Plecanatide Improved Patient Global Assessment of IBS Symptoms in Adult Patients With IBS-C

Christopher Chang, MD, PhD[1,2,3], Kelly Chong, PhD[1], Howard Franklin, MD[4]

[1]University of New Mexico School of Medicine, Department of Internal Medicine, Albuquerque, NM, United States; [2]New Mexico VA Health Care System, Division of Gastroenterology, Albuquerque, NM, United States; [3]University of New Mexico School of Medicine, Division of Gastroenterology/Hepatology, Albuquerque, NM, United States; [4]Salix Pharmaceuticals, Inc., Bridgewater, NJ, United States

Background

- Irritable bowel syndrome with constipation (IBS-C) is a chronic condition affecting approximately 5% of the United States population (~16 million people),[1] though prevalence may be underestimated as many people exhibit IBS-C symptoms without a formal diagnosis.[2]
- IBS-C is characterized by recurrent abdominal pain related to defecation and/or is associated with reduced stool frequency and lumpy/hard stools.[3]
- IBS-C significantly impacts patients' quality of life, work productivity, personal activity, and healthcare expense burden,[2,4-7] with many treated patients reporting low levels of treatment satisfaction with current IBS-C therapies.[4,5,7]
- Plecanatide is structurally similar to human uroguanylin, but includes an amino acid substitution (glutamic acid for aspartic acid in the 3rd position); both contain 2 disulfide bonds and 2 charged amino acids within the pH-sensitive region.
  - These features are important for the peptide conformation required for binding to the guanylyl cyclase C (GC-C) receptor, and the amino acid substitution in plecanatide enhances the affinity of plecanatide to the GC-C receptor, demonstrating 8 times greater binding to GC-C vs uroguanylin in preclinical models.
  - Based on preclinical studies, plecanatide appears to act in the more acidic environment of the proximal small intestine, coinciding with physiological areas of fluid secretion.
  - This unique feature confers potential safety benefits for plecanatide, including decreased incidence of diarrhea.
- Plecanatide 3 mg is approved for the treatment of adults with chronic idiopathic constipation or IBS-C.[8]

Objective

- To evaluate the impact of plecanatide on patient-reported outcomes of global ratings of disease status in patients with IBS-C treated in two phase 3 clinical trials

Methods

- Two identical 12-week, randomized, double-blind, placebo-controlled studies were conducted in patients who met Rome III criteria for IBS-C.[9,10]
- Upon completion of the 2-week baseline/screening period, patients were randomized (1:1:1) to placebo, plecanatide 3 mg, or plecanatide 6 mg (stratified by gender).
  - Medication was taken once daily with or without food.
- Patients enrolled in these trials were adults (aged 18 years) who met modified Rome III criteria for IBS-C.
- The primary efficacy endpoint was the percentage of overall responders, defined as patients who were both abdominal pain intensity weekly responders (reported ≥30% reduction from baseline in worst abdominal pain) and stool frequency weekly responders (reported an increase of ≥1 complete spontaneous bowel movement [CSBM] per week from baseline) in the same week for ≥6 of the 12 treatment weeks.
- Patient-reported outcomes included the Patient Global Assessment of Change for Abdominal Pain (PGA–Abdominal Pain), the Patient Global Assessment of Change for IBS Symptoms (PGA–IBS Symptoms), and Patient Global Assessment for IBS Disease Severity (PGA–Disease Severity).
  - Patients were asked to rate PGA–Abdominal Pain, PGA–IBS Symptoms, and PGA–Disease Severity on a 5-point scale, with lower scores being better.
  - Patient global assessment questionnaires were administered at site visits at Day 1 and Weeks 4, 8, and 12 during treatment.

Results

- A total of 2189 patients were included in the combined intention-to-treat efficacy population.

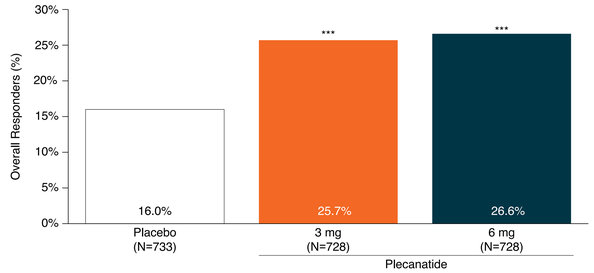
Table 1. Demographic and Baseline Characteristics (ITT-E Population)

