POSTER NUMBER

D0269

Plecanatide Improves Symptoms of Chronic Idiopathic Constipation and Irritable Bowel Syndrome With Constipation Across Age Subgroups: an Analysis of Four Phase 3 Trials

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INTRODUCTION

- Chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C) are common disorders of gut-brain interaction that may exist on a disease severity continuum[1]
- Constipation is associated with increasing age[2] and is a common reason for individuals to seek medical care[3]
- Plecanatide is a guanylate cyclase-C agonist that is approved in the United States for the treatment of adults with CIC or IBS-C[4]
  - Efficacy and safety of plecanatide were demonstrated in 4 randomized, double-blind, placebo-controlled, phase 3 trials (CIC [n=2]; IBS-C [n=2]),[5-7] including in those aged ≥65 years[8]

OBJECTIVE

- To further assess the potential impact of age on the efficacy and safety of plecanatide in an analysis of adults with CIC or IBS-C

METHODS

- Post hoc analysis of data pooled from 2 CIC or pooled from 2 IBS-C randomized, double-blind, placebo-controlled trials[5-7]
- Populations included adults who received plecanatide 3 mg (US Food and Drug Administration-approved dose) or placebo once daily for 12 weeks
  - Data were subgrouped by patient age (<40 years, 40-59 years, and ≥60 years)
- Primary protocol-defined efficacy endpoints
  - CIC trials: the percentage of patients with durable overall complete spontaneous bowel movement (CSBM) response
    - Weekly response defined as ≥3 CSBMs/week and an increase from baseline of ≥1 CSBM for the same week
    - Durable overall response was a weekly response for ≥9 weeks and a weekly response for ≥3 of the last 4 weeks of treatment
  - IBS-C trials: the percentage of patients with overall response
    - Response defined as a ≥30% reduction from baseline in worst abdominal pain *and* increase from baseline of ≥1 CSBM/week in the same week for ≥6 weeks
- Treatment-emergent adverse events (AEs) were evaluated by age group

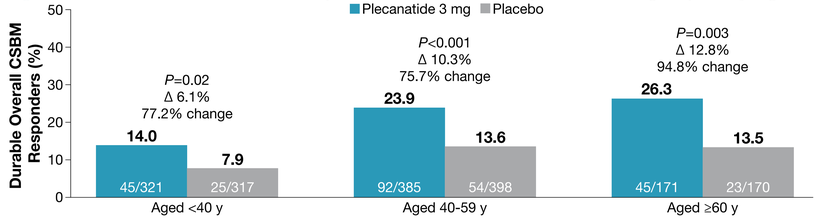
RESULTS

Chronic Idiopathic Constipation

- Of the 1762 patients with CIC, 638 (36.2%) were aged <40 years, 783 (44.4%) aged 40 to 59 years, and 341 (19.4%) aged ≥60 years
- A statistically significantly greater percentage of patients with CIC treated with plecanatide were durable overall CSBM responders compared with placebo across the 3 age groups (**Figure 1**)

RESULTS

Figure 1. Durable Overall CSBM Responder Rate* in CIC Population, Subgrouped by Age



*≥3 CSBMs/week and increase from baseline of ≥1 CSBM for same week for ≥9 weeks, including ≥3 of last 4 treatment weeks (ie, durable).
CIC = chronic idiopathic constipation; CSBM = complete spontaneous bowel movement.

- Plecanatide treatment was well tolerated across the 3 age groups (**Table 1**)
  - Discontinuation rates overall and due to diarrhea were low across the age groups

Table 1. Summary of AEs in CIC Population, Subgrouped by Age*

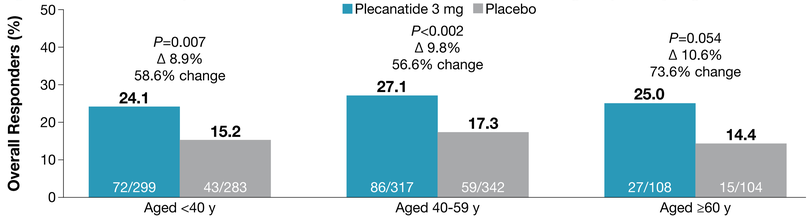
	Aged <40 y		Aged 40-59 y		Aged ≥60 y	
AE, n (%)	Plecanatide 3 mg (n=319)	Placebo (n=314)	Plecanatide 3 mg (n=385)	Placebo (n=394)	Plecanatide 3 mg (n=171)	Placebo (n=167)
≥1 AE	93 (29.2)	88 (28.0)	120 (31.2)	123 (31.2)	60 (35.1)	47 (28.1)
≥1 drug-related AE	25 (7.8)	12 (3.8)	31 (8.1)	16 (4.1)	10 (5.8)	8 (4.8)
≥1 SAE	4 (1.3)	4 (1.3)	5 (1.3)	5 (1.3)	4 (2.3)	3 (1.8)
Discontinuation due to ≥1 AE	12 (3.8)	8 (2.5)	16 (4.2)	6 (1.5)	10 (5.8)	6 (3.6)
Due to diarrhea-related AE	5 (1.6)	2 (0.6)	10 (2.6)	0	4 (2.3)	2 (1.2)
≥1 AE, by intensity†						
Mild	57 (17.9)	51 (16.2)	64 (16.6)	67 (17.0)	32 (18.7)	28 (16.8)
Moderate	31 (9.7)	32 (10.2)	50 (13.0)	52 (13.2)	19 (11.1)	14 (8.4)
Severe	5 (1.6)	4 (1.3)	6 (1.6)	4 (1.0)	9 (5.3)	5 (3.0)

