jjogastroenterology.org

Japanese Journal of Gastroenterology

ISSN 2832-4870

DIRECTIVE PUBLICATIONS

Research Article

Efficacy and Safety of Linaclotide in Indian Patients with Chronic Constipation- A Randomized, Multicentre, Double Blind, Placebo Controlled, Parallel-Group Study.

Saroj Kant Sinha[1], Manas Kumar Mondal[2], D P Yadav[3], B Ramesh Kumar[4], Anumula Kavitha[5], Piyush Agarwal*[6], Brajesh Kumar Jha[6], Jaganmohan Somagoni[6], Sanketh Kumar Chakilam[6], Pramod Kumar Potluri[6].

Affiliations:

[1] *Post Graduate Institute of Medical Education and Research (PGIEMR), Chandigarh, India*
[2] *Department of Gastroenterology, Nil Ratan Sirkar Medical College and Hospital, Kolkata, India*
[3] *Institute of Medical Sciences, Banaras Hindu University (BHU), Varanasi, India.*
[4] *Osmania General Hospital, Department of Gastroenterology, Hyderabad, India*
[5] *Government General Hospital, Department of Gastroenterology, Guntur, India.*
[6] *Global Clinical Management, Dr. Reddy's Laboratories Ltd, Hyderabad, India*

Short running title: Efficacy and Safety of Linaclotide in Chronic Constipation.

Abstract

Background: Linaclotide is a minimally absorbed peptide agonist of the guanylate cyclase C receptor, that causes secretion of chloride and bicarbonate into the intestinal lumen, increasing luminal fluid secretion and accelerating intestinal transit. In this study, we aimed to determine the efficacy and safety of Linaclotide over 12-weeks treatment for chronic constipation in Indian patients.

Methods: The current study was a randomized, double-blind, parallel-group, placebo-controlled phase III trial aimed at assessing the efficacy and safety of Linaclotide (72 mcg/145 mcg) in Indian patients with chronic constipation over a treatment duration of 12 weeks. The study intended to include patients who had chronic constipation lasting at least 6 months and met the Rome IV criteria for functional constipation. The efficacy endpoints for this trial were proportion of patients with complete spontaneous bowel movement (CSBM) and spontaneous bowel movement (SBM) overall response.

Results: Between April, 2023, and June, 2024, 316 patients were randomized into the 12-week trial. In mITT population [N=283 (Linaclotide=142 and placebo=141)], the responder proportions for CSBM and SBM between Linaclotide and placebo demonstrated significant statistical differences of 9.08% (95% CI: 0.79%, 17.37%) and 20.79% (95% CI: 9.54%, 32.04%), respectively. The most common adverse event (AE) was abdominal pain [Linaclotide=5 patients (3.2%) vs placebo=8 patients (5.1%)].

Conclusions: Linaclotide was well tolerated and improved bowel movement within twelve weeks of treatment in Indian patients with chronic constipation.

Keywords: *Linaclotide, Defecation, Guanylate cyclase C receptor, Constipation, Intention to treat analysis.*

INTRODUCTION

Chronic constipation (CC) affects between 16% to 25% of the Indian population. The prevalence is higher in elderly population [1]. According to a population based study from India, the prevalence of constipation by the Rome II criteria was found to be 16.8% and self-reported constipation to be 24.8% [2]. A comprehensive multicentric study interviewed 2785 patients with chronic lower gastrointestinal symptoms and 4500 non-complaining subjects. Among those with symptoms, 53% reported self-perceived constipation, while in the non-complaining group, 18% and 23% reported straining during bowel movements and incomplete stool evacuation, respectively [3]. These findings highlight the importance of addressing chronic constipation as a public health concern in India.

The most common symptoms of chronic constipation are hard stools, infrequent bowel movements, straining, and a feeling

***Corresponding Author:** **Dr. Piyush Agarwal**, Global Clinical Management, IPDO, Dr. Reddy's Laboratories Ltd., Hyderabad, India. **Phone:** (+91) 9619097755, **Email:** piyushagarwal@drreddys.com.
Received: 10-July-2025, Manuscript No. JJOGASTRO - 4979 **; Editor Assigned:** 11-July-2025 **; Reviewed:** 25-July-2025, QC No. JJOGASTRO - 4979 **;** **Published:** 29-July-2025, **DOI:** 10.52338/jjogastro.2025.4979.
Citation: **Dr. Piyush Agarwal**. Efficacy and Safety of Linaclotide in Indian Patients with Chronic Constipation- A Randomized, Multicentre, Double Blind, Placebo Controlled, Parallel-Group Study. Japanese Journal of Gastroenterology. 2025 July; 12(1). doi: 10.52338/jjogastro.2025.4979.

of incomplete evacuation [4]. Symptoms affect individuals of different ages, ethnicities, socioeconomic backgrounds, and nationalities. These symptoms have a detrimental effect on patient's quality of life (QOL) and socioeconomic status [5].

