Plecanatide Produces a More Rapid and Sustained Clinical Response Compared With Placebo in Patients With Irritable Bowel Syndrome With Constipation

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INTRODUCTION

- Irritable bowel syndrome with constipation (IBS-C) is characterized by recurrent abdominal pain associated with defecation and/or decreased stool frequency and hardened stool form[1]
- IBS is estimated to affect 5.3% of the US population (based on Rome IV criteria); patients with IBS-C experience a spectrum of symptoms, including abdominal pain, bloating, and infrequent bowel movements[1,2]
- Plecanatide (Trulance, Salix Pharmaceuticals) is a pH-sensitive analogue of human uroguanylin that induces intestinal fluid secretion and peristalsis by binding to guanylate cyclase-C receptors[3,4]
- Plecanatide is approved in the United States for the treatment of IBS-C in adults and has demonstrated efficacy and safety in two phase 3 trials[5]
- This post hoc analysis evaluated time to achieve clinical response and sustained treatment effect in adults with IBS-C

METHODS

- Methods for conducting two identical phase 3, double-blind, placebo-controlled studies in IBS-C based on Rome III criteria have been previously described[6]
- In this post hoc analysis, data from the two studies were pooled and all instances of duplicate patients were excluded
- Results are presented for plecanatide 3 mg (n=724) and placebo (n=729)
- Clinical responses were defined as follows:

Response Type	Definition
Bowel movement response	≥3 complete spontaneous bowel movements per week (CSBMs/week)
Pain response	≥30% reduction from baseline in abdominal pain
Bloating response	≥30% reduction from baseline in abdominal bloating
Sustained response	Achievement of weekly response for ≥9 of 12 treatment weeks

- Time to achieve clinical response was defined by the number of study weeks until a patient achieved their first week of response using a nonparametric log-rank test and Kaplan-Meier plots[6,7]
  - Patients were excluded if they did not achieve a response during the 12-week study or if they did not report symptom status for the total 12 weeks
- Odds ratios of achieving a response with plecanatide versus placebo were calculated for ≥1 study week up to 12 study weeks for each response type
  - For each response type, the number of study weeks (7-day intervals) with response was counted for each patient and cumulated; then, the odds ratio of achieving cumulative response was calculated (ie, likelihood of achieving at least a certain number of weeks with response)
  - Study weeks were not necessarily consecutive
  - Odds ratios >1 favored plecanatide

RESULTS

- Baseline characteristics were similar in patients receiving plecanatide 3 mg and placebo (Table 1)

Table 1. Baseline Characteristics

Parameter, Mean (SD)	Plecanatide 3 mg (n=724)	Placebo (n=729)
CSBMs/week	0.2 (0.5)	0.2 (0.5)
Abdominal pain*	6.26 (1.7)	6.26 (1.7)
Abdominal bloating*	6.48 (1.7)	6.47 (1.8)

*Measured using an 11-point rating scale (0 = no symptom; 10 = worst possible symptom). CSBM, complete spontaneous bowel movement.

- As treatment weeks progressed, fewer nonresponders remained (Figure 1)
- Plecanatide-treated patients experienced a significantly shorter time to achieve bowel movement response (≥3 CSBMs/week); 25% of plecanatide-treated patients achieved a response by 2 weeks compared with 5 weeks with placebo [*P*<0.001]; Figure 1A)
- Plecanatide-treated patients experienced a significantly shorter median time to achieve abdominal pain response (plecanatide = 5 weeks; placebo = 9 weeks [*P*<0.001]; Figure 1B)
- Plecanatide-treated patients experienced a significantly shorter median time to achieve bloating response (plecanatide = 7 weeks; placebo = 11 weeks [*P*<0.001]; Figure 1C)
- Across outcomes, more plecanatide-treated patients achieved sustained response for ≥9 of 12 treatment weeks compared with placebo (Table 2)

Table 2. Patients With IBS-C Achieving Sustained Response (≥9 of 12 Weeks)

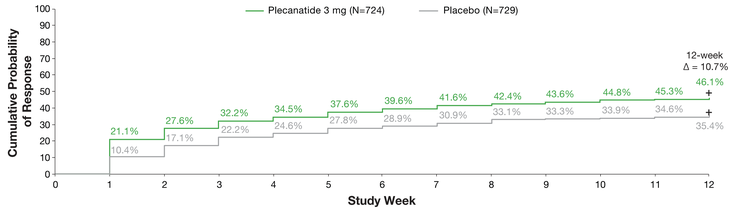
Patients, n (%)	Plecanatide 3 mg (n=724)	Placebo (n=729)	*P*-value vs Placebo
Bowel movement response	108 (14.9)	58 (8.0)	<0.001
Pain response	205 (28.3)	148 (20.3)	0.001
Bloating response	171 (23.6)	115 (15.8)	<0.001

IBS-C = irritable bowel syndrome with constipation.

