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Plecanatide Improves Abdominal Pain, Bloating, and Straining Symptoms in Adults With Irritable Bowel Syndrome With Constipation: A New Composite Endpoint Analysis of Two Randomized, Phase 3 Trials

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BACKGROUND

- Plecanatide (Trulance®, Salix Pharmaceuticals) is a guanylate cyclase-C agonist indicated for the treatment of chronic idiopathic constipation and irritable bowel syndrome (IBS) with constipation (IBS-C) in adults (3 mg once daily)[1]
- Phase 3, randomized, placebo-controlled trials have demonstrated that plecanatide improves multiple objective gastrointestinal (GI) symptoms, including stool frequency[2-4]
- Patients with IBS commonly experience multiple, concurrent, subjective sensory-related symptoms (eg, abdominal pain, bloating, straining),[5] and healthcare providers must rely on symptom improvement to measure treatment success
- Therefore, a composite endpoint analysis of sensory-related symptoms would help to evaluate the efficacy of IBS-C treatment

AIM

- To evaluate plecanatide treatment for simultaneously improving patient-reported, sensory-related outcomes, using a composite endpoints analysis

METHODS

- Pooled data from 2 identically designed, randomized, placebo-controlled phase 3 trials (ClinicalTrials.gov identifiers: NCT02387359 and NCT02493452) were analyzed post hoc[2]
  - Adults with IBS-C (Rome III) with a body mass index of 18-40 kg/m^2 were treated with plecanatide 3 mg, plecanatide 6 mg, or placebo once daily for 12 weeks (randomized population excluding duplicate patients)
  - Symptoms were recorded in a daily diary, with abdominal pain, bloating, and straining intensity individually rated using an 11-point scale (range, 0 [“no”] to 10 [“worst possible”])

Composite Endpoints

- Abdominal pain plus bloating: ≥30% decrease from baseline in abdominal pain and bloating in the same week for ≥6 of the 12 weeks of treatment
- Abdominal pain plus straining: ≥30% decrease from baseline in abdominal pain and straining in the same week for ≥6 of the 12 weeks of treatment

Other

- Individual symptoms of the composite endpoints were also assessed (ie, abdominal pain, bloating, straining)

RESULTS

- A total of 2176 adults (26.0% male; overall mean [SD] age, 43.5 [14.1] years) were included in the analysis (Table)
  - Mean baseline scores across the 3 treatment groups were similar for abdominal pain, bloating, and straining

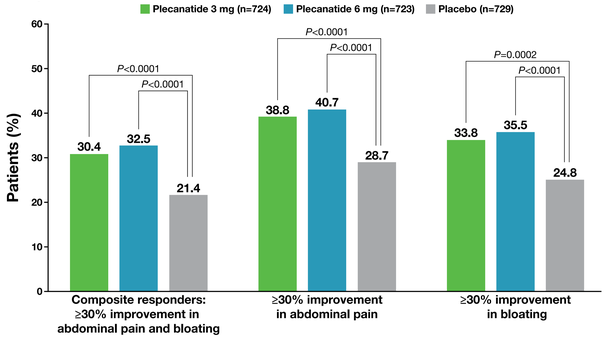
Table. Demographic and Baseline Characteristics

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/ethnicity, 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)
Abdominal pain score, mean (SD)*	6.3 (1.7)†	6.2 (1.8)‡	6.3 (1.7)§
Bloating score, mean (SD)*	6.5 (1.7)†	6.4 (1.8)‡	6.5 (1.8)§
Straining score, mean (SD)*	6.7 (1.9)¶	6.7 (1.9)#	6.6 (1.9)**

*Abdominal pain, bloating, and straining were measured using an 11-point scale (range, 0 [“no”] to 10 [“worst possible”]). †n=719. ‡n=716. §n=717. ¶n=690. #n=674. **n=676.
BMI = body mass index.

- A significantly greater percentage of patients treated with plecanatide 3 mg or plecanatide 6 mg were composite responders for abdominal pain and bloating versus placebo (Figure 1; *P*<0.0001 for both doses)

Figure 1. Composite* and Individual† Abdominal Pain and Bloating Responders

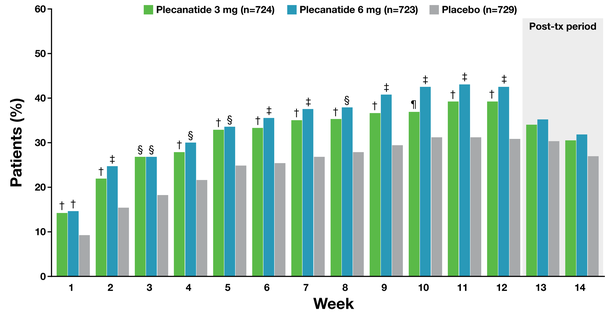


*≥30% decrease from baseline in abdominal pain and bloating in the same week for ≥6 of the 12 weeks of treatment.
†≥30% decrease from baseline in the individual symptom for ≥6 of the 12 weeks of treatment.