Use of available treatment options such as contact stimulant laxatives (like sennoside and sodium picosulfate hydrate), saline laxatives (like magnesium oxide, lactulose, sorbitol, and PEG) and medications that change the function of the intestinal epithelium (like lubiprostone) is associated with side effects of abdominal pain, diarrhea, nausea, dehydration and electrolyte abnormalities like hypermagnesemia [6]. Long term use or abuse of stimulant laxatives has been reported to be associated with increased risk of resistance or habituation and atonic colon [7,8]. Although various treatment options for constipation exist, the search for effective medications to address the needs of patients with chronic constipation endures.

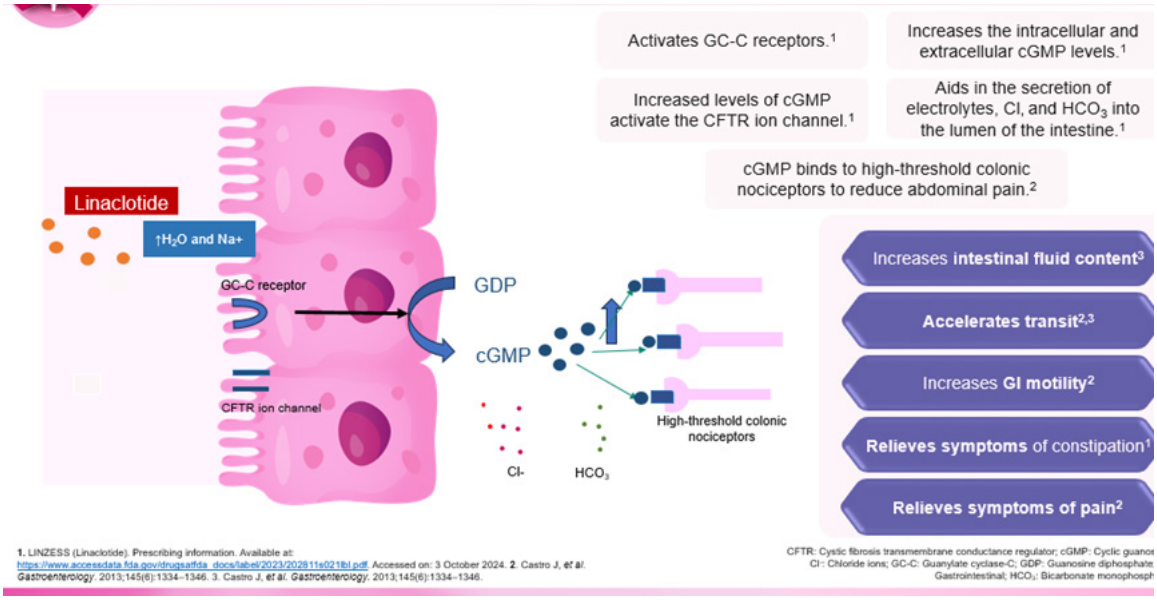
Linaclotide is a novel, 14-amino-acid synthetic peptide structurally related to the endogenous guanylin peptide family. It binds to and activates the guanylate cyclase C (GC-C) receptor on the luminal surface of the intestinal epithelium. Activation of guanylate cyclase C results in the generation of cyclic guanosine monophosphate (cGMP). This activation causes secretion of chloride and bicarbonate into the intestinal lumen, increasing luminal fluid secretion and accelerating intestinal transit [9]. In addition, Linaclotide also reduces abdominal pain by inhibiting nociceptors, which are pain-sensing nerve cells in the intestine (**Figure 1**). It achieves this by activating receptor GC-C on intestinal epithelial cells, leading to increased levels of cGMP. This cGMP then acts on the nociceptors, reducing their activity and decreasing pain signaling [10]. In animal model of visceral pain, Linaclotide is reported to reduce abdominal muscle contraction and decreased the activity of pain-sensing nerves by increasing extracellular cGMP [11].

Linaclotide 72/145 mcg dose was approved by the US Food and Drug Administration for chronic constipation. The FDA-recommended dose of Linaclotide for the chronic idiopathic indication is 72 mcg or 145 mcg orally, once daily, based on individual presentation or tolerability.

Based on the findings of safety and efficacy in phase III trials and approved dose regimen [11,12], a dose of 72 mcg/145 mcg of Linaclotide was selected for the current study.

Objective of the present trial was to assess the efficacy and safety of once-daily Linaclotide over 12 weeks in Indian patients with chronic constipation.

Figure 1. Mechanism of action of Linaclotide.



MATERIALS AND METHODS

Study design and participants

This was a prospective, multicenter, randomized, double blind, parallel group, placebo controlled, phase III study to evaluate the efficacy and safety of Linaclotide capsule in patients with chronic constipation.

The study planned to enroll eligible male and female patients aged 18 to 65 years (both inclusive), with chronic constipation of at least 6 months' duration. Patients were diagnosed based on Rome IV criteria [13] for functional constipation i.e. fewer than three SBMs per week (defined as bowel movements occurring spontaneously and independently of administration of rescue medication for at least 24 h), with at least one of the following symptoms during 25% or more of bowel movements: straining at defecation, lumpy or hard stools, and sensation of incomplete evacuation.

