Safety, Tolerability, and Effectiveness of Plecanatide in Patients with Constipation-predominant Irritable Bowel Syndrome: Long-term Evidence from an Open-label Study

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Introduction

- Irritable bowel syndrome with constipation (IBS-C) is a functional bowel disorder presenting with multiple symptoms that include abdominal pain improved with defecation, a change in stool frequency (generally ≤3 bowel movements per week), and a change in stool form (graded by the Bristol Stool Form Scale).[1] In IBS-C, >25% of bowel movements have a BSFS 1–2 and <25% have a BSFS 6–7. The abdominal pain component appears to be related to visceral hypersensitivity involving the intestines.
- The prevalence of IBS-C in United States (US) is estimated at 4–7% (~13–23 million people).[2]
- IBS-C is associated with worsened quality of life (QOL), reduced productivity, and increased healthcare utilization and costs.[3-5]
- Plecanatide is the most recently approved prescription option for IBS-C, approved in the United States for the treatment of adults with chronic idiopathic constipation or IBS-C.
- Plecanatide is an analog of human uroguanylin, an endogenous peptide found in the gastrointestinal tract. With the exception of a single amino acid substitution (glutamic acid for aspartic acid in the 3rd position), plecanatide is structurally identical to uroguanylin. The amino acid substitution in plecanatide enhances its affinity for the guanylate cyclase-C (GC-C) receptor. Plecanatide, like uroguanylin, contains 2 disulfide bonds and 2 charged amino acids within the pH-sensitive region. These structural features are important for the peptide conformation required for optimal binding to the GC-C receptor, which occurs under slightly acidic conditions.
  - Replicating the activity of uroguanylin, plecanatide binds in a pH-sensitive manner to GC-C receptors expressed on epithelial cells that line the intestinal lumen, leading to intracellular accumulation of cyclic GMP. Subsequent activity leads to secretion of water into the intestinal lumen, hydrating stool and contributing to normal bowel movements.
  - Activation of GC-C receptors has been linked, through a mechanism involving basolateral release of cyclic GMP, to suppression of visceral afferent firing in preclinical studies, with therapeutic potential for attenuating visceral hypersensitivity, a key characteristic of IBS-C.
- The clinical efficacy of plecanatide (3 mg and 6 mg) in adults with IBS-C was demonstrated in two identically-designed, phase 3, double-blind, randomized, placebo-controlled trials.[6]
  - Both 12-week studies met the primary endpoint (patients had to achieve a combined weekly improvement in stool frequency and reduction in abdominal pain for at least 6 of 12 weeks), as well as a key secondary endpoint (sustained responder), for which a patient had to be an overall responder plus a weekly responder for ≥2 of the final 4 weeks of treatment. In addition, plecanatide-treated patients had significant improvements from baseline in stool frequency, stool consistency, straining, and abdominal symptoms (i.e., pain, bloating, discomfort, cramping, and fullness) compared to placebo.
  - Plecanatide treatment, at both doses, was generally safe and well tolerated, with low rates of adverse events (AEs) and discontinuations due to AEs.
- IBS-C is a chronic condition; therefore, it is of importance and interest to conduct a long-term study evaluating the safety and tolerability of a chronically administered therapy such as plecanatide.

Objective

- To evaluate the long-term safety, tolerability, and effectiveness of once-daily oral plecanatide 6 mg for the treatment of adults with IBS-C.

Methods

- This was a multi-center, open-label, study of once-daily plecanatide 6 mg administered orally for up to 53 weeks in patients with IBS-C.
  - *ClinicalTrials.gov* registration identifier: NCT02706483

Inclusion/exclusion criteria

- Patients were enrolled either from previous double-blind studies or were new patients that had not previously enrolled in any plecanatide study.[6]
- All patients had documented diagnosis of IBS-C according to Rome III criteria.
- Patients were excluded if: (1) they were unwilling or unable to participate in the study for the required duration, (2) they were of childbearing potential and were confirmed pregnant (or lactating) or did not agree to use adequate contraception for the duration of the study, (3) they experienced a significant worsening of health status during a previous study, or (4) they used linaclotide or lubiprostone within 15 days of the baseline visit.
- For new patients, inclusion and exclusion criteria were similar to that of the previously conducted double-blind studies.

