve statistical significance compared to placebo, as this phase 2 dose-finding study was not powered to do so. A similar dose–response trend was observed in the secondary endpoints of change from baseline in CSBMs per week, stool consistency, and straining severity. Although evaluated only in patients aged 12–17 years, linaclotide 145 µg appeared to have minimal additional efficacy benefit versus the lower doses. These findings support the initiation of an appropriately powered phase 3 study to confirm the efficacy trends observed in this dose-finding study.

There are some possible explanations for the lack of significant differences. Given the relatively small sample size of this study, the presence of noticeable outliers in the placebo group could have significantly impacted the results. In addition to the wide data spread, a high placebo response was observed in this trial. High placebo response rates have also been reported in previous trials examining investigational therapies in pediatric patients aged 6 months to 18 years with disorders of gut–brain interaction.[14–16] Possible causes of high placebo response rates have been explored, such as the use of subjective measures.[17] This trial used an objective primary endpoint but also relied on subjective secondary improvement measures that could leave room for interpretation (e.g., straining and pediatric bristol stool form scale). Moreover, pediatric trials have the added complication of more external influences from caregivers;

15364801, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jpn3.12184 by Osu Central Accounts Payable, Wiley Online Library on [02/04/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 Key efficacy results: ITT population ($n = 157$) and 145-µg-dose group ($n = 16$).

	Placebo (n = 41)	Linaclotide dose A (n = 36)	Linaclotide dose B (n = 41)	Linaclotide dose C (n = 39)	Linaclotide 145 µg (n = 16)
Linaclotide dose, µg					
Participants aged 6–11 years					
18 to <35 kg		9	18	36	–
≥35 kg		18	36	72	–
Participants aged 12–17 years		18	36	72	145
Primary efficacy endpoint					
CFB in 4-week overall SBM frequency rate[a]					
Mean (SD)	2.05 (3.27)	1.32 (1.81)	1.82 (2.36)	2.37 (2.47)	2.62 (4.11)
Median (minimum–maximum)	0.92 (−1.74 to 14.32)	0.72 (−1.93 to 6.75)	1.21 (−2.41 to 7.78)	2.52 (−2.41 to 7.61)	1.68 (−4.83 to 14.44)
p Value[b]	–	0.31	0.74	0.52	–
Secondary efficacy endpoints					
CFB in 4-week overall CSBM frequency rate[c]					
Mean (SD)	1.31 (2.37)	0.81 (1.80)	1.03 (1.67)	1.32 (1.96)	1.99 (3.03)
Median (minimum–maximum)	0.24 (−0.91 to 10.30)	0.30 (−1.93 to 7.23)	0.50 (−1.48 to 5.00)	0.72 (−1.93 to 7.31)	1.00 (−1.93 to 10.37)
p Value[b]	–	0.35	0.59	0.86	–
CFB in 4-week daytime abdominal bloating[d]					
Mean (SD)	−0.48 (0.75)	−0.21 (0.62)	−0.30 (0.96)	−0.23 (1.01)	−0.53 (0.88)
Median (minimum–maximum)	−0.26 (−2.88 to 0.48)	0.00 (−2.25 to 1.18)	−0.12 (−3.15 to 2.35)	0 (−3.85 to 2.73)	−0.11 (−2.36 to 0.40)
p Value[b]	–	0.75	0.85	0.79	–
CFB in 4-week daytime abdominal pain[e]					
Mean (SD)	−0.43 (0.85)	−0.28 (0.66)	−0.31 (0.85)	−0.12 (0.88)	−0.50 (0.72)
Median (minimum–maximum)	−0.15 (−3.12 to 1.32)	−0.05 (−2.5 to 0.74)	−0.15 (−2.73 to 1.40)	0 (−3.41 to 1.36)	−0.34 (−2.07 to 0.33)
p Value[b]	–	0.78	0.99	0.41	–

15364801, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jpn3.12184 by Osu Central Accounts Payable, Wiley Online Library on [02/04/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 (Continued)