Patients experiencing constipation needed to have documented results from a colonoscopy or sigmoidoscopy conducted within the two years leading up to their screening visit to rule out any organic causes of constipation.

The following conditions disqualified the patients from participation: prior intestine or rectum surgery (except for a simple appendectomy); prohibited medications, organic disorders of the intestine, such as mechanical obstruction; ischemic colitis, inflammatory bowel disease, colorectal cancers and pre-malignant colonic disease (e.g., familial adenomatous polyposis or hereditary non-polyposis colorectal cancer) or other forms of familial colorectal cancer. The study consisted sequentially of a screening period of upto 28 days followed by the randomized treatment period. Patients reporting more than 3 SBM per week on average during screening period were excluded from the study. The treatment period started with randomization visit (Day 0) and continued for 12 weeks. The efficacy endpoints were assessed on week 12.

Intervention and Randomization

Eligible patients, recruited from 22 clinical sites in India, were randomized using interactive web response systems (IWRS) in 1:1 ratio (either to Linaclotide or placebo treatment groups). Randomized patients took the assigned study drug once per day before breakfast and were monitored in an outpatient setting. Per assignment, each randomized patient had to take 1 capsule of the investigational product (Linaclotide 72 mcg or placebo) once a day orally in the first four weeks. Based on the patient's symptoms in the fourth week, the dose was increased to 145 mcg or placebo for the remainder of the total treatment period of 12 weeks. Placebo capsules matching test products in appearance were used.

Allocation Concealment

Group assignment was concealed from patients, investigators, sponsors, and data analysts.

Implementation of Blinding

The patients and investigator (and other personnel involved in the study) were unaware of the study drug(s) administered to the patients. The sponsor was also blinded during the study. The placebo capsules and its packaging and labeling were identical in appearance to that of test products.

Study objectives and outcomes

The primary objective of the study was to evaluate the efficacy of Linaclotide. Efficacy variable was the proportion of patients who were CSBM and SBM overall responders at week 12, compared between Linaclotide and placebo groups. A CSBM overall responder was defined as a patient who had at least 3 CSBMs for at least 9 weeks out of the 12-weeks. Likewise, the SBM overall responders were defined as patients who had at least 3 SBMs for at least 9 weeks out of the 12-weeks.

Other efficacy variables included change from baseline in the average weekly CSBM frequency change from baseline in the average weekly SBM frequency, change from baseline in the average weekly stool consistency score (scored using BSFS) [14], over the treatment period when compared between Linaclotide and placebo groups.

Determination of Sample Size

A total of 316 patients with chronic constipation participated in the study. They were randomized in a 1:1 ratio into two groups: Linaclotide 72/145mcg and placebo, with 158 patients in each arm.

Statistical analysis

Statistical analyses were conducted using SAS® version 9.4. Continuous data was summarized with mean, SD, median, 95% CI, range, and sample size, while categorical data was presented with counts and percentages.

Efficacy assessments were conducted in the modified intent-to-treat (mITT) population, including all randomized patients who met inclusion/exclusion criteria, received at least one dose, and had a post-dose primary evaluation. Efficacy comparisons between Linaclotide and placebo were assessed using chi-square tests, with non-parametric tests applied where appropriate. Mean treatment differences were analyzed using ANCOVA, incorporating baseline covariates, with two-sided 95% CI for Least Square Mean (LSM) differences. Week 12 changes from baseline were evaluated using two-sample t-tests, with two-sided 95% CI provided.

The safety population included all randomized patients who received at least one dose of the investigational drug, forming the basis for all safety analyses.

Data collection and Management

During the 12-week treatment period, patients recorded daily bowel movements, stool consistency (BSFS), sensation of complete emptying, and rescue medication use in paper diaries. Weekly assessments included constipation severity and additional laxative use, continuing until end-of-treatment (EOT).

