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Plecanatide Simultaneously Improves Multiple Symptoms of Irritable Bowel Syndrome With Constipation: A Unique Composite Endpoint Analysis of Randomized, Phase 3 Trials

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BACKGROUND

- Plecanatide (Trulance®, Salix Pharmaceuticals) 3 mg oral once daily is indicated for the treatment of chronic idiopathic constipation (CIC) and irritable bowel syndrome (IBS) with constipation (IBS-C) in adults[1]
- Phase 3, randomized, placebo-controlled trials have previously demonstrated that plecanatide significantly improves both abdominal pain intensity and bowel movement frequency in patients with CIC or IBS-C[2-4]
- In addition to abdominal pain and bowel movement infrequency, patients with IBS often experience other bothersome abdominal symptoms, including discomfort, bloating, cramping, and fullness[5-6]

AIM

- To evaluate plecanatide for improvement of these additional abdominal symptoms (ie, discomfort, bloating, cramping, fullness) using a composite endpoint analysis

METHODS

- Data from 2 identically designed, randomized, phase 3 trials were pooled and analyzed post hoc[2]
- Adults with IBS-C (Rome III criteria) and a body mass index of 18 to 40 kg/m^2 were randomly assigned to treatment with plecanatide 3 mg, plecanatide 6 mg, or placebo once daily for 12 weeks
- Intensity of abdominal discomfort, bloating, cramping, and fullness were rated daily by patients using an 11-point scale (scale range, 0 [“no”] to 10 [“worst possible”])
- Population analyzed included all nonduplicate patients randomly assigned to treatment; *P* values were calculated based on the Cochran-Mantel–Haenszel test, stratified by sex

Composite Endpoints Analyzed

- Abdominal discomfort and bloating: ≥30% decrease from baseline in abdominal discomfort and bloating in the same week for ≥6 of the 12 weeks of treatment
- Abdominal discomfort and cramping: ≥30% decrease from baseline in abdominal discomfort and cramping in the same week for ≥6 of the 12 weeks of treatment
- Abdominal fullness and bloating: ≥30% decrease from baseline in abdominal fullness and bloating in the same week for ≥6 of the 12 weeks of treatment

RESULTS

- 2176 patients (74.0% female; median age, 43.0 y) with IBS-C were included in the analysis (**Table**)
- Mean baseline symptom scores were similar across groups for abdominal discomfort (6.4 each), bloating (6.4-6.5), cramping (5.9-6.0), and fullness (6.4-6.5)

Table. Demographic and Baseline Characteristics

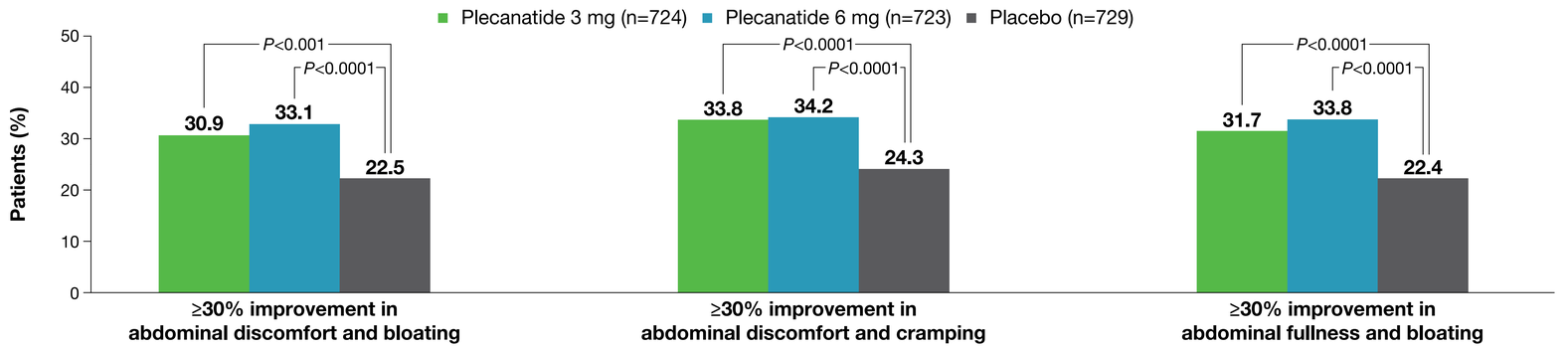
Characteristic	Plecanatide 3 mg (n=724)	Plecanatide 6 mg (n=723)	Placebo (n=729)
Age, y, mean (SD)	43.5 (14.2)	43.1 (13.8)	43.9 (14.2)
Sex, n (%)			
Female	534 (73.8)	536 (74.1)	540 (74.1)
Male	190 (26.2)	187 (25.9)	189 (25.9)
BMI, kg/m^2, mean (SD)	28.2 (4.8)	28.1 (4.9)	28.0 (4.8)
Race, n (%)			
White	527 (72.8)	515 (71.2)	536 (73.5)
Black	155 (21.4)	177 (24.5)	160 (21.9)
Asian	33 (4.6)	25 (3.5)	25 (3.4)
Other	9 (1.2)	6 (0.8)	8 (1.1)
Hispanic or Latino ethnicity, n (%)	365 (50.4)	363 (50.2)	376 (51.6)
SBMs/week, mean (SD)	1.5 (1.1)	1.5 (1.1)	1.4 (1.1)
CSBMs/week, mean (SD)	0.2 (0.5)	0.3 (0.5)	0.2 (0.5)
Abdominal pain score, mean (SD)*	6.3 (1.7)†	6.2 (1.8)‡	6.3 (1.7)§
Abdominal discomfort score, mean (SD)*	6.4 (1.6)†	6.4 (1.7)‡	6.4 (1.6)§
Bloating score, mean (SD)*	6.5 (1.7)†	6.4 (1.8)‡	6.5 (1.8)§
Cramping score, mean (SD)*	6.0 (1.9)†	5.9 (2.0)‡	6.0 (2.0)‡
Fullness score, mean (SD)*	6.5 (1.7)†	6.4 (1.8)‡	6.5 (1.7)‡