	Placebo (n = 41)	Linaclotide dose A (n = 36)	Linaclotide dose B (n = 41)	Linaclotide dose C (n = 39)	Linaclotide 145 μg (n = 16)
CFB in 4-week straining severity[f]					
Mean (SD)	−0.61 (1.03)[g]	−0.57 (1.13)[h]	−0.91 (0.96)[g]	−0.91 (0.93)[g]	−1.14 (1.04)[i]
Median (minimum–maximum)	−0.40 (−3.58 to 1.67)	−0.23 (−3.09 to 1.86)	−0.78 (−3.00 to 0.56)	−0.85 (−2.65 to 0.57)	−0.82 (−3.37 to 0.00)
p Value[b]	–	0.79	0.58	0.33	–
CFB in 4-week stool consistency[j]					
Mean (SD)	0.38 (1.46)[g]	0.71 (0.97)[h]	0.66 (1.18)[g]	1.03 (1.46)[g]	1.78 (1.75)[i]
Median (minimum–maximum)	0.19 (−3.33 to 5.11)	0.39 (−1.00 to 3.04)	0.48 (−2.14 to 3.29)	0.85 (−2.50 to 4.23)	1.52 (−0.81 to 5.41)
p Value[b]	–	0.79	0.75	0.27	–

Note: No treatment comparison was performed between the linaclotide 145 μg group and the placebo group.

Abbreviations: BM, bowel movement; CFB, change from baseline; CSBM, complete spontaneous bowel movement; ITT, intention-to-treat; p-BSFS, pediatric bristol stool form scale; SBM, spontaneous bowel movement; SD, standard deviation.

[a]SBM rate (SBMs per week) during the 4-week treatment period.

[b]Calculated from analysis of covariance model estimates/t-tests comparing least squares estimates for placebo versus specified treatment group.

[c](Total number of CSBMs in the analysis period/number of days in the analysis period) × 7.

[d]Based on scores "no" and 4-point (1–4) scales for abdominal bloating severity.

[e]Based on scores "no" and 4-point (1–4) scales for abdominal pain severity.

[f]Observed weighted average of daily straining scores (assessed for each BM via a 5-point [0–4] severity scale) during the treatment period.

[g]$n = 34$.

[h]$n = 32$.

[i]$n = 14$.

[j]Observed weighted average of daily p-BSFS scores (assessed for each BM via a 7-point ordinal scale) during the treatment period.

15364801, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jpn3.12184 by Osu Central Accounts Payable, Wiley Online Library on [02/04/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 2 Summary of AEs.[a]

n (%)	Placebo (*n* = 41)	Linaclotide dose A (*n* = 36)	Linaclotide dose B (*n* = 41)	Linaclotide dose C (*n* = 39)	Linaclotide 145 μg[b] (*n* = 16)
Linaclotide dose, μg					
Participants aged 6–11 years					
18 to <35 kg		9	18	36	–
≥35 kg		18	36	72	–
Participants aged 12–17 years		18	36	72	145
TEAEs	9 (22.0)	6 (16.7)	12 (29.3)	15 (38.5)	4 (25.0)
Treatment-related TEAEs	0	1 (2.8)	3 (7.3)	6 (15.4)	2 (12.5)
SAEs	0	1 (2.8)	0	0	1 (6.3)
AEs leading to discontinuation	0	2 (5.6)	0	1 (2.6)	0
TEAEs in ≥5% of patients					
Diarrhea[c]	0	1 (2.8)	3 (7.3)	4 (10.3)	2 (12.5)
Headache[d]	1 (2.4)	1 (2.8)	0	4 (10.3)	0
Vomiting	1 (2.4)	1 (2.8)	0	0	1 (6.3)
Fecaloma[e]	0	0	0	2 (5.1)	0
Viral sinusitis	0	0	0	0	1 (6.3)
ALT increased	1 (2.4)	0	0	0	1 (6.3)
AST increased	1 (2.4)	0	0	0	1 (6.3)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[a]No AEs of special interest or deaths occurred.