Ethical considerations

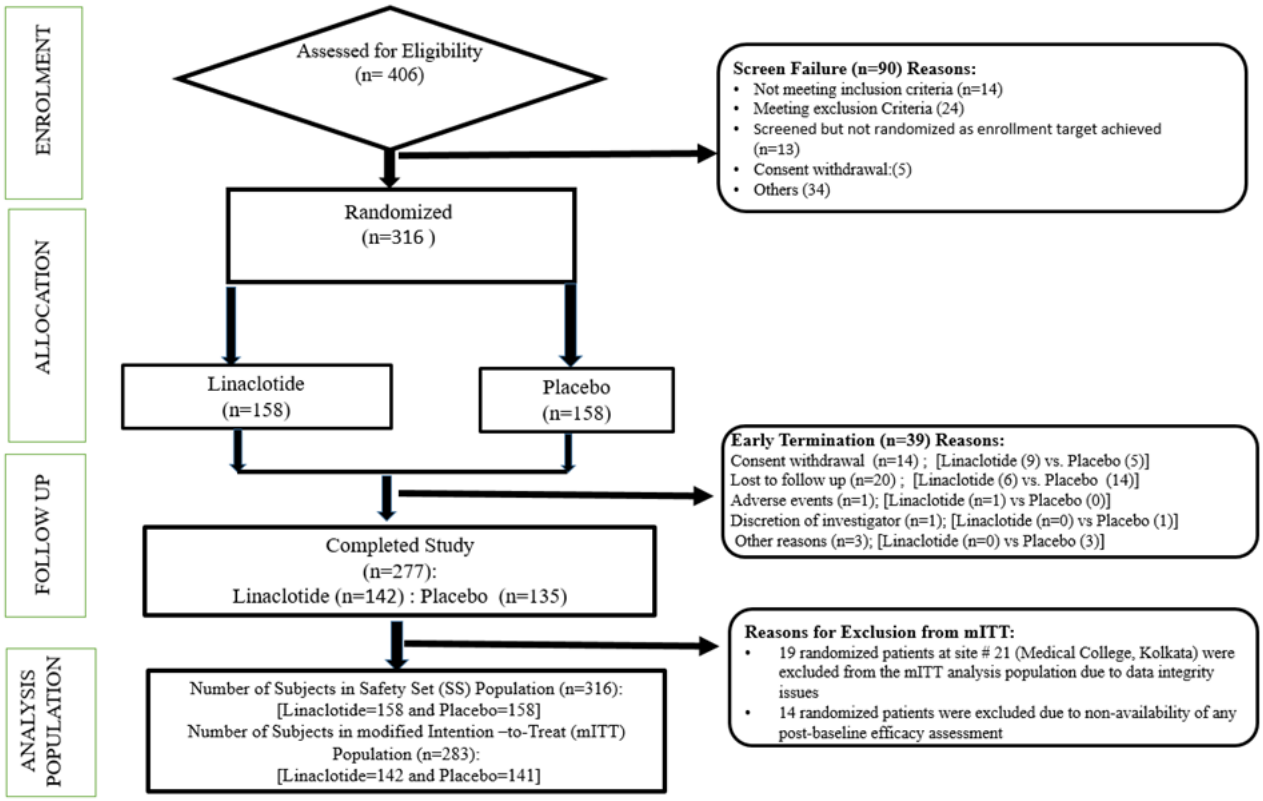
The study was conducted in compliance with the ethical principles that originate in the Declaration of Helsinki and the International Conference on Harmonization (ICH) guidelines for good clinical practice (GCP). The study was approved by institutional ethics committee of each participating centres. Written informed consent was obtained from each patient prior to screening on the approved informed consent form (ICF). Patients received a defined conveyance allowance in the study. This trial is registered at CTRI [Clinical Trial Registry of India] with the Trial Registration number CTRI/2023/03.

RESULTS

Study population characteristics

Between April, 2023, and June, 2024, a total of 406 patients were screened at 22 sites across India, of which 316 patients were randomized and 90 patients were screen failures (**Figure 2**). All the 316 patients (who received at least 1 dose of study drug) were included in the safety analysis population and 283 patients (89.6 %) were in modified Intent-to-treat (mITT) population (Linaclotide=142 and placebo=141).

Figure 2. CONSORT diagram displaying the flow of participants through the study.



Of the 316 patients who received at least 1 dose of study drug, 180 (57%) were males and 136 (43.00%) were females. The median age of enrolled patients was 39.5 years (ranging from 18 to 64 years). The mean (SD) baseline height (cm) and body weight (kg), were 160 (8.97) and 60.4 (10.07) respectively (**Table 1**). All the patients were Asian (Indian). Demographic characteristics were comparable between the two treatment groups.

Table 1. Summary of baseline demography.

Demographic Variable	Statistic	Linaclotide72mcg/145mcg (n=158)	Placebo (n=158)	Total (n=316)
Age (Year)	Mean (SD)	40.4 (12.58)	40.0 (12.12)	40.2 (12.34)
	Median (min-max)	40 (18.0-64.0)	39.0 (19.0-64.0)	39.5 (18.0-64.0)
Gender	Female	66 (41.80%)	70 (44.40%)	136(43.00%)
	Male	92(58.20%)	88(55.60%)	180(57.00%)
Height (cm)	Mean (SD)	160 (8.73)	160 (9.23)	160 (8.97)
	Median (min-max)	159 (140, 180)	160 (123, 192)	160 (123, 192)
Weight (kg)	Mean (SD)	60.4 (10.07)	61.1 (9.04)	60.8 (9.56)
	Median (min-max)	60.0 (38, 91)	61.0 (45, 85)	60.4 (38, 91)

Abbreviations: SD, Standard deviation; cm, centimeter; kg, kilogram; min-max, minimum-maximum Demographic characteristics were compared between treatment groups using two sample t-test

Efficacy results

In primary analysis at week 12 [N=283 (Linaclotide=142 and placebo=141)] (mITT population), the proportion of CSBM overall responders was found to be significantly higher in the Linaclotide group (19.72%, 28/142) compared to the placebo group (10.64%, 15/141). The absolute difference in response rates between Linaclotide and placebo was 9.08% (95% CI: 0.79%, 17.37%), indicating statistical significance (p=0.0337) (**Figure 3**). Similarly, the proportion of SBM overall responders was statistically higher for Linaclotide (68.31%, 97/142) versus placebo (47.52%, 67/141), with a difference in response rates of 20.79% (95% CI: 9.54%, 32.04%), demonstrating strong statistical significance (p=0.0004) (**Figure 4**).

