

Assessment of Heartburn and Regurgitation in Symptomatic