Plecanatide for Patients with Chronic Idiopathic Constipation and Irritable Bowel Syndrome–Constipation: Analysis of Abdominal Pain from Four Randomized Phase 3 Clinical Trials

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BACKGROUND

- Functional bowel disorders, such as chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C), represent a spectrum of chronic gastrointestinal (GI) disorders characterized by abdominal pain, bloating, distention, and bowel habit abnormalities (e.g., constipation).[1]
- In North America, prevalence estimates for CIC range from 2% to 27%.[2] The estimated US prevalence of IBS is 14.1%.[3]
- The diagnostic criteria for IBS includes the presence of abdominal pain, which must be long term (>6 months), recurrent (>1 day/week in the last 3 months), and associated with changes in bowel movements.[1]
- The Rome III criteria for diagnosis of CIC does not include assessment of abdominal pain; however, moderate to severe abdominal pain is reported in ~23% of patients with CIC.[4]
- Plecanatide is a locally-acting 16-amino-acid gastrointestinal peptide that is a structural analog of human uroguanylin. The 3 mg dose is approved by the FDA for the treatment of IBS-C and CIC in adults.[5]
- In two pivotal, randomized, double-blind, placebo-controlled, phase 3 studies in CIC (NCT01982240, NCT02122471[6,7]) and two in IBS-C (NCT02387359, NCT02493452[8]), plecanatide has been shown to be safe and efficacious in the treatment of patients with CIC and IBS-C.
  - In patients with IBS-C, plecanatide treatment significantly improved the weekly frequency of complete spontaneous bowel movements (CSBMs), as well as the intensity of abdominal pain—a defining symptom of IBS-C.[8]
  - In patients with CIC, treatment with plecanatide significantly and durably improved the weekly number of CSBMs and abdominal symptoms (including bloating, discomfort, and pain).[6,7]

OBJECTIVE

- To determine the impact of plecanatide on abdominal pain in patients with CIC and IBS-C from four randomized, phase 3, placebo-controlled studies stratified by baseline abdominal pain severity.

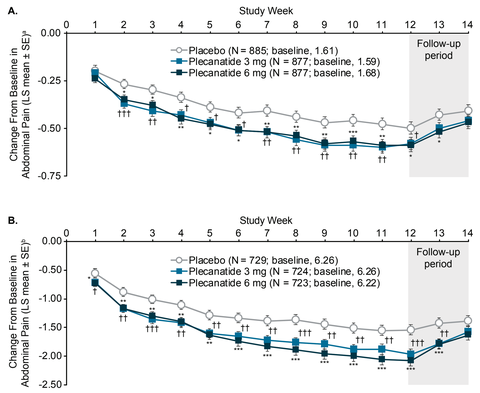
METHODS

- Four separate trials were conducted on patients who met modified Rome III criteria for CIC or IBS-C.
- In all trials, patients were randomly assigned (1:1:1) to receive plecanatide 3 mg, plecanatide 6 mg, or placebo for 12 weeks.
- Using electronic diaries, patients recorded daily abdominal pain symptoms during the pre-treatment, treatment (12 weeks), and post-treatment (2 weeks) periods.
  - Patients with CIC utilized a Likert scale (0 = none to 4 = very severe).
  - Patients with IBS-C used a numeric rating scale ("NRS"; 0 = none to 10 = worst possible pain).
- Abdominal pain (least-squares mean) differences were compared within groups from baseline to week 12 and between active and placebo groups for each study.
- To compare efficacy results in subpopulations with more or less pain at baseline, the intention-to-treat population was stratified by baseline severity. Based on the structures of the individual scales, these categories were defined as:
  - CIC: minimal/mild pain (0–2); moderate/severe pain (3–4)
  - IBS-C: minimal/mild pain (0–5); moderate/severe pain (6–10)

RESULTS

- Patients who met modified Rome III criteria for CIC (N = 2639) and IBS-C (N = 2176) were included in the analysis.
- Baseline characteristics were comparable between groups within the CIC studies and within the IBS-C studies.

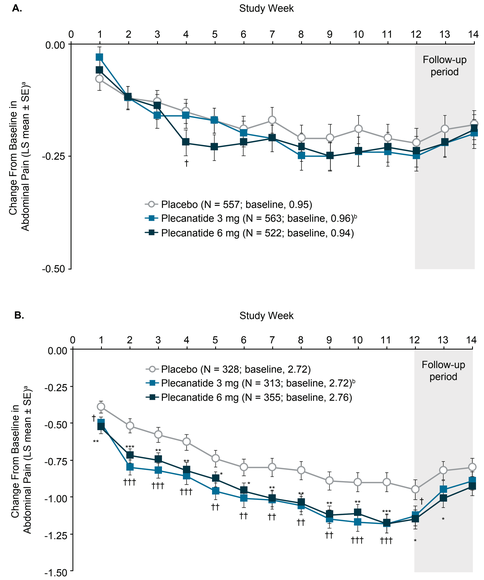
Figure 1. Change From Baseline in Abdominal Pain Scores Weeks 1 Through 14 in CIC (A) and IBS-C (B)



Plecanatide 3 mg: †P<0.05, ††P≤0.01, †††P≤0.001 vs placebo. Plecanatide 6 mg: *P<0.05, **P≤0.01, ***P≤0.001 vs placebo.
LS = least squares; SE = standard error.
[a]Abdominal pain symptoms were measured with a Likert Scale (0 = none to 4 = very severe) in patients with CIC; [b]Abdominal pain symptoms were measured with a numeric rating scale (0 = none to 10 = worst possible) for patients with IBS-C.