Figure 3. Proportion of patients showing CSBM response (CSBM responder)

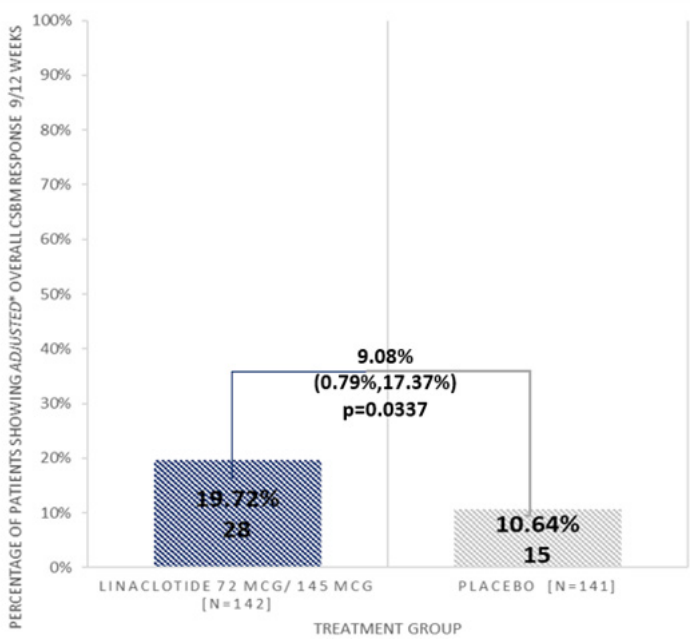
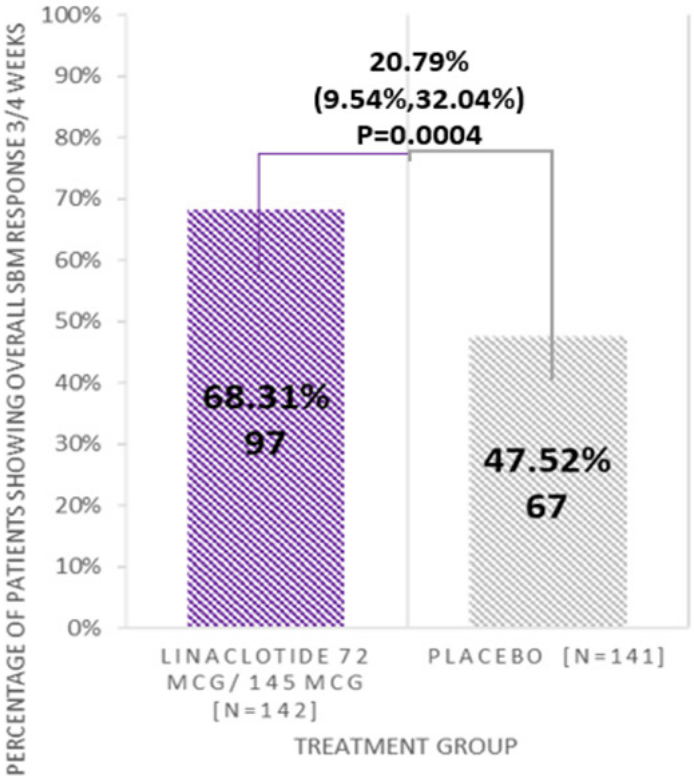


Figure 4. Proportion of patients showing SBM response (SBM responder)



Additionally, sensitivity analysis was performed for CSBM responder at 12 weeks based on the dose escalation considering CSBM frequency instead of SBM frequency at the end of 4 weeks. A total of 28 (38.4%) patients in Linaclotide 145 mcg group and 16 (19.2 %) patients in the placebo group were CSBM responders at the end of 12 weeks, with a 19.08 % difference in proportions (95% CI: 5.06, 33.10).

Over the course of 12 weeks, the least square mean (LSM) difference in weekly CSBM frequency from baseline demonstrated statistical significance at weeks 4, 8, and 12. The observed values were 0.49 (95% CI: 0.08, 0.90) at week 4, 0.47 (95% CI: 0.07, 0.86) at week 8, and 0.38 (95% CI: 0.00, 0.76) at week 12 (**Figure 5**). Similarly, the LSM difference in the weekly SBM frequency change from baseline was statistically significant at weeks 4, 8, and 12. The respective values recorded were 0.59 (95% CI: 0.19, 0.99) at week 4, 0.67 (95% CI: 0.25, 1.09) at week 8, and 0.59 (95% CI: 0.19, 0.99) at week 12 (**Figure 6**).