Safety, Tolerability, and Effectiveness Measures

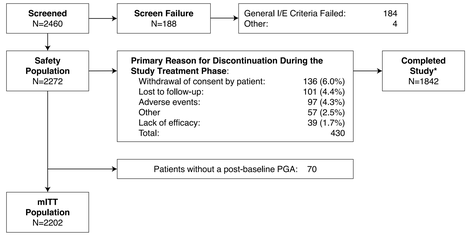
- Patients returned to the study site during treatment weeks 4, 12, 24, 36, and 53 (or at last study treatment visit) to undergo safety and tolerability assessments, as well as for the evaluation of patients' self-assessment of disease severity and adequacy of treatment.
- Safety and tolerability were measured by the number and nature of treatment-emergent AEs, serious AEs (SAEs), withdrawals due to AEs, and the percentage of patients remaining in the study at each week.
- For effectiveness, Patient Global Assessments (PGAs) were used to evaluate disease severity, patient satisfaction with treatment, and desire for treatment continuation.
  - PGA of IBS symptom relief (PGA-Relief): 5-point scale where 2 = significantly relieved, 1 = moderately relieved, 0 = unchanged, -1 = moderately worse, and -2 = significantly worse
  - PGA of treatment satisfaction (PGA-Satisfaction): 5-point scale where 1 = not at all satisfied, 2 = a little satisfied, 3 = moderately satisfied, 4 = quite satisfied, 5 = very satisfied
  - Treatment continuation (assessed at last visit only): 5-point scale where 1 = not at all likely, 2 = a little likely, 3 = moderately likely, 4 = quite likely, 5 = very likely.

Statistical Analysis

- Baseline and safety assessments were evaluated using the safety population, which included all enrolled patients who received at least one dose of study medication.
- PGAs were evaluated using the modified intent-to-treat (mITT) population, which included all enrolled patients who received at least one dose of study medication and who had at least one post-baseline PGA assessment.
- All results are descriptive.

Results

Figure 1. Patient Disposition



*Includes patients who were active in the study and receiving study drug at the time of study closure. I/E: inclusion/exclusion; mITT: modified intent-to-treat; PGA: Patient Global Assessment.

- A total of 2272 patients were enrolled, comprising the safety population. The mITT population comprised 2202 patients (**Figure 1**).

Table 1. Demographic and Baseline Characteristics

	Safety Population N=2272
Age, years, mean (range)	45.3 (18–84)
Gender	
Female	76.8%
Male	23.2%
Race	
White	74.5%
Black	22.2%
Other	3.3%
BMI, kg/m^2, mean (range)	28.4 (17–42)

BMI: body mass index.

- Demographic and baseline characteristics are summarized in **Table 1**.
  - This study had a relatively high percentage of male patients (23.2%), similar to other studies of plecanatide and greater than studies of other secretagogues.

Table 2. Overview of Safety and Tolerability

Patients, n (%)	Safety Population N=2272
≥1 Adverse event (AE)	620 (27.3%)
AE by maximum severity	
Mild	311 (13.7%)
Moderate	249 (11.0%)
Severe	60 (2.6%)
AE leading to discontinuation	97 (4.3%)

One death was reported for this study. The patient was involved in a fatal road traffic accident after receiving 45 days of study drug treatment. The investigator assessed the event as having no reasonably possibility of a relationship to study drug.

- Most AEs were mild to moderate in severity (**Table 2**).
- Overall AE rates decreased over time, with 260 patients (11.4%) experiencing an AE during the first 4 weeks of treatment and declining to 126 patients (5.5%) in the second 4 weeks.

