Plecanatide Produces a More Rapid and Durable Clinical Response Compared to Placebo in Patients With Chronic Idiopathic Constipation: A Post Hoc Analysis of Two Randomized Controlled Trials

P1448

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INTRODUCTION

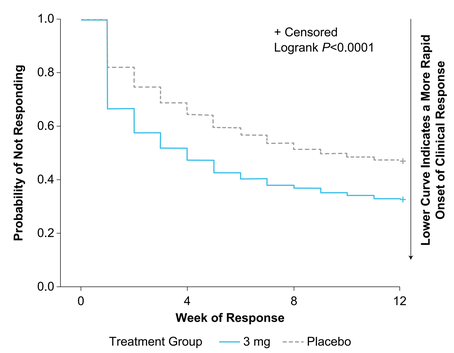
- Chronic idiopathic constipation (CIC) is a common and bothersome disorder of gut-brain interaction that affects approximately 7% to 14% of the US population.[1,2]
  - CIC is associated with decreased health-related quality of life, reduced work/school productivity and attendance, as well as with significant healthcare costs.[3-6]
- Plecanatide is a pH-sensitive analog of human uroguanylin, which has been shown to replicate binding to guanylate cyclase-C receptors.
  - The activity is primarily in the small intestine where it induces fluid secretion and increases bowel movement frequency.[7,8]
  - Plecanatide exhibits anti-nociceptive activity and has been shown to reduce visceral hypersensitivity, thus alleviating abdominal symptoms.[9,10]
  - Plecanatide has demonstrated clinical efficacy and tolerability in patients with CIC in two phase 3 clinical trials and is FDA-approved in the United States.[11,12]
- The objectives of this post hoc analysis were to evaluate the time to achieve the first weekly clinical response and durability of weekly response (for ≥9 of the total 12 study weeks) in patients with CIC receiving plecanatide versus placebo.

METHODS

- Data from two multicenter, double-blind, placebo-controlled phase 3 trials (NCT01982240, NCT02122471)[11,12] were pooled.
  - In both studies, adults with CIC were randomized to once-daily plecanatide 3 mg, 6 mg (data not shown), or placebo.
  - All instances of duplicate patients were excluded.
  - Results are presented for plecanatide 3 mg (n=877) and placebo (n=885).
- Patients recorded number and characteristics of bowel movements daily in electronic diaries throughout the 12-week treatment period.
  - Abdominal symptoms (bloating, pain, and discomfort) were rated using a 5-point Likert scale (0=none; 4=very severe).
- Outcomes included time to first weekly response and number of weeks with response over 12 treatment weeks of study.
- Weekly response was defined in three ways:
  - Complete spontaneous bowel movement (CSBM) response: ≥3 complete spontaneous bowel movements in a given week
  - Abdominal pain response: ≥30% reduction from baseline in abdominal pain severity score in a given week
  - Bloating response: ≥30% reduction from baseline in bloating severity score in a given week
- The time to achieve the first weekly response was defined by the number of study weeks (7-day interval) until a patient achieved their first week of response using a Cox proportional hazards model.

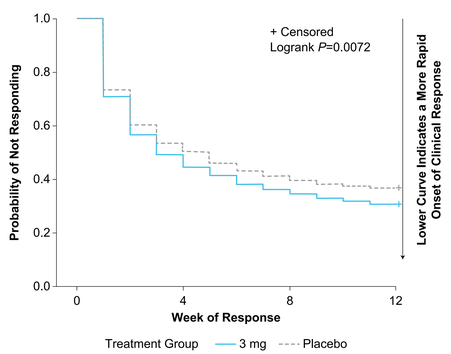
RESULTS

Figure 1. Time to First Weekly Response: ≥3 CSBMs



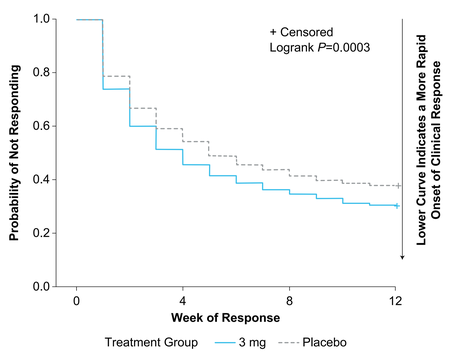
- Plecanatide resulted in significantly shorter time to bowel movement response (≥3 CSBMs/week) compared with placebo (3 weeks vs 10 weeks, respectively, *P*<0.001; Figure 1).

Figure 2. Time to First Weekly Response: ≥30% Reduction From Baseline in Abdominal Pain



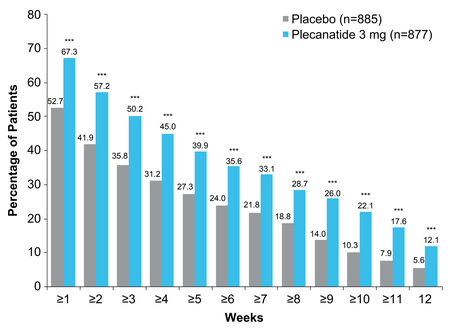
- Plecanatide resulted in significantly shorter time to abdominal pain response (≥30% reduction) compared with placebo (3 weeks vs 5 weeks, respectively, *P*<0.01; Figure 2).