Figure 5. Average weekly frequency of CSBMs.

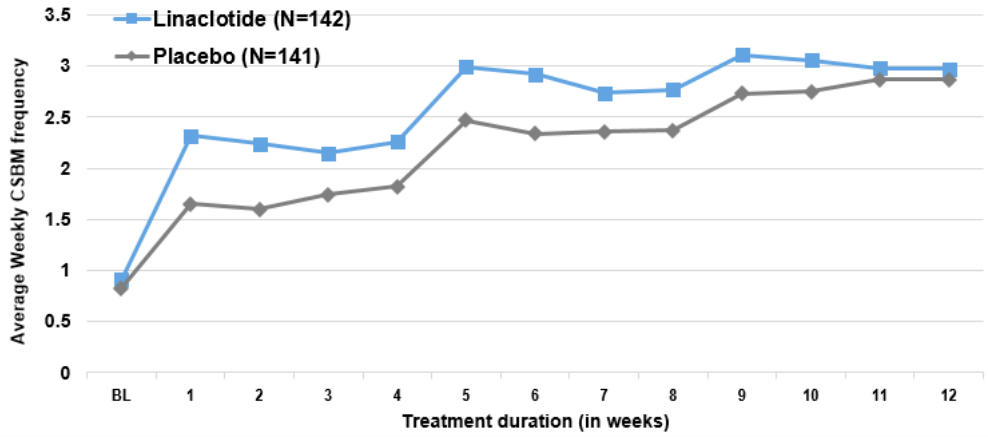
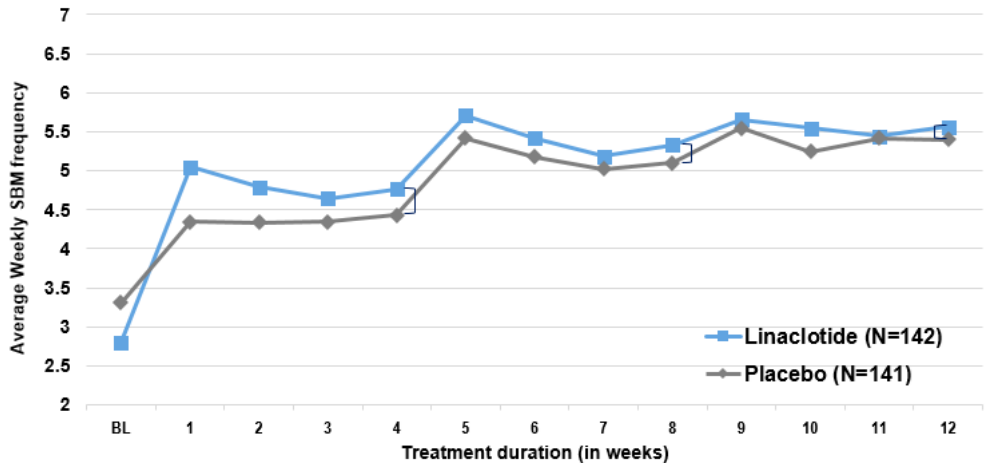
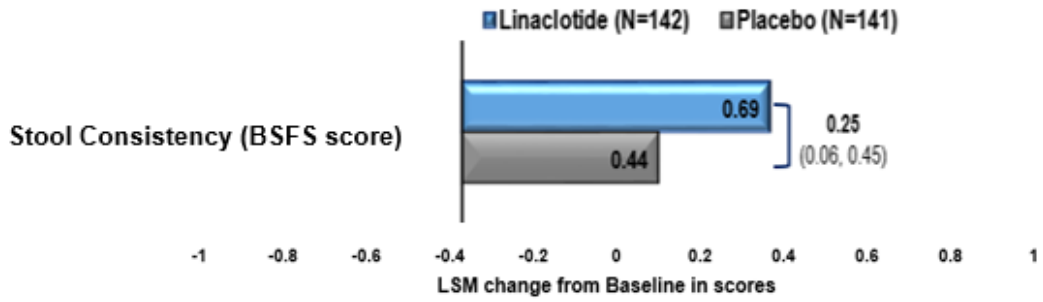


Figure 6. Average weekly frequency of SBMs.



Furthermore, the LSM difference in stool consistency scores (using BSFS) between Linaclotide and placebo was statistically significant, with a recorded difference of 0.25 (95% CI: 0.06, 0.45). The LS mean (SD) was 0.69 (0.98) for Linaclotide and 0.46 (0.88) for placebo (**Figure 7**).

Figure 7. Change from baseline in stool consistency (BSFS score).