*Index case dataset for patients with ≥1 identifier (eg, participated at ≥1 site or trial) was confirmed, and duplicative (newer) datasets for these patients were excluded for the safety analysis. †General descriptors: mild—asymptomatic or mild symptoms; clinical or diagnostic observations only, with intervention not indicated; moderate—minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL; eg, preparing meals, shopping); severe—medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (eg, bathing, dressing/undressing, not bedridden). AE = adverse event; CIC = chronic idiopathic constipation; SAE = serious adverse event.

Irritable Bowel Syndrome With Constipation

- Of the 1453 patients with IBS-C, 582 (40.1%) were aged <40 years, 659 (45.4%) were aged 40 to 59 years, and 212 (14.6%) were aged ≥60 years
- A statistically significantly greater percentage of patients with IBS-C treated with plecanatide in the aged <40 years and 40-to-59 years subgroups were overall responders compared with placebo (**Figure 2**)
  - In the ≥60 years age group, which contained a lower number of patients, a numeric difference of overall responses favoring plecanatide versus placebo was observed

Figure 2. Overall Responder Rate* in Population With IBS-C, Subgrouped by Age



*≥30% reduction from baseline in worst abdominal pain and increase from baseline of ≥1 CSBM/week in the same week for ≥6 weeks.
CSBM = complete spontaneous bowel movement; IBS-C = irritable bowel syndrome with constipation.

- Plecanatide treatment was well tolerated across the 3 age groups (**Table 2**)
- Discontinuation rates overall and due to diarrhea were low across the 3 age groups (**Table 2**) and were lower than that observed for the CIC population (**Table 1**)

Table 2. Summary of AEs in IBS-C Population, Subgrouped by Age*

	Aged <40 y		Aged 40-59 y		Aged ≥60 y	
AE, n (%)	Plecanatide 3 mg (n=299)	Placebo (n=283)	Plecanatide 3 mg (n=316)	Placebo (n=339)	Plecanatide 3 mg (n=108)	Placebo (n=104)
≥1 AE	70 (23.4)	48 (17.0)	74 (23.4)	66 (19.5)	28 (25.9)	22 (21.2)
≥1 drug-related AE	13 (4.3)	5 (1.8)	16 (5.1)	11 (3.2)	10 (9.3)	3 (2.9)
≥1 SAE	1 (0.3)	4 (1.4)	5 (1.6)	1 (0.3)	0	1 (1.0)
Discontinuation due to ≥1 AE	6 (2.0)	3 (1.1)	11 (3.5)	0	1 (0.9)	0
Due to diarrhea-related AE	1 (0.3)	0	7 (2.2)	0	1 (0.9)	0
≥1 AE, by intensity†						
Mild	40 (13.4)	27 (9.5)	38 (12.0)	44 (13.0)	18 (16.7)	14 (13.5)
Moderate	22 (7.4)	16 (5.7)	28 (8.9)	21 (6.2)	9 (8.3)	7 (6.7)
Severe	8 (2.7)	5 (1.8)	8 (2.5)	1 (0.3)	1 (0.9)	1 (1.0)

*Index case dataset for patients with ≥1 identifier (eg, participated at ≥1 site or trial) was confirmed, and duplicative (newer) datasets for these patients were excluded for the safety analysis. †See Table 1 for general descriptors. AE = adverse event; IBS-C = irritable bowel syndrome with constipation; SAE = serious adverse event.

CONCLUSIONS

- **Once-daily plecanatide 3 mg is an effective and well-tolerated therapy for patients with CIC or IBS-C across various age groups, including the elderly**
  - **However, due to the smaller sample size of the ≥60-year-old age demographic, interpretation of results for the IBS-C population may have been effected**
  - **Overall, rates of diarrhea-related discontinuation in patients treated with plecanatide with CIC or IBS-C were low across the age groups**

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ACKNOWLEDGMENTS: These analyses were supported by Salix Pharmaceuticals. Technical editorial and medical writing assistance were provided under direction of the authors by Mary Beth Moncrief, PhD, and Sophie Bolick, PhD, Synchrony Medical Communications, LLC, West Chester, PA. Funding for this assistance was provided by Salix Pharmaceuticals.

DISCLOSURES: KS reports serving as a consultant to Arena Pharmaceuticals, Inc. (acquired by Pfizer), Gelesis, and GI Supply; and receiving research support from Ironwood Pharmaceuticals, Inc. and Urovant Sciences, Inc. APL and CA are employees of Salix Pharmaceuticals. LN reports having nothing to disclose. WDC reports serving as a consultant for Biomerica, Cosmo Pharmaceuticals NV, Mauna Kea Technologies, Nestlé Health Science, QOL Medical, LLC, and Salix Pharmaceuticals; and receiving research support from Biomerica, QOL Medical, LLC, and Salix Pharmaceuticals, LC reports having nothing to disclose.

American College of Gastroenterology (ACG) 2022 Annual Scientific Meeting • October 21–26, 2022 • Charlotte, NC

Research funded by: Salix Pharmaceuticals