[b]Assigned only in the 12- to 17-years age group.

[c]Diarrhea occurred in three patients in the 6- to 11-years age group (linaclotide dose A, *n* = 1; linaclotide dose C, *n* = 2) and seven patients in the 12–17 years age group (linaclotide dose B, *n* = 3; linaclotide dose C, *n* = 2; linaclotide 145 μg, *n* = 2).

[d]Headache occurred in two patients in the 6- to 11-years age group (linaclotide dose A, *n* = 1; linaclotide dose C, *n* = 1) and four patients in the 12- to 17-years age group (placebo, *n* = 1; linaclotide dose C, *n* = 3).

[e]Fecaloma is a medically recognized term and refers to a mass of hard dry stool, typically in the colon or rectum.

previous studies have demonstrated that parents/guardians and physicians can have a pervasive role in pediatric-patient disease management.[14,18] For example, positive parental reinforcement and parental expectations can modify a child's behavior.[14] Additionally, education, reassurance, and time provided by the physician can directly impact the child and exert an indirect effect by changing caregivers' attitudes.[18] In this trial, the placebo response was pronounced in patients aged 6–11 years, a result that may reflect an increased effect of caregivers on younger children. Other factors such as trial duration[19,20] and fluctuations in disease course can also contribute to benefits in the placebo group. The data spread in this trial represents the heterogeneity in response in the full patient population but is pronounced in the younger age group.

Interestingly, although higher efficacy was observed with higher doses of linaclotide, we did not see any additional efficacy in the primary endpoint in 12- to 17-year-olds treated with linaclotide 145 versus 72 μg. Dose–response trends have not always been observed in other pediatric FC trials: dosage had no impact on efficacy in children aged 6 months to 18 years treated with prucalopride[14] or in children aged 6–17 years treated with lubiprostone.[21] These two studies were not designed to explore dose response, however, and treatment doses were based on weight. Nonetheless, the authors suggested that the treatment doses may have been too low to produce the desired treatment effect.[14,21] Meanwhile, in a retrospective review of pediatric patients aged 8–17 years treated with linaclotide for FC, 83% (*n* = 50) started with a dose of

15364801, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jpn3.12184 by Osu Central Accounts Payable, Wiley Online Library on [02/04/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

145 μg daily (vs. linaclotide 72 μg), and although efficacy data were not presented by dose, the authors suggested that the symptom improvements could have reflected the use of higher doses.[22] Further research to define potential dose responses in pediatric patients of different ages is warranted.

Other reasons for the observed results in this trial may arise from differences between the younger and older pediatric patients. Pathophysiology of FC varies by age and can be impacted by stool withholding and fear of defecation.[1,21] These behavioral components might not be overcome by a 4-week pharmacologic intervention. Evidence in this area is limited; however, few placebo-controlled trials in children with adequate sample size and durations in treatment have been performed.[14,18]

This trial demonstrated that linaclotide was well tolerated across all doses and pediatric age groups. Its safety profile was consistent with that of studies of adults with chronic idiopathic constipation, as the most common AE in them was diarrhea.[11,23,24] In this pediatric population, these cases were uncommon, with diarrhea AEs occurring in three patients in the 6- to 11-years age group (linaclotide dose A: $n = 1$ [moderate]; linaclotide dose C: $n = 2$ [mild]) and seven patients in the 12- to 17-years age group (linaclotide dose B, $n = 3$ [mild]; linaclotide dose C, $n = 1$ [mild] and $n = 1$ [moderate]; linaclotide dose 145 μg, $n = 2$ [mild]). High tolerability with nonsignificant efficacy has been seen in other pediatric trials in children aged 6 months to 17 years or 6–17 years[14,21]; conversely, in the retrospective review of children aged 8–17 years with FC or constipation-predominant IBS, AEs were relatively common, leading to discontinuation in almost one-third of the children.[22] Plasma concentrations of linaclotide and its active metabolite remained below the limit of quantitation in most pediatric patients. Some initial concerns were that children could have an exaggerated pharmacodynamic response to linaclotide, as data suggested increased GC-C receptor density in children.[25] However, a recently published study confirmed uniform levels of GC-C mRNA expression in children of the age group studied here.[26]