Safety results

Of the 316 patients included in the safety analyses, 58 patients (18.4%) reported at least one treatment emergent adverse event (TEAE). The distribution of patients with TEAEs between treatment groups Linaclotide and placebo was fairly even, at 26 (16.5%) and 32 (20.3%), respectively. TEAEs were categorized as mild [n=52 (16.5%); Linaclotide= 21(13.3%) vs placebo= 31(19.6%)] and moderate [n=6(1.9%); Linaclotide=5(3.2 %) vs placebo=1(0.6%] in severity. The most common TEAEs were abdominal pain [Linaclotide=5 patients (3.2%); vs placebo=8 patients (5.1%)], abdominal pain upper [Linaclotide=5 patients (3.2%); vs placebo=1 patient (0.6)], and vomiting [Linaclotide=2 patients (1.3%) vs placebo=1 patient (0.6%)]. No deaths or serious adverse events (SAEs) occurred in the study (**Table 2**). No clinically significant abnormalities were observed in vital signs, clinical laboratory parameters, and physical examination data.

Table 2. Summary of Treatment Emergent Adverse Events (TEAEs)-safety population.

Description	Linactide72mcg/145mcg n (%)	Placebo n (%)	Total n (%)
Patients Randomized	158	158	316
Patients with at least one TEAE	26 (16.5%)	32 (20.3%)	58 (18.4%)
No. of TEAEs reported	26 (16.5%)	32 (20.3%)	58 (18.4%)
Mild	21 (13.3%)	31 (19.6%)	52 (16.5%)
Moderate	5 (3.2%)	1 (0.6%)	6 (1.9%)
Common treatment emergent adverse events	Patients n (%)	Patients n (%)	Patients n (%)
Abdominal pain	5 (3.2%)	8 (5.1%)	13 (4.1%)
Abdominal pain (upper)	5 (3.2%)	1 (0.6%)	6 (1.9%)
Vomiting	2 (1.3%)	1 (0.6%)	3 (0.9%)

DISCUSSION

The study demonstrated superior outcomes for Linaclotide on the endpoints of change from baseline in CSBM and SBM overall responder proportions, average weekly frequency of CSBMs and SBMs, and change from baseline in weekly stool consistency (by Bristol Stool Form Score) with a twelve-week treatment with Linaclotide self-administered once daily, in comparison to placebo. A statistical significant difference in proportion of CSBM and SBM overall responder was observed with Linaclotide treatment, specifically a pronounced significant difference in proportion of SBM responders (20.79%). A relatively lower difference in proportion of CSBM responders (9.08%) could be attributed to ethnic variation and the high placebo effect. Needless to say, the rigorous response end point required that patients should have normalization of bowel function (i.e., three or more CSBMs per week) for at least 75% of the treatment period. Moreover, patients also received treatment with osmotically active laxatives in preparation for colonoscopy during the screening phase, and the effects of this treatment may have continued into randomized treatment phases. This could help explain the high response rate to placebo.

A clinically meaningful improvement in weekly stool consistency (by Bristol Stool Form Score) perhaps offer multi-symptom relief to patients with chronic constipation. This could be most likely a consequence of increased luminal fluid, with an acceleration of intestinal transit. In fact, Linaclotide has been shown to reduce visceral hypersensitivity in animal models by means of a guanylate cyclase C–cGMP mechanism. These results obtained in current study serve to corroborate the findings of efficacy and safety for orally administered once daily Linaclotide treatment in patients with chronic constipation, over a duration of 12 weeks, that are reported by the innovator in their pivotal phase III trials [11,12].

In the previous studies, Linaclotide treatment was well-tolerated with gastro-intestinal adverse events being the most frequently reported category of treatment emergent adverse events. Gastrointestinal adverse events like abdominal pain, diarrhea and nausea are known adverse events with Linaclotide (and also seen with several other laxative), besides being a manifestation of the disease itself [10,11]. Similarly, treatment emergent adverse event profiles observed for Linaclotide in the current study was comparable to placebo with no striking difference in the incidence. Reported adverse events pertaining to the gastro-intestinal system, chiefly abdominal pain was mild or moderate and largely resolved by the end of the study.

This study is the first randomized, double-blind, and placebo-controlled trial that shows the safety and statistically significant efficacy of Linaclotide in Indian patients with chronic functional constipation. Patients who met the criteria for chronic functional constipation according to the ROME IV guidelines were recruited from various centers throughout India, making the results generalizable to Indian patients dealing with this condition.

Overall, Linaclotide was determined to be generally safe and well-tolerated during the 12 weeks of treatment, with no

serious adverse events (SAEs) or fatalities reported in this trial.

In conclusion, this study demonstrated that Linaclotide, a peptide agonist of the guanylate cyclase C receptor, was effective in 12-week treatment of chronic constipation in Indian patients and was well-tolerated. Good tolerability, treatment durations and convenient once-daily dosing are perceptible benefits with the guanylate cyclase C receptor agonist class of drugs, enhancing the available therapeutic options for poorly understood and often difficult to treat chronic functional constipation.

