Predictors of Placebo Response in Patients With Irritable Bowel Syndrome With Constipation: A Post-hoc Analysis From Pooled Phase 2b/3 Studies Assessing the Safety and Efficacy of Linaclotide

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OBJECTIVE

This post-hoc analysis of pooled Phase 2/3 linaclotide clinical trials aimed to identify potential factors associated with the magnitude of placebo response in patients with irritable bowel syndrome with constipation (IBS-C)

CONCLUSIONS

In this pooled analysis of IBS-C linaclotide clinical studies, baseline variation in abdominal pain and baseline abdominal pain score exhibited a strong impact on placebo response for the abdominal pain responder endpoint

Higher baseline variation in abdominal pain was associated with higher placebo response and higher drug response, which may not affect the placebo-drug difference

Higher mean baseline abdominal pain score was associated with a lower placebo response and no correlation to drug response, particularly for patients in the 25th and 75th quantiles; including patients with higher pain during baseline monitoring could reduce the placebo effect while maintaining drug effect

Further research is needed to better understand the impact of these and other predictors on the placebo response in studies of IBS-C

Disclosures

AbbVie Inc., Ironwood Pharmaceuticals, Inc., and the authors thank the participants, study sites, and investigators who participated in this clinical trial.

Allergan plc (prior to acquisition by AbbVie Inc.) and Ironwood Pharmaceuticals, Inc. funded this analysis and participated in the design, research, analysis, data collection, interpretation of data, and the review and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. Writing and editorial assistance were provided by Anjaca Petersen, PhD, and Adam Paton, BA, of Complete HealthVizion, IPG Health Medical Communications, and funded by AbbVie Inc. and Ironwood Pharmaceuticals, Inc.

Financial arrangements of the authors with companies whose products may be related to the present report are listed below, as declared by the authors. Anthony Lembo serves as a consultant for Allermos, Arena, Bayer, Gemelli Biotech, Ironwood, OptiNativ, Salix, Takeda, and Vibrant. He also owns stock in Bristol Myers Squibb and Johnson & Johnson. Katherine Kosch is an employee of AbbVie Inc. and may own company stock and/or stock options. James Wu is an employee of Ironwood Pharmaceuticals, Inc. and may own company stock and/or stock options. Cristina Almansa is a former employee of Ironwood Pharmaceuticals, Inc. and may own company stock. Judy Nee, John Kelley, and Sarah Ballou have no conflicts of interest to declare.

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Presented at the American College of Gastroenterology (ACG) 2022 Annual Scientific Meeting, October 21–26, 2022, Charlotte, NC, USA

INTRODUCTION

Background

- The placebo response is a frequent factor that influences the observed differences in outcomes between study drug and inert treatment in clinical trials[1,2]
  - Several factors have been determined to contribute to the placebo response, including the natural history of the disease, regression to the mean, and the placebo effect itself, whereby expectations of a positive treatment could trigger neurobiological and psychological changes[1,2]
- As the placebo response impedes the statistical power of randomized clinical trials to establish superiority of active treatment vs. placebo, further understanding of the factors that drive the placebo response in patients can improve clinical study design[2]
- IBS-C is a gastrointestinal disorder in which the placebo response is particularly problematic, as studies in irritable bowel syndrome (IBS) include subjective patient-reported outcomes with objective quantitative measures[3,4]
  - In an analysis of clinical studies of IBS, the pooled placebo response rate was 34% for the abdominal pain responder endpoint[5]

METHODS

Analysis

- This post-hoc analysis assessed patient data from one Phase 2b (NCT02559206)[6] and three Phase 3 (NCT00948818, NCT00938717, NCT03573908)[7–9] randomized, double-blind, placebo-controlled trials that investigated the safety and efficacy of linaclotide 290 µg treatment in patients with IBS-C
- Adult patients (⩾18 years of age) with a baseline abdominal pain severity score ⩾3 (11-point numerical rating scale) who met modified Rome II criteria and were randomized 1:1 to receive linaclotide 290 µg or placebo once daily for ⩾12 weeks were included in this pooled analysis; data assessed in this study were truncated to 12 weeks
- Demographics and baseline characteristics analyzed as potential predictors of placebo response included age, anxiety, baseline Bristol Stool Form Scale (BSFS) score, baseline pain conditions, baseline spontaneous bowel movement, depression, mean baseline abdominal pain score, Food and Drug Administration (FDA) approval status of the therapeutic, prior gastrointestinal (GI) drug taken, sex, and variation of the baseline abdominal pain score
  - Baseline pain conditions included bladder pain, fatigue syndrome, cystitis interstitial, dyspareunia, dyspepsia, fibromyalgia, migraine, migraine with aura, pelvic pain, somatic symptom disorder, and somatoform disorder
  - Categorical predictors (yes vs. no) were anxiety, baseline pain conditions, depression, FDA approval status, and prior GI drug taken, as well as sex (male vs. female); all other predictors were continuous
- The same 11 factors were also assessed in a separate model as predictors of drug response for patients treated with linaclotide 290 µg