Figure 3. Time to First Weekly Response: ≥30% Reduction From Baseline in Abdominal Bloating



- Plecanatide resulted in significantly shorter median time to abdominal bloating response (≥30% reduction) compared with placebo (4 weeks vs 5 weeks, respectively, *P*<0.001; Figure 3).

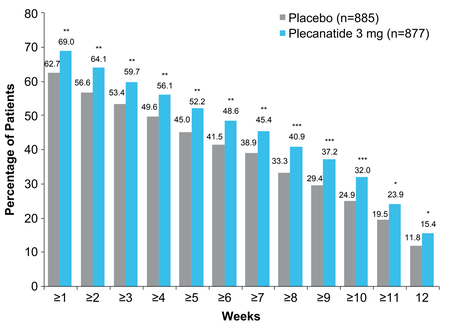
Figure 4. Number of Study Weeks With ≥3 CSBMs



***P≤0.001 vs placebo. Study weeks (7-day intervals) are not necessarily consecutive.

- A higher percentage of plecanatide patients were bowel symptom responders (≥3 CSBMs/week) for ≥9 of the total 12 study weeks compared with placebo (26% vs 14%, respectively, *P*<0.001, Figure 4).
  - Significantly more plecanatide-treated patients reported ≥3 CSBMs in ≥1 study week compared with placebo (67% vs 53%, respectively, *P*<0.001; Figure 4).

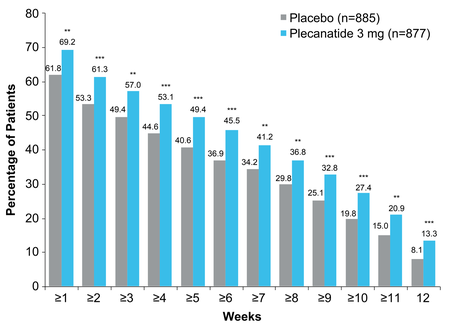
Figure 5. Number of Study Weeks With ≥30% Reduction From Baseline in Abdominal Pain



*P<0.05, **P<0.01, ***P≤0.001 vs placebo. Study weeks (7-day intervals) are not necessarily consecutive.

- A higher percentage of plecanatide patients were weekly pain responders (≥30% reduction from baseline) for ≥9 of the total 12 study weeks compared with placebo (37% vs 29%, respectively, *P*<0.001, Figure 5).
  - Significantly more plecanatide-treated patients reported a ≥30% reduction from baseline in abdominal pain in ≥1 study week compared with placebo (69% vs 63%, respectively, *P*<0.01; Figure 5).

Figure 6. Number of Study Weeks With ≥30% Reduction From Baseline in Bloating



**P<0.01, ***P≤0.001 vs placebo. Study weeks (7-day intervals) are not necessarily consecutive.

- A higher percentage of plecanatide patients were weekly bloating responders (≥30% reduction from baseline) for ≥9 of the total 12 study weeks compared with placebo (33% vs 25%, respectively, *P*<0.001, Figure 6).
  - Significantly more plecanatide-treated patients reported a ≥30% reduction from baseline in abdominal bloating in ≥1 study week compared with placebo (69% vs 62%, respectively, *P*<0.01; Figure 6).

KEY FINDINGS

- Across 12 weeks of treatment, patients with CIC treated with plecanatide 3 mg versus placebo demonstrated a more rapid onset of clinical response.
  - Compared to placebo plecanatide-treated patients achieved shorter times to weekly responses defined as ≥3 CSBMs/week, ≥30% reduction in abdominal pain severity, and ≥30% improvement in bloating severity.
  - Greater reductions in the probability of non-response were seen in Week 1, with smaller reductions continuing through Week 12, which suggest that continued plecanatide therapy may be necessary to achieve additional treatment effects.
- Weekly response durability was significantly greater with plecanatide versus placebo.
  - A greater percentage of plecanatide-treated patients achieved clinical responses (≥3 CSBMs/week, ≥30% abdominal pain improvement, and ≥30% bloating improvement) in ≥9/12 study weeks compared to placebo.

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Disclosures

Eric Shah, Alfred Nelson, and Brian Lacy have nothing to disclose. William D. Chey is a Consultant for Allergan, Biomerica, IM Health, Ironwood, QOL Medical, Ritter, Salix Pharmaceuticals, Takeda, and Urovant, and has been a researcher for Biomerica, Ironwood, Nestle, Urovant, Vibrant, and Zespri. Sarah M. Lorenzen was an employee at Salix Pharmaceuticals at the time of data analysis.

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