# Plecanatide Produces a More Rapid and Sustained Clinical Response Compared to 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, a pH-sensitive analogue of human uroguanylin that induces intestinal fluid secretion and peristalsis by binding to guanylate cyclase-C receptors, is approved for IBS-C treatment in the US and has demonstrated efficacy and safety across 12 treatment weeks during two phase 3 registration studies.[3-5]
- This post hoc analysis evaluates time to achieve clinical response and sustained treatment effect in patients with IBS-C.

## METHODS

- Methods for conducting two identical phase 3, double-blind, placebo-controlled studies in IBS-C based on Rome III criteria (NCT02387359, NCT02493452) were previously described.[5]
- In this post hoc analysis, data from these 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 ≥9/12 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 non-parametric Logrank 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 symptoms 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 (i.e., likelihood of achieving at least a certain number of weeks with response).
  - Study weeks were not necessarily consecutive.
  - Odds ratios >1 favor plecanatide.

## RESULTS

**Table 1. Baseline characteristics**

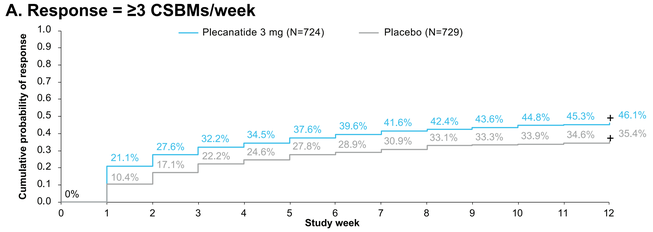
| Mean (SD) | Placebo | Plecanatide 3 mg |
|---|---|---|
| CSBMs/week | 0.2 (0.5) | 0.2 (0.5) |
| Abdominal pain* | 6.26 (1.7) | 6.26 (1.7) |
| Abdominal bloating* | 6.47 (1.8) | 6.48 (1.7) |

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

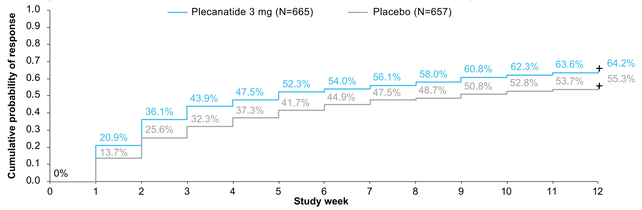
- Baseline characteristics were similar in patients receiving plecanatide 3 mg and placebo (**Table 1**).

**Figure 1. Kaplan-Meier curves of time to first week with response**

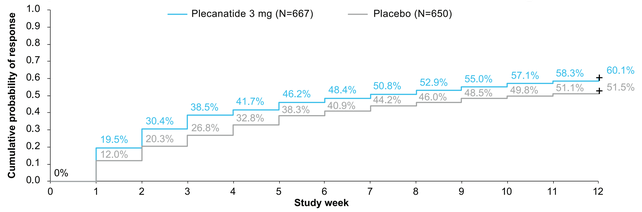
**A. Response = ≥3 CSBMs/week**




**B. Response = ≥30% reduction from baseline in abdominal pain***




**C. Response = ≥30% reduction from baseline in abdominal bloating***




**Patients were excluded if they did not achieve a response during the 12-week study or if they did not report symptoms for the total 12 weeks. CSBM, complete spontaneous bowel movement.*

- As treatment weeks progressed, fewer non-responders 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 to 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**).

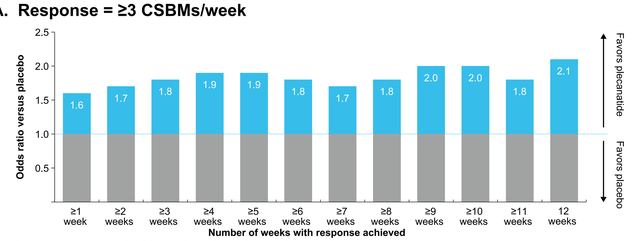
**Table 2. IBS-C patients achieving sustained response (≥9/12 weeks)**

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

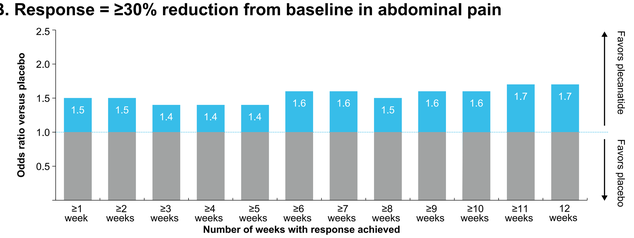
- Across outcomes, more plecanatide-treated patients achieved sustained response for ≥9 of 12 treatment weeks compared to placebo (**Table 2**).

**Figure 2. Odds ratios of achieving response for ≥1 study week***

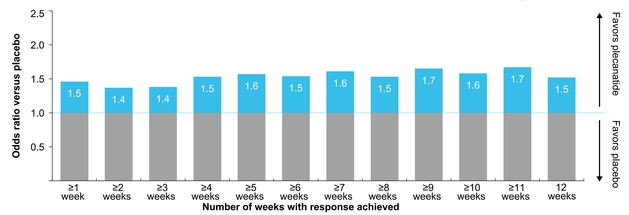
**A. Response = ≥3 CSBMs/week**




**B. Response = ≥30% reduction from baseline in abdominal pain**




**C. Response = ≥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.*

- For each period analyzed (i.e., ≥1 week to 12 weeks), the odds ratios of achieving each weekly response type favored plecanatide compared to placebo (**Figure 2**).
- Plecanatide-treated patients were twice as likely to achieve ≥3 CSBMs/week for ≥9 of 12 treatment weeks compared to 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 to 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 to placebo (**Figure 2C**).

## KEY FINDINGS

- Plecanatide was associated with a more rapid onset of clinical response in the key symptoms of IBS-C, including stool frequency, pain, and bloating, compared to placebo.
- More plecanatide-treated patients achieved sustained responses (i.e., for ≥9 of 12 treatment weeks) for bowel movement (≥3 CSBMs/week), pain (≥30% reduction from baseline), and bloating (≥30% reduction from baseline) compared to placebo.
- Plecanatide was more likely to be associated with a sustained effect than placebo.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## Disclosures

**Eric D. Shah** has nothing to disclose. **Jill K. Deutsch** has nothing to disclose. **Zeev Heimanson** and **Christopher Allen** are employees at Salix Pharmaceuticals, Inc. (Bridgewater, NJ, USA). **William D. Chey** is a consultant for Allergan, Biomerica, IM Health, Ironwood, QOL Medical, Ritter, Salix, Salix Pharmaceuticals Inc., Takeda, and Urovant, and has been a researcher for Biomerica, Ironwood, Nestle, Urovant, Vibrant, and Zespri. **Lin Chang** has served as a consultant or advisory board member of Ironwood, Allergan, Alfasigma, Shire-Takeda, IM Health Sciences, and Arena Pharmaceuticals, and has been a speaker for Salix Pharmaceuticals Inc.


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