Outcomes

- The four efficacy endpoints of interest were as follows:
  - **Abdominal pain responder**, defined as ⩾30% improvement from a 2-week baseline in average daily worst abdominal pain score for ⩾50% of the first 12 weeks on treatment
  - **Complete spontaneous bowel movement (CSBM) +1 responder**, defined as an increase of ⩾1 CSBM from baseline for ⩾50% of the first 12 weeks on treatment
  - **Adequate relief responder**, defined as patient-reported adequate relief (yes or no) for ⩾50% of the first 12 weeks on treatment
  - **Abdominal pain and constipation (APC) +1 responder**, defined as a patient who met both combined endpoints of abdominal pain responder and CSBM +1 responder

Statistical Analysis

- Predictors of placebo response of the four efficacy endpoints were identified using backward selection via a regression analysis from a list of 11 demographic and baseline disease characteristics
- Standardized coefficients (SCs) were calculated to rank the magnitude of association of each selected predictor with the response
  - For binary-variable predictors, a positive coefficient indicates that "yes" corresponds to more likely to respond
  - For continuous-variable predictors, a positive coefficient indicates the higher the value the more likely to respond, whereas a negative coefficient indicates the higher the value the less likely to respond

RESULTS

Patient Demographics and Characteristics

- The pooled intent-to-treat population comprised 2,350 patients (placebo, n=1,172; linaclotide 290 µg, n=1,178)
- Demographics and characteristics were similar between the placebo and linaclotide 290 µg treatment groups (**Table 1**)
  - The majority of patients in the placebo group were female (86.8%) and white (72.4%); mean age was 44.7 years

Factors Associated With a Significant Placebo or Drug Response

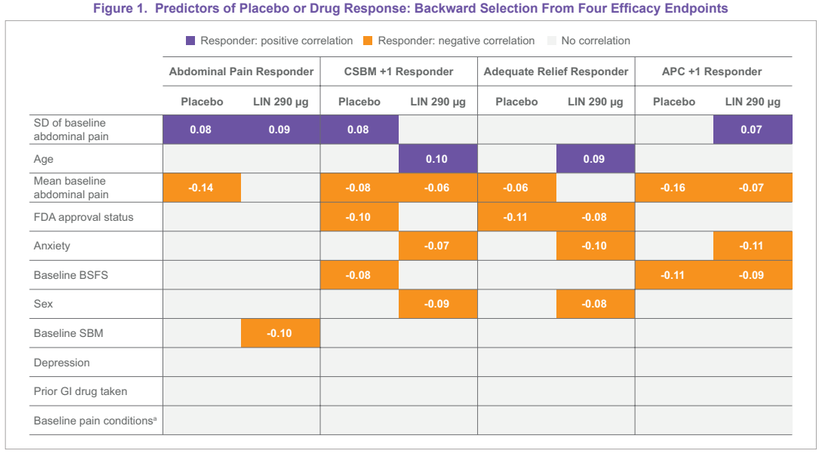
- **For the abdominal pain responder endpoint**, two factors were identified as having a strong impact on the placebo response (**Figure 1**)
  - Higher baseline variation in abdominal pain; associated with higher placebo response (coefficient, standard error [SE]: 0.20, 0.07; P=.0032)
    - Also associated with higher response to linaclotide 290 µg (coefficient, SE: 0.21, 0.06; P=.0012)
  - Higher mean baseline abdominal pain score; associated with lower placebo response (coefficient, SE: -0.15, 0.02; P<.0001)
    - No correlation with linaclotide 290 µg

Table 1. Demographic and Baseline Characteristics of Patients From Four Pooled IBS-C Studies (ITT Population)

Parameter	Placebo (N=1,172)	Linaclotide 290 µg (N=1,178)
Age, years		
Mean (SD)	44.7 (13.6)	44.6 (13.5)
<65, n (%)	1,088 (92.8)	1,099 (93.3)
⩾65, n (%)	84 (7.2)	79 (6.7)
Sex, n (%)		
Female	1,017 (86.8)	1,029 (87.4)
Race, n (%)		
White	848 (72.4)	862 (73.2)
Black	248 (21.2)	235 (19.9)
Asian	47 (4.0)	56 (4.8)
Other	29 (2.5)	25 (2.1)
Ethnicity, n (%)		
Hispanic or Latino	186 (15.9)	200 (17.0)
BMI, kg/m^2, mean (SD)	28.2 (6.4)	28.5 (6.4)

BMI, body mass index; IBS-C, irritable bowel syndrome with constipation; ITT, intent to treat; SD, standard deviation

Figure 1. Predictors of Placebo or Drug Response: Backward Selection From Four Efficacy Endpoints