RESULTS

- Statistically significant differences in the percentage of composite responders for abdominal pain and bloating favoring plecanatide 3 mg and plecanatide 6 mg versus placebo were observed at Week 1 and maintained through 12 weeks of treatment (Figure 2)

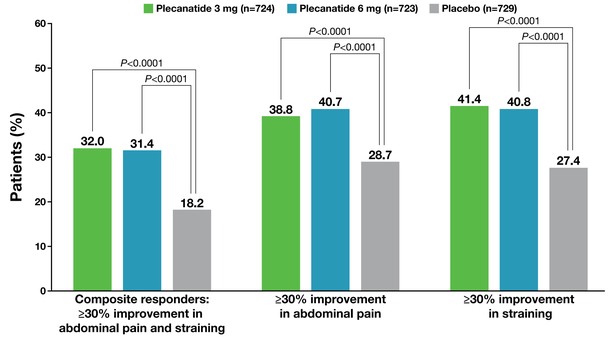
Figure 2. Composite Abdominal Pain and Bloating Responders, by Week*



*≥30% decrease from baseline in abdominal pain and bloating in the same week. †*P*<0.01 vs placebo. ‡*P*≤0.0001 vs placebo. §*P*≤0.001 vs placebo. ¶*P*=0.03 vs placebo.
Tx = treatment.

- In addition, a significantly greater percentage of patients treated with plecanatide 3 mg or plecanatide 6 mg were composite responders for abdominal pain and straining versus placebo (Figure 3; *P*<0.0001 for both doses)

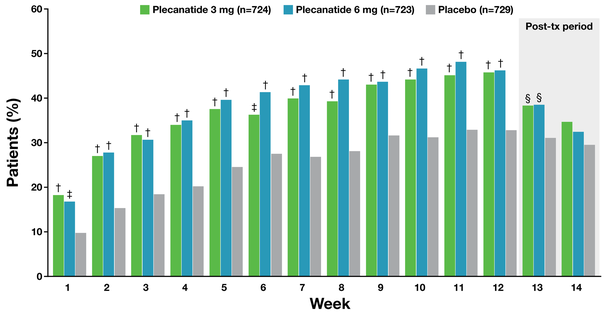
Figure 3. Composite* and Individual† Abdominal Pain and Straining Responders



*≥30% decrease from baseline in abdominal pain and straining in the same week for ≥6 of the 12 weeks of treatment.
†≥30% decrease from baseline in the individual symptom for ≥6 of the 12 weeks of treatment.

- Statistically significant differences in the percentage of composite responders for abdominal pain and straining favoring plecanatide 3 mg and plecanatide 6 mg versus placebo were observed by Week 1 and maintained through 12 weeks of treatment and 1 week posttreatment (Figure 4)

Figure 4. Composite Abdominal Pain and Straining Responders, by Week*



*≥30% decrease from baseline in abdominal pain and straining in the same week. †*P*<0.0001 vs placebo. ‡*P*≤0.001 vs placebo. §*P*=0.01 vs placebo.
Tx = treatment.

- For the individual components of the composite endpoints, a significantly higher percentage of patients treated with plecanatide 3 mg or plecanatide 6 mg versus placebo were responders (≥30% improvement in individual symptom for ≥6 weeks of the 12 weeks of treatment) for abdominal pain (*P*<0.0001 for both doses [Figures 1 and 3]), bloating (*P*≤0.0002 for both doses [Figure 1]), and straining (*P*<0.0001 for both doses [Figure 3])

CONCLUSIONS

- Plecanatide treatment significantly improved multiple, concurrent, sensory-related symptoms (abdominal pain, bloating, straining) in adults with IBS-C
- Treatment discontinuation at Week 13 showed a return of sensory-related symptoms, supporting a true drug effect with plecanatide
- Thus, patient adherence to treatment is an important consideration for those with recurrent symptoms, as adherence is important for maintaining long-term effectiveness

REFERENCES: **1.** Trulance tablets, for oral use. Prescribing information. Salix Pharmaceuticals; 2021. **2.** Brenner DM, Fogel R, Dorn SD, et al. *Am J Gastroenterol.* 2018;113(5):735-745. **3.** Miner PB Jr, Koltun WD, Wiener GJ, et al. *Am J Gastroenterol.* 2017;112(4):613-621. **4.** DeMicco M, Barrow L, Hickey B, et al. *Therap Adv Gastroenterol.* 2017;10(11):837-851. **5.** Lacy BE, Mearin F, Chang L, et al. *Gastroenterology.* 2016;150(6):1393-1407.

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