*Measured using an 11-point scale (range, 0 [“no”] to 10 [“worst possible”]).
†n=719. ‡n=716. §n=717.
BMI = body mass index; CSBM = complete spontaneous bowel movement; SBM = spontaneous bowel movement.

RESULTS

- A significantly greater percentage of patients treated with plecanatide 3 mg or plecanatide 6 mg were composite responders for abdominal discomfort and bloating, abdominal discomfort and cramping, and abdominal fullness and bloating (**Figure 1**; *P*<0.001 or *P*<0.0001 for all)

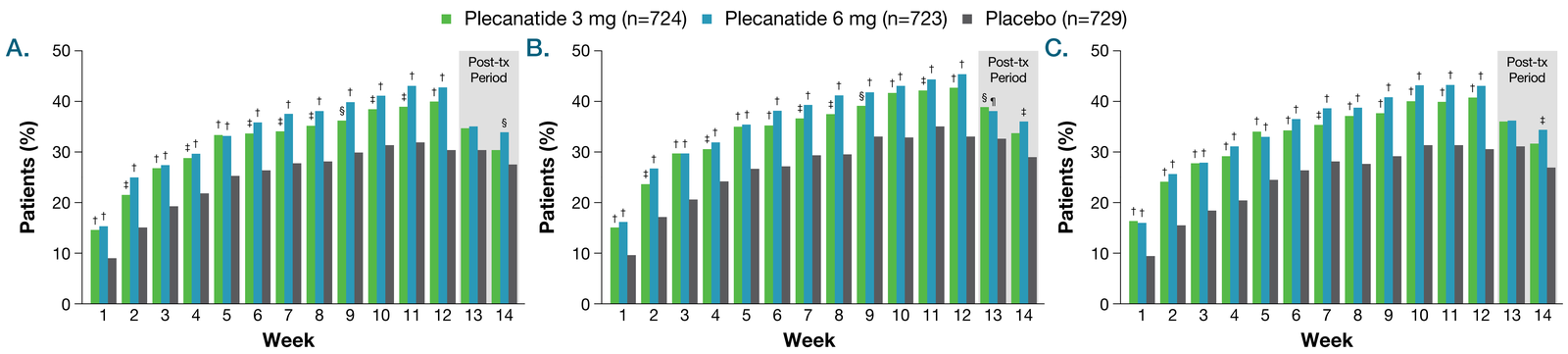
Figure 1. Composite IBS-C Abdominal Symptom Responders*



*Patients with ≥30% improvement from baseline in both symptoms (abdominal discomfort and bloating; abdominal discomfort and cramping; abdominal fullness and bloating) in the same week for ≥6 of 12 weeks.
IBS-C = irritable bowel syndrome with constipation.