Predictors are ranked in logistic regression by their strength of impacting to the response. The numbers in the figure are the absolute value of the standardized coefficients that rank the coefficients within a responder endpoint from highest to lowest, in order of strength of association with the outcome. No conclusions should be drawn across the 4 responder endpoints.
[a]Baseline pain conditions included bladder pain, fatigue syndrome, cystitis interstitial, dyspareunia, dyspepsia, fibromyalgia, migraine, migraine with aura, pelvic pain, somatic symptom disorder, and somatoform disorder
APC, abdominal pain and constipation; BSFS, Bristol Stool Form Scale; CSBM, complete spontaneous bowel movement; FDA, Food and Drug Administration; GI, gastrointestinal; LIN, linaclotide; SBM, spontaneous bowel movement; SD, standard deviation

- **For the CSBM +1 responder endpoint**, a higher variation in baseline abdominal pain was also associated with a higher response to placebo; however, there was no correlation with linaclotide 290 µg (**Figure 1**)
  - FDA approval status and higher baseline BSFS were also associated with a lower response to placebo and no correlation with linaclotide 290 µg
- **For the adequate relief responder and APC +1 responder endpoints**, a higher mean baseline abdominal pain score was also associated with a lower placebo response (**Figure 1**), as well as
  - FDA approval status for adequate relief responder and higher baseline BSFS for APC +1 responder
- Depression, prior GI drugs taken, and baseline pain conditions were not found to impact on the placebo or drug response for any efficacy endpoint analyzed (**Figure 1**)

Additional Analyses of the Abdominal Pain Responder Endpoint

- Further analyses of the placebo response were conducted for the abdominal pain responder endpoint, evaluating durability of response (responder for ⩾50% vs ⩾75% of weeks on treatment) and subsets of baseline pain severity (quantiles)
- In assessing the abdominal pain responders for ⩾50% and ⩾75% of weeks on treatment, a higher baseline variation of abdominal pain score continued to be associated with a higher placebo and linaclotide 290 µg response (SC; placebo, 0.08, linaclotide 290 µg, 0.09; placebo, 0.10, linaclotide 290 µg, 0.08, respectively) [**Table 2**]
  - Similarly, a higher mean baseline abdominal pain score was associated with a lower placebo response for abdominal pain responders for ⩾50% and ⩾75% of weeks on treatment, and with linaclotide 290 µg for ⩾75% of weeks on treatment
- When baseline variation of abdominal pain was examined by quantiles, only patients in the 25% and 50% quantiles continued to have an association with a higher placebo response (**Table 3**)
  - In contrast, all quantiles of baseline abdominal pain score were associated with a lower placebo response, with a diminishing strength as the quantile increased (25th quantile, SC -0.11; 75th quantile, SC -0.6)

Table 2. Predictors of Placebo and Drug Response for the Abdominal Pain Endpoint: Responders for 50% or 75% of the First 12 Weeks on Treatment

	Placebo (N=1,172)			Linaclotide 290 µg (N=1,178)		
	Estimated coefficient (SE)	P value	SC	Estimated coefficient (SE)	P value	SC
Abdominal pain responder for ⩾50% of the first 12 weeks on treatment, n	1,027			1,046		
Predictors						
Mean baseline abdominal pain	-0.15 (0.02)	<.0001	-0.14	–	–	–
SD of baseline abdominal pain	0.20 (0.07)	.0032	0.08	0.21 (0.06)	.0012	0.09
Baseline SBM	–	–	–	-0.15 (0.04)	.0002	-0.10
Abdominal pain responder for ⩾75% of the first 12 weeks on treatment, n	751			764		
Predictors						
Mean baseline abdominal pain	-0.16 (0.03)	<.0001	-0.15	-0.09 (0.03)	.0002	-0.09
SD of baseline abdominal pain	0.23 (0.10)	.0206	0.10	0.18 (0.08)	.0232	0.08
Baseline BSFS	-0.26 (0.08)	.0012	-0.14	–	–	
Baseline SBM	–	–	–	-0.12 (0.06)	.0383	-0.08
Sex	–	–	–	-0.59 (0.28)	.0378	-0.10

BSFS, Bristol Stool Form Scale; SBM, spontaneous bowel movement; SC, standardized coefficient; SD, standard deviation; SE, standard error

Table 3. Predictors of Placebo and Drug Response for the Abdominal Pain Endpoint: Breakdown by Quantile

	Placebo (N=1,172)			Linaclotide 290 µg (N=1,178)		
	Estimated coefficient (SE)	P value	SC	Estimated coefficient (SE)	P value	SC
Abdominal pain responder for ⩾50% of the first 12 weeks on treatment, n	1,027			1,046		
Predictors						
Mean baseline abdominal pain						
25% quantile	-0.15 (0.02)	<.0001	-0.11	–	–	–
50% quantile	-0.16 (0.03)	<.0001	-0.09	-0.11 (0.04)	.0053	-0.06
75% quantile	-0.17 (0.03)	<.0001	-0.06	–	–	–
SD of baseline abdominal pain						
25% quantile	0.20 (0.09)	.0187	0.08	0.26 (0.08)	.0023	0.09
50% quantile	0.36 (0.13)	.0059	0.13	–	–	–
75% quantile	–	–	–	–	–	–

SC, standardized coefficient; SD, standard deviation; SE, standard error