5 | CONCLUSION

This trial identified trends in numerical differences of efficacy in the higher linaclotide doses without compromising safety. But as is commonly the case with research in the pediatric field, it was limited by small sample size, short treatment duration, and high placebo response. The results of this dose-finding phase 2 trial were validated in a pivotal phase 3 trial (NCT04026113), and linaclotide 72 μg was approved by the United States Food and Drug Administration for the treatment of pediatric FC in June 2023.

ACKNOWLEDGMENTS

AbbVie Inc. and Ironwood Pharmaceuticals, Inc. funded this study and participated in the study design, research, analysis, data collection, data interpretation, review, and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of the publication. No honoraria or payments were made for authorship. The writers would like to thank Taryn Weissman of AbbVie Inc. and Wilmin Bartolini of Ironwood Pharmaceuticals, Inc. for their contributions to the study. Writing and editorial support were provided to the authors by Elle Lindsay, PhD, and Jane Beck, MA, of Complete HealthVizion, IPG Health Medical Communications, funded by AbbVie Inc. and Ironwood Pharmaceuticals, Inc.

CONFLICT OF INTEREST STATEMENT

C. D. L. is a consultant for Allergan, Innovative Health Solutions, Ironwood, Mallinckrodt, QOL, and Takeda. S. N. is a consultant for Innovative Health Solutions and Sucampo. J. S. H. is on advisory boards for AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, Lilly, Janssen, and Pfizer and is a consultant for Takeda and Thetis. G. R.-A. is an employee of AbbVie and holds stock or stock options. C. A. is an employee of Janssen Pharmaceutical Companies of Johnson and Johnson and holds stock or stock options. V. S. is an employee of Ironwood Pharmaceuticals, Inc. and may hold stock or stock options. M. Sa. received honoraria for a scientific advisory panel for Innovative Health Solutions and a pediatric advisory panel for QOL Medical and for acting as a consultant for IQVIA, Sucampo, and Takeda. M. Si. serves as an investigator for Pfizer, Sanofi Pasteur, Moderna, Dermavant, GlaxoSmithKline, Incyte, Merck, and AbbVie.

DATA AVAILABILITY STATEMENT

AbbVie and Ironwood are committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (e.g., protocols and clinical study reports), as long as the trials are not part of an ongoing or planned regulatory submission. This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

15364801, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jpn3.12184 by Osu Central Accounts Payable, Wiley Online Library on [02/04/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