- Significant differences favoring plecanatide 3 mg and plecanatide 6 mg for the percentage of composite responders versus placebo were observed at Week 1 and continued through Week 12 for abdominal discomfort and bloating (*P*<0.02; **Figure 2A**), abdominal discomfort and cramping (*P*<0.02; **Figure 2B**), and abdominal fullness and bloating (*P*<0.01; **Figure 2C**)

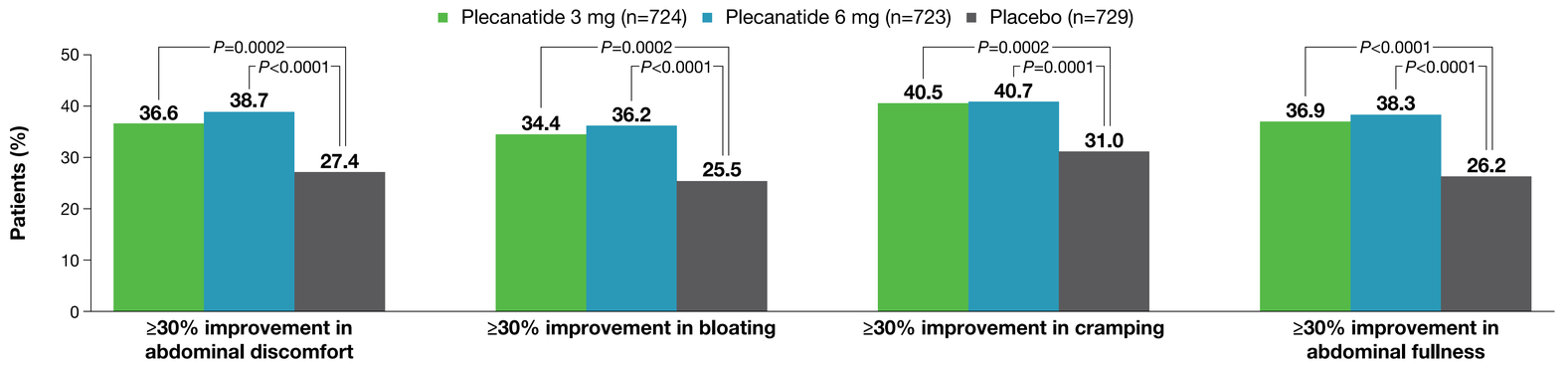
Figure 2. Composite Responders* for Abdominal Discomfort and Bloating (A), Abdominal Discomfort and Cramping (B), and Abdominal Fullness and Bloating (C), by Week



*Patients with ≥30% improvement from baseline in both symptoms (abdominal discomfort and bloating; abdominal discomfort and cramping; abdominal fullness and bloating) in the same week for ≥6 of 12 weeks of treatment.
†*P*≤0.002 versus placebo. ‡*P*≤0.01 versus placebo. §*P*=0.02 versus placebo. ¶*P*=0.04 versus placebo.
tx = treatment.

- For the individual symptoms of the composite endpoints, a significantly greater percentage of patients treated with plecanatide 3 mg or plecanatide 6 mg versus placebo were responders (≥30% improvement in individual symptoms for ≥6 of 12 weeks) for abdominal discomfort (*P*≤0.0002 for both), bloating (*P*≤0.0002 for both), cramping (*P*≤0.0002 for both), and abdominal fullness (*P*<0.0001 for both; **Figure 3**)

Figure 3. Individual Symptom Responders*



*Patients with ≥30% improvement from baseline in individual symptom for ≥6 of 12 weeks of treatment.

CONCLUSION

- Plecanatide simultaneously improved multiple symptoms (ie, abdominal discomfort, bloating, cramping, and abdominal fullness), suggesting the potential to effectively address combinations of abdominal symptoms beyond pain and constipation in IBS-C

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DISCLOSURES: GSS reports being a consultant for AbbVie Inc, Alnylam Pharmaceuticals, Inc, Ardelyx, GI Health Foundation, Ironwood Pharmaceuticals, Inc., and Salix Pharmaceuticals. He also reports being a consultant and author for the Rome Foundation and International Foundation for Gastrointestinal Disorders. APL and CA are employees of Salix Pharmaceuticals. PSS reports being an advisory board member, consultant, and speaker for AbbVie Inc, Ardelyx, Ironwood Pharmaceuticals, Inc., and Salix Pharmaceuticals; and serving as an advisory board member and consultant for Phathom Pharmaceuticals and Sanofi.

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