- Significant change in abdominal pain with plecanatide 3 mg was apparent by week 2 in CIC (**Figure 1A**) and by week 1 in IBS-C (**Figure 1B**) and was sustained through the end of treatment period (week 12).
- Though diminished abdominal pain responses were observed across all study groups in the post-treatment follow-up period, no abdominal pain worsening was seen in either CIC or IBS-C post-treatment period (suggesting a lack of "rebound effect" upon discontinuation of plecanatide).
- In IBS-C, significant improvement was sustained from 2 weeks post-treatment to the end of the study (**Figure 1B**).
- Baseline mean abdominal pain scores for CIC were relatively lower (range 1.59-1.68) than IBS-C scores (range 6.22-6.26), as expected.
- Significant reductions in abdominal pain were found across the 12-week treatment period for both CIC (P<0.01 both doses) and IBS-C (P<0.001 both doses) groups.

Figure 2. Change From Baseline in Abdominal Pain Scores Weeks 1 Through 14 in Patients With CIC and Minimal to Mild Pain at Baseline (A) and Moderate to Severe Pain at Baseline (B)



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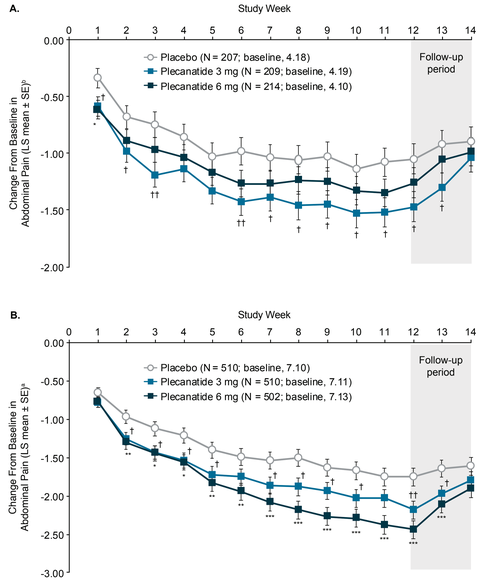
LS = least squares; SE = standard error.
[a]Abdominal pain symptoms were measured with a Likert Scale (0 = none to 4 = very severe) in patients with CIC. [b]One patient with missing baseline pain was not included.

- Patients with CIC who reported minimal to mild pain at baseline reported numerically greater improvements in pain scores than did those treated with placebo, though differences were not significant (**Figure 2A**).
- Patients with CIC and moderate to severe pain at baseline demonstrated significant improvements compared to placebo starting at week 1 (**Figure 2B**)
- At week 12, CIC patients with moderate to severe pain at baseline demonstrated significant improvements in pain scores compared with placebo (P<0.05 both doses).

Figure 3. Change From Baseline in Abdominal Pain Scores Weeks 1 Through 14 in Patients With IBS-C and Minimal to Mild Pain at Baseline (A) and Moderate to Severe Pain at Baseline (B)



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LS = least squares; SE = standard error.
[a]Abdominal Pain symptoms were measured with a numeric rating scale (0 = none to 10 = worst possible) for patients with IBS-C.

- Patients with IBS-C experienced significant improvements in pain scores after plecanatide treatment, compared with placebo, regardless of the baseline pain severity (**Figure 3**).
- At week 12, IBS-C patients with moderate to severe pain at baseline demonstrated significant improvements in pain scores compared to placebo (3 mg, P=0.006; 6 mg, P<0.001).
- Patients with minimal to mild baseline pain also showed significant pain improvement at week 12 when treated with plecanatide 3 mg (P=0.017).

DISCUSSION

- Baseline abdominal pain scores were higher for patients with IBS-C than for those with CIC, as anticipated.
- Overall CIC and IBS-C groups had a significant improvement in abdominal pain with plecanatide treatment, beginning at 1 week for IBS-C and at 2 weeks for CIC with full treatment effect seen in later weeks.
- Improvement of pain with plecanatide treatment occurred in patients with IBS-C regardless of baseline pain severity; however, in CIC patients, only those who had more moderate to severe pain at baseline improved with treatment.
- By the end of the follow-up period, plecanatide treated groups experienced less pain reduction than at the end of the treatment period and differences between groups were no longer significant, which highlights the need for ongoing use of plecanatide in order to sustain improvements in abdominal pain.

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