Ethical statements

The study was conducted in compliance with the ethical principles that originate in the Declaration of Helsinki and the International Conference on Harmonization (ICH) guidelines for good clinical practice (GCP). The study was approved by institutional ethics committee of each participating centres. Written informed consent was obtained from each patient prior to screening on the approved informed consent form (ICF). Patients received a defined conveyance allowance in the study. All authors had access to all data and take full responsibility for the submission.

Conflict Of Interest/Disclosure Statement

The authors SKS, MKM, DPY, BRK, and AK are the trial investigators and they declared that no competing interests exist.The authors SKS, MKM, DPY, BRK, and AK entered into a contract for the patient recruitment and clinical conduct of the study at their respective sites. PA, BKJ, JM, SKC and PKP are full time employees of Dr. Reddy's Laboratories Limited.

Sources Of Funding

The study was sponsored (completely funded) by Dr Reddy's Laboratories Limited, a for-profit organization involved in development, registration, licensing and commercialization of drug products.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Clinical Trial Registry Number

CTRI/2023/03/050482

Author Contributions

PA conceived and designed the study. PKP managed the collection of the study data. SKC conducted the data analysis. PA, BKJ, JS, and SKC interpreted the data. BKJ prepared drafts of the manuscript. PA, JS, BKJ, SKC, PKP critically reviewed the manuscript. SKS, MKM, DPY, BRK, and AK recruited patients and reviewed the manuscript. PA approved the manuscript to be communicated for publication.

Acknowledgements

The authors thank all the participants, site staff and Ethics Committees involved for their co-operation in smooth conduct of the study. The authors acknowledge the service provided by Seveillar Clinical Supplies Services Pvt. Ltd., Maharashtra 412 220, India, for the clinical trial supply management of investigational product, Metropolis Healthcare Limited, Worli, 400 030, Mumbai, India, for central laboratory services, and Croissance Clinical Research, Miyapur, Hyderabad, Telangana 500 049, India, for clinical data management.

Ethical Consideration

The study was approved by institutional ethics committee of each centre in the participating countries. Written informed consent was obtained from each patient prior to screening on the approved informed consent form (ICF). The study was conducted in compliance with the ethical principles that originate in the Declaration of Helsinki and the International Conference on Harmonization (ICH) guidelines for good clinical practice (GCP) and applicable regulatory requirements.

REFERENCES

1. Ghoshal UC, Sachdeva S, Pratap N, et al. Indian consensus on chronic constipation in adults: A joint position statement of the Indian Motility and Functional Diseases Association and the Indian Society of Gastroenterology. Indian J Gastroenterol. 2018; 37:526-544.

2. Rajput M, Saini SK. Prevalence of constipation among the general population: a community-based survey from India. Gastroenterol Nurs. 2014; 37:425-429.

3. Ghoshal UC, Abraham P, Bhatt C, et al. Epidemiological and clinical profile of irri-table bowel syndrome in India: report of the Indian Society of Gastroenterology Task Force. Indian J Gastroenterol. 2008; 27:22-28.

4. Andrews CN, Storr M. The pathophysiology of chronic constipation. Can J Gastro-enterol. 2011; 25 (Suppl B):16B-21B.

5. Kinnunen O. Study of constipation in a geriatric hospital, day hospital, old people's home and at home. Aging. 1991; 3:161-170.

6. Noergaard M, Traerup Andersen J, Jimenez-Solem E, et al.. Long term treatment with stimulant laxatives - clinical evidence for effectiveness and safety? Scand J Gas-troenteroal. 2019:54:27-34.

7. Balekuduru A, Sahu MK. Habit forming properties of laxatives for chronic consti-pation: a review. F1000Research. 2023:11:803.

8. Joo JS, Ehrenpreis ED, Gonzalez L, et al. Alterations in colonic anatomy induced by chronic stimulant laxatives:

the cathartic colon revisited. J Clin Gastroenterol. 1998; 26:283-286.

9. Andresen, V, Camilleri, M, Busciglio, IA, et al. Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. Gastroenterology 2007; 133:761-768.

10. Castro J, Harrington AM, Hughes PA, et al. Linaclotide inhibits colonic nocicep-tors and relieves abdominal pain via guanylate cyclase-C and extracellular cyclic gua-nosine 3',5'-monophosphate. Gastroenterology. 2013;145(6).

11. Lembo AJ, Schneier HA, Shiff SJ, et al. Two randomized trials of linaclotide for chronic constipation. N Engl J Med 2011; 365: 527–53.

12. Schoenfeld P, Lacy BE, Chey WD et al. Low-Dose Linaclotide (72 µg) for Chron-ic Idiopathic Constipation: A 12-Week, Randomized, Double-Blind, Placebo-Controlled Trial. Am J Gastroenterol. 2018; 113:105-114.

13. Mearin F, Lacy BE, Chang L, et al. Bowel Disorders. Gastroenterology.2016;18: 00222-5.

14. O'Donnell LJ, Virjee J, Heaton KW. Detection of pseudodiarrhoea by simple clini-cal assessment of intestinal transit rate. BMJ. 1990; 300:439-440.