REFERENCES

1. Dehghani SM, Kulouee N, Honar N, et al. Clinical manifestations among children with chronic functional constipation. *Middle East J Dig Dis*. 2015;7(1):31-35.
2. Vernon-Roberts A, Alexander I, Day AS. Systematic review of pediatric functional gastrointestinal disorders (Rome IV criteria). *J Clin Med*. 2021;10(21):5087.
3. Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology*. 2016;150(6):1456-1468.
4. Belsey J, Greenfield S, Candy D, Geraint M. Systematic review: impact of constipation on quality of life in adults and children. *Aliment Pharmacol Ther*. 2010;31(9):938-949.
5. Bongers MEJ, van Wijk MP, Reitsma JB, Benninga MA. Long-term prognosis for childhood constipation: clinical outcomes in adulthood. *Pediatrics*. 2010;126(1):e156-e162.
6. Choung RS, Shah ND, Chitkara D, et al. Direct medical costs of constipation from childhood to early adulthood: a population-based birth cohort study. *J Pediatr Gastroenterol Nutr*. 2011;52(1):47-54.
7. Koppen IJN, Lammers LA, Benninga MA, Tabbers MM. Management of functional constipation in children: therapy in practice. *Pediatric Drugs*. 2015;17(5):349-360.
8. Tabbers MM, DiLorenzo C, Berger MY, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr*. 2014;58(2):258-274.
9. de Geus A, Koppen IJN, Flint RB, Benninga MA, Tabbers MM. An update of pharmacological management in children with functional constipation. *Pediatric Drugs*. 2023;25(3):343-358.
10. US Food and Drug Administration. Linzess® (linaclotide). Highlights of prescribing information. 2021.
11. Lembo AJ, Schneier HA, Shiff SJ, et al. Two randomized trials of linaclotide for chronic constipation. *N Engl J Med*. 2011;365(6):527-536.
12. Rao S, Lembo AJ, Shiff SJ, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. *Am J Gastroenterol*. 2012;107(11):1714-1724.
13. Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol*. 2012;107(11):1702-1712.
14. Mugie SM, Korczowski B, Bodi P, et al. Prucalopride is no more effective than placebo for children with functional constipation. *Gastroenterology*. 2014;147(6):1285-1295.
15. Saps M, Youssef N, Miranda A, et al. Multicenter, randomized, placebo-controlled trial of amitriptyline in children with functional gastrointestinal disorders. *Gastroenterology*. 2009;137(4):1261-1269.
16. Saps M, Nurko S, Benninga MA, et al. A collaborative effort to advance drug development in pediatric constipation and irritable bowel syndrome. *J Pediatr Gastroenterol Nutr*. 2021;73(2):145-149.
17. Chen J, Liu X, Bai T, Hou X. Impact of clinical outcome measures on placebo response rates in clinical trials for chronic constipation: a systematic review and meta-analysis. *Clin Transl Gastroenterol*. 2020;11(11):e00255.
18. Benninga MA, Mayer EA. The power of placebo in pediatric functional gastrointestinal disease. *Gastroenterology*. 2009;137(4):1207-1210.
19. Ford AC, Moayyedi P. Meta-analysis: factors affecting placebo response rate in the irritable bowel syndrome. *Aliment Pharmacol Ther*. 2010;32(2):144-158.
20. Musial F. Placebo responses in patients with gastrointestinal disorders. *World J Gastroenterol*. 2007;13(25):3425-3429.
21. Benninga MA, Hussain SZ, Sood MR, et al. Lubiprostone for pediatric functional constipation: randomized, controlled, double-blind study with long-term extension. *Clin Gastroenterol Hepatol*. 2022;20(3):602-610.
22. Baaleman DF, Gupta S, Benninga MA, et al. The use of linaclotide in children with functional constipation or irritable bowel syndrome: a retrospective chart review. *Pediatric Drugs*. 2021;23(3):307-314.
23. Lacy BE, Schey R, Shiff SJ, et al. Linaclotide in chronic idiopathic constipation patients with moderate to severe abdominal bloating: a randomized, controlled trial. *PLoS ONE*. 2015;10(7):e0134349.
24. Schoenfeld P, Lacy BE, Chey WD, et al. Low-dose linaclotide (72 μg) for chronic idiopathic constipation: a 12-week, randomized, double-blind, placebo-controlled trial. *Am J Gastroenterol*. 2018;113(1):105-114.
25. Cohen MB, Guarino A, Shukla R, Giannella RA. Age-related differences in receptors for *Escherichia coli* heat-stable enterotoxin in the small and large intestine of children. *Gastroenterology*. 1988;94(2):367-373.
26. Cohen MB, Gold BD, Xanthakos SA, et al. Intestinal guanylate cyclase-C mRNA expression in duodenum and colon of children. *J Pediatr Gastroenterol Nutr*. 2021;73(6):703-709.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Di Lorenzo C, Nurko S, Hyams JS, et al. Clinical trial: randomized controlled trial of linaclotide in children aged 6–17 years with functional constipation. *J Pediatr Gastroenterol Nutr*. 2024;1-10. doi:10.1002/jpn3.12184

15364801, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jpn3.12184 by Osu Central Accounts Payable, Wiley Online Library on [02/04/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License