Table 3. Summary of Treatment-Emergent Adverse Events

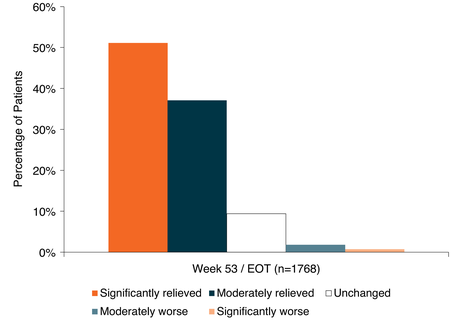
Patients, n (%)	Safety Population N=2272
Diarrhea	153 (6.7%)
URTI	43 (1.9%)
UTI	34 (1.5%)
Nasopharyngitis	34 (1.5%)
Nausea	29 (1.3%)
Headache	25 (1.1%)
Sinusitis	23 (1.0%)

URTI: upper respiratory tract infection; UTI: urinary tract infection.

- The most common AE was diarrhea (6.7%), with all other AEs occurring in less than 2% of patients (**Table 3**).
  - 107 patients (4.7%) experienced diarrhea within the first 4 weeks of treatment, and 22 (1.0%) experienced diarrhea between 4 and 8 weeks of treatment.
  - Severe diarrhea occurred in 14 patients (0.6%).
- Diarrhea was the most common AE leading to study discontinuation, which occurred in 61 patients (2.7%). Other AEs leading the discontinuation occurred in <3 patients.

Figure 2. Patient Global Assessment of IBS Symptom Relief

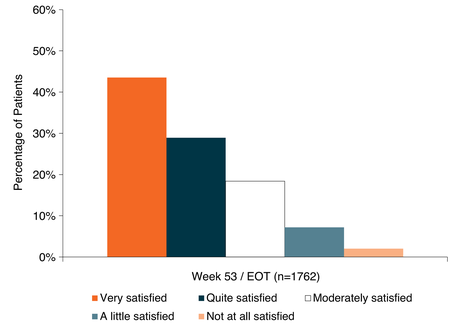
- The combined percentage of patients that reported being "significantly relieved" or "moderately relieved" with plecanatide treatment remained steady over time, with >83% of patients reporting relief at all time points and 88.2% of patients reporting relief at week 53 (**Figure 2**).



EOT: end of treatment (At closure of the study, patients who were still participating in the trial returned to have week 53 assessments completed.).

Figure 3. Patient Global Assessment of Treatment Satisfaction

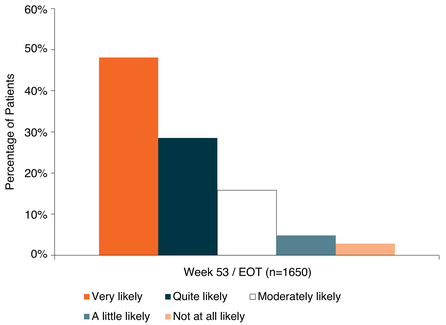
- The combined percentage of patients that reported being "very satisfied" or "quite satisfied" with treatment increased steadily from week 4 (58.1%) to week 53 (or end-of-treatment; 72.4%) following plecanatide treatment (**Figure 3**).



EOT: end of treatment (At closure of the study, patients who were still participating in the trial returned to have week 53 assessments completed.).

Figure 4. Patient Desire to Continue With Treatment

- The combined percentage of patients that reported being "very likely" or "quite likely" to continue use of plecanatide for IBS-C relief beyond study participation was 76.6% (**Figure 4**).



EOT: end of treatment (At closure of the study, patients who were still participating in the trial returned to have week 53 assessments completed.).

Discussion

- **In this long-term trial of IBS-C patients, plecanatide was well tolerated, with low AE rates and low discontinuation rates.**
  - **In addition, rates of diarrhea and discontinuations due to diarrhea were low.**
- **Results from the PGAs indicate that most patients felt relief from their IBS-C symptoms, were satisfied with treatment, and were likely to continue treatment if given the opportunity.**
- **Combined with previous experience of the short-term studies of IBS-C, the AE profile of plecanatide does not appear to change with chronic use and is generally safe and well tolerated.**
- **Based on the short-term efficacy and safety studies and these long-term safety results, plecanatide continues to be a promising new therapy for the treatment of IBS-C.**

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