	Placebo N=733	Plecanatide 3 mg N=728	Plecanatide 6 mg N=728
Age, years, mean (range)	43.9 (18–81)	43.5 (18–83)	43.1 (18–83)
Sex, n (%)			
Female	544 (74.2%)	537 (73.8%)	539 (74.0%)
Male	189 (25.8%)	191 (26.2%)	189 (26.0%)
Race, n (%)			
White	538 (73.4%)	529 (72.7%)	518 (71.2%)
Black	162 (22.1%)	156 (21.4%)	179 (24.6%)
Other	33 (4.5%)	43 (5.9%)	31 (4.2%)
BMI, kg/m^2, mean (range)	28.0 (18–40)	28.2 (18–40)	28.0 (17–42)
Disease characteristics, mean (SD)			
CSBMs/week	0.23 (0.5)	0.24 (0.5)	0.27 (0.5)
Stool consistency (BSFS)	2.0 (1.0)	2.0 (0.9)	1.9 (0.9)
Straining severity*	6.6 (1.9)	6.7 (1.9)	6.7 (1.9)
Abdominal pain*	6.3 (1.7)	6.3 (1.7)	6.2 (1.8)

*Rated on a scale from 0 (no) to 10 (worst possible). BMI, body mass index; BSFS, Bristol Stool Form Scale; CSBM, complete spontaneous bowel movement; ITT-E, intention-to-treat–efficacy; SD, deviation.

- Demographics and baseline characteristics were balanced across treatment groups (**Table 1**).

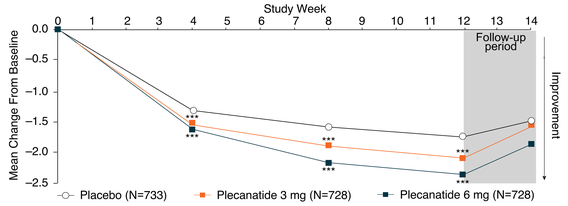
Figure 1. Percentage of Patients Who Were Overall Responders



***P<0.001 vs placebo.

- Plecanatide treatment resulted in a significantly greater percentage of Overall Responders compared with placebo (**Figure 1**).

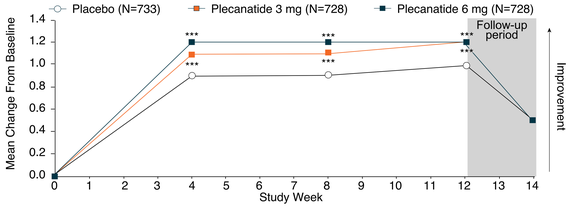
Figure 2. Change From Baseline in Patient Global Assessment of Change for Abdominal Pain



***P<0.001 vs placebo.

- PGA–Abdominal Pain demonstrated statistically significant improvements with plecanatide treatment vs placebo beginning at Week 4 and across the 12-week treatment period (P<0.001 vs placebo, all comparisons) (**Figure 2**).

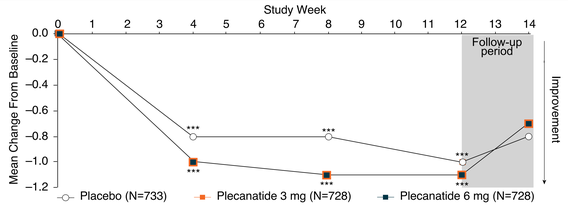
Figure 3. Change From Baseline in Patient Global Assessment of Change for IBS Symptoms



***P<0.001 vs placebo.

- PGA–IBS Symptoms demonstrated statistically significant improvements with plecanatide treatment vs placebo beginning at Week 4 and across the 12-week treatment period (P<0.001 vs placebo, all comparisons) (**Figure 3**).

Figure 4. Change From Baseline in Patient Global Assessment of IBS Disease Severity



***P<0.001 vs placebo.

- PGA–Disease Severity demonstrated statistically significant improvements with plecanatide treatment vs placebo beginning at Week 4 and across the 12-week treatment period (P<0.001 vs placebo, all comparisons) (**Figure 4**).

Conclusions

- **The hallmark symptoms of IBS-C (abdominal pain and infrequent stools), as well as secondary symptoms (stool consistency, straining severity, abdominal bloating), were significantly improved with 12 weeks of plecanatide treatment compared with placebo.**
- **Patients showed improvements in global ratings of disease status – an important aspect of treating patients who suffer with IBS-C.**
- **These findings further support the previously presented phase 3 clinical trial results, which demonstrated the efficacy of plecanatide in treating both the abdominal pain and the symptoms of IBS-C.**

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Disclosures

Drs. Chang and Chong report no conflicts of interest. Dr. Franklin is an employee and stockholder at Salix Pharmaceuticals, Inc.

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