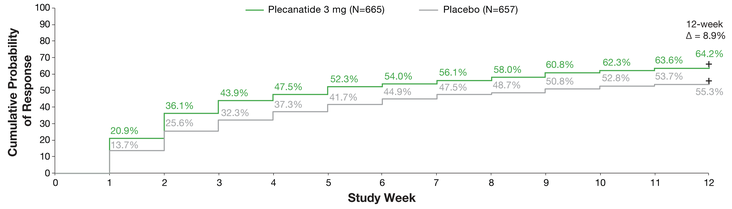
- For each period analyzed (ie, ≥1 week to 12 weeks), the odds ratios of achieving each weekly response type favored plecanatide compared with placebo (Figure 2)
- Plecanatide-treated patients were twice as likely to achieve ≥3 CSBMs/week for ≥9 of 12 treatment weeks compared with placebo (Figure 2A)
- Plecanatide-treated patients were 1.6 times more likely to achieve pain response (≥30% reduction from baseline) for ≥9 of 12 treatment weeks compared with placebo (Figure 2B)
- Plecanatide-treated patients were 1.7 times more likely to achieve bloating response (≥30% reduction from baseline) for ≥9 of 12 treatment weeks compared with placebo (Figure 2C)

Figure 1. Kaplan-Meier Curves of Time to First Week With Response

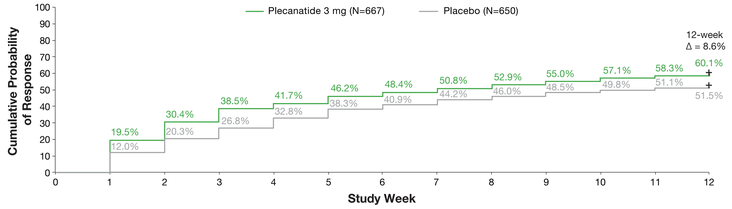
A. Response of ≥3 CSBMs/Week



B. Response of ≥30% Reduction From Baseline in Abdominal Pain*



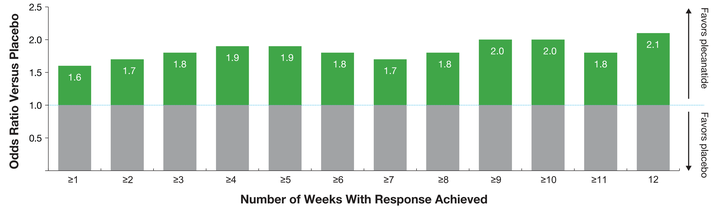
C. Response of ≥30% Reduction From Baseline in Abdominal Bloating*



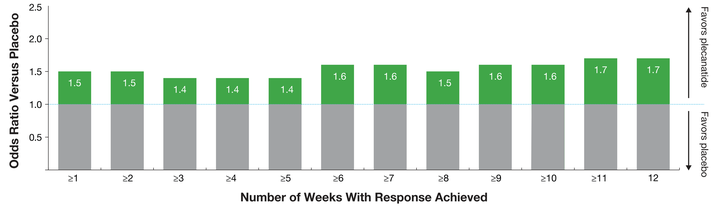
*Patients were excluded if they did not achieve a response during the 12-week trials or if they did not report symptom status for the total 12 weeks. CSBM = complete spontaneous bowel movement.

Figure 2. Odds Ratios of Achieving Response for ≥1 Study Week*

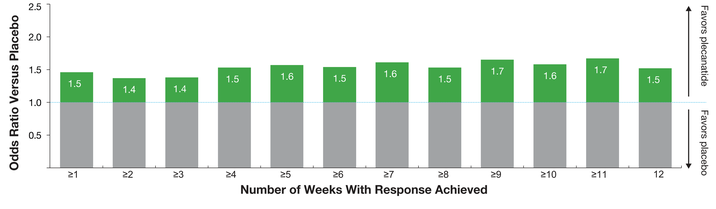
A. Response of ≥3 CSBMs/Week



B. Response of ≥30% Reduction From Baseline in Abdominal Pain



C. Response of ≥30% Reduction From Baseline in Abdominal Bloating



*For each response type, the number of study weeks (7-day intervals) with response was counted for each patient and cumulated. Then, the odds ratio of achieving cumulative response was calculated (ie, likelihood of achieving at least a certain number of weeks with response). Study weeks were not necessarily consecutive. CSBM = complete spontaneous bowel movement.

KEY FINDINGS

- **Plecanatide provided a more rapid onset of clinical response versus placebo for the key symptoms of IBS-C, including stool frequency, abdominal pain, and bloating**
- **More plecanatide-treated patients achieved sustained responses (ie, for ≥9 of 12 treatment weeks) for bowel movement frequency, abdominal pain, and bloating**
- **Plecanatide was more likely to be associated with a sustained effect than placebo**

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