Efficacy and Safety of Plecanatide in Patients With Irritable Bowel Syndrome With Constipation: Per Protocol Analysis of Two Pooled, Randomized Phase 3 Studies

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BACKGROUND

- In the US, 4.3% of the population is reported to experience irritable bowel syndrome with constipation (IBS-C).[1]
- IBS-C is a chronic condition that impacts quality of life.
  - Patients with IBS-C report poorer health-related quality of life, increased work productivity loss, and greater activity impairment than did matched comparators.[2]
  - In a US survey of respondents who met Rome II criteria (N=557), most respondents (76%) rated their constipation as extremely, very, or somewhat bothersome; approximately 70% experienced work impairment and reported negative effects on personal and social life because of constipation symptoms.[3]
- Plecanatide is a locally acting 16-amino acid gastrointestinal peptide that is structurally similar to uroguanylin (a naturally occurring GI peptide), differing by a single-amino acid substitution.[4,5]
- Plecanatide was evaluated in 2 identically designed, 12-week, phase 3 trials of adults with IBS-C (NCT02387359 and NCT02493452).
  - Plecanatide treatment significantly improved the weekly frequency of complete spontaneous bowel movements (CSBMs), as well as the intensity of abdominal pain—the hallmark symptoms of IBS-C.[6]
  - Key secondary endpoints (including stool consistency and changes in straining), were also significantly improved by plecanatide treatment.[6]
- Plecanatide is approved in the United States for the treatment of adults with chronic idiopathic constipation and IBS-C.[7]

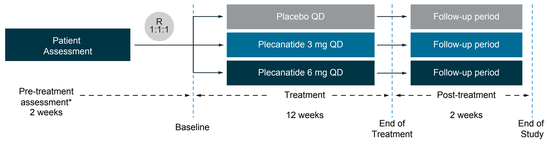
OBJECTIVE

- Evaluate the safety and efficacy of plecanatide in adults with IBS-C by utilizing pooled data from the per protocol populations from two phase 3 studies.

METHODS

- Two phase 3, randomized, double-blind, placebo-controlled studies were identically designed to assess once-daily oral plecanatide for the treatment of adults with IBS-C in the United States (Figure 1).

Figure 1. Study Design Schematics for the Phase 3 Studies



*Electronic diary assessment for eligibility, compliance, and baseline parameters was completed during the last 2 weeks of the pretreatment period. R, randomization; QD, once daily.

- Eligible patients (aged 18–85 yrs; BMI of 18-40 kg/m^2) meeting IBS-C Rome III criteria were randomized (1:1:1) to placebo, plecanatide 3 mg, or plecanatide 6 mg.
- Patients must have demonstrated the following during the 2-week pretreatment assessment:
  - Completed ≥5 of the 7 daily diary entries in both weeks
  - Reported ≤3 CSBMs per week or ≤6 spontaneous bowel movements (SBMs) per week
  - Did not report Bristol Stool Form Scale (BSFS) score of 7 for ≥1 day/week or 6 for >1 day/week for either of the 2 weeks
  - Did not report worst abdominal pain intensity score (11-point numeric rating scale) of 0 for >2 days/week or an average score of <3 for either of the 2 baseline weeks
- Primary efficacy endpoint in both trials was the percentage of overall responders (OR), defined as patients who were both abdominal pain responders (≥30% decrease in worst abdominal pain vs baseline) and stool frequency responders (increase ≥1 complete spontaneous bowel movement vs baseline) in the same week for ≥6 of 12 treatment weeks (Figure 2).

Figure 2. Definition of Responder Endpoints

*Measured daily. CSBM, complete spontaneous bowel movement; WAPI, weekly abdominal pain intensity.

- Key secondary efficacy endpoints included: sustained efficacy responder (Figure 2), change from baseline in stool consistency, and change from baseline in straining severity.
- Other endpoints included change from baseline in CSBM frequency, severity of abdominal symptoms, and percentage of patients experiencing a CSBM or SBM within 24 hours after first dose.
- Safety and tolerability were assessed by the incidence, nature, and severity of treatment-emergent adverse events (TEAEs).
- Results were analyzed using the per protocol patient population: patients who completed treatment or discontinued due to an AE or lack of efficacy and were diary/treatment compliant with no major protocol violations.

RESULTS

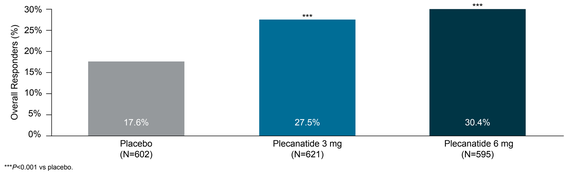
Table 1. Demographics and Baseline Characteristics of Per Protocol Patients

Patients	Placebo (N=602)	Plecanatide 3 mg (N=621)	Plecanatide 6 mg (N=595)
Age, years, mean (SD)	44.7 (14.3)	44.0 (14.3)	43.5 (13.9)
Sex: female, n (%)	445 (73.9)	461 (74.2)	443 (74.5)
Race, (n, %)			
White	449 (74.6)	457 (73.6)	426 (71.6)
Black	123 (20.4)	128 (20.6)	142 (23.9)
Other	30 (5.0)	36 (5.8)	27 (4.5)
BMI, kg/m^2, mean (SD)	28.1 (4.7)	28.3 (4.8)	28.0 (4.9)
Disease characteristics, mean (SD)			
CSBMs/week	0.25 (0.458)	0.25 (0.513)	0.27 (0.521)
Stool consistency	2.04 (1.021)	1.97 (0.896)	1.96 (0.941)
Straining severity	6.47 (1.952)	6.66 (1.877)	6.68 (1.890)
Abdominal pain	6.18 (1.677)	6.26 (1.704)	6.18 (1.770)
Abdominal bloating	6.38 (1.768)	6.49 (1.720)	6.36 (1.802)

BMI, body mass index; CSBM, complete spontaneous bowel movement; SD, standard deviation.

- A total of 2176 patients were included in the pooled intention-to-treat population excluding duplicates; 1818 patients were included in the per protocol population (placebo, N=602; 3 mg, N=621; 6 mg, N=595).
- Demographics were similar between treatment groups and across studies (Table 1).

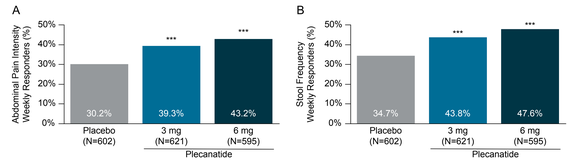
Figure 3. Percentage of Patients Who Were Overall Responders in the Per Protocol Population



***P<0.001 vs placebo.

- Plecanatide treatment resulted in a significantly greater percentage of overall responders than did placebo (placebo, 17.6%; 3 mg, 27.5%; 6 mg, 30.4%; P<0.001 for both doses; Figure 3).

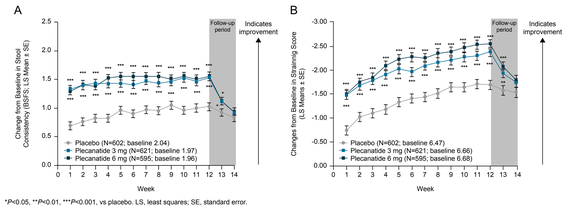
Figure 4. Percentage of Abdominal Pain Weekly Responders (A) and Stool Frequency Responders (B) for ≥6 of 12 Treatment Weeks



***Ps0.001 vs placebo.

- A significantly greater percentage of plecanatide-treated patients were weekly abdominal pain responders (P<0.001 for both doses) and weekly stool frequency responders (3 mg, P=0.001; 6 mg, P<0.001) for ≥6 of 12 weeks (Figure 4).

Figure 5. Changes From Baseline in (A) Weekly Stool Consistency (BSFS score) and (B) Weekly Straining Severity



*P<0.05, **P<0.01, ***P<0.001, vs placebo. LS, least squares; SE, standard error.

- Plecanatide significantly improved patient-reported symptoms (including stool consistency and straining severity) at Week 12 with significant improvements seen by Week 1 (P<0.001 for both doses, Figure 5).

Table 2. Change From Baseline in Secondary Endpoints[a]

	Placebo (N=602)	Plecanatide 3 mg (N=621)	Plecanatide 6 mg (N=595)
CSBMs/week, LS mean (SE)	0.82 (0.090)	1.33 (0.089)	1.65 (0.090)
P value vs placebo		*P*<0.001	*P*<0.001
Stool consistency, LS mean (SE)[b]	0.91 (0.059)	1.44 (0.058)	1.50 (0.060)
P value vs placebo		*P*<0.001	*P*<0.001
Straining severity, LS mean (SE)[c]	–1.37 (0.086)	–2.02 (0.084)	–2.18 (0.086)
P value vs placebo		*P*<0.001	*P*<0.001
Abdominal pain, LS mean (SE)[c]	–1.23 (0.076)	–1.57 (0.075)	–1.69 (0.077)
P value vs placebo		*P*<0.001	*P*<0.001
Abdominal bloating, LS mean (SE)[c]	–1.17 (0.075)	–1.50 (0.074)	–1.62 (0.075)
P value vs placebo		*P*=0.001	*P*<0.001

[a]LS mean values are the overall average estimate across the 12-week treatment period. [b]Measured using the 7-point Bristol Stool Form Scale. [c]Measured using an 11-point scale, where 0=none and 10=worst possible. LS, least squares; SE, standard error.

- Limited differences between plecanatide 3 mg and 6 mg were identified (Table 2).

Table 3. Summary of Treatment-Emergent Adverse Events (TEAEs) in the Safety Population

Patients, n (%)	Placebo (N=730)	Plecanatide 3 mg (N=726)	Plecanatide 6 mg (N=726)
≥1 TEAE	136 (18.6)	173 (23.8)	144 (19.8)
Diarrhea	7 (1.0)	31 (4.3)	29 (4.0)
TEAE by maximum severity			
Mild	85 (11.6)	96 (13.2)	78 (10.7)
Moderate	44 (6.0)	60 (8.3)	55 (7.6)
Severe	7 (1.0)	17 (2.3)	11 (1.5)
TEAE leading to discontinuation	3 (0.4)	18 (2.5)	16 (2.2)
Diarrhea	0	9 (1.2)	10 (1.4)
Treatment-emergent Serious AEs	6 (0.8)	6 (0.8)	5 (0.7)

Two deaths were reported during the study and were considered unrelated to the study drug. Causes of death were pulmonary embolism during screening (patient did not receive study drug) and accidental drowning (post-randomization).

- AEs were similar in all groups; diarrhea was the only AE occurring in ≥2% of patients with an incidence greater than placebo (placebo, 1.0%; 3 mg, 4.3%; 6 mg, 4.0%).
- Rates of discontinuation due to diarrhea were low (placebo, 0%; 3 mg, 1.2%; 6 mg, 1.4%).

DISCUSSION

- In the pooled per protocol study population, plecanatide 3 mg and 6 mg resulted in a significantly greater overall responder rate—the primary efficacy endpoint—compared to placebo in patients with IBS-C.
- Secondary endpoints related to bowel movements and abdominal symptoms also significantly improved with both doses of plecanatide compared to placebo over 12 weeks of treatment.
- In plecanatide-treated patients, low rates of serious AEs, overall AEs, and AE-related discontinuation were observed compared to placebo.
- Plecanatide is a safe and effective treatment option for patients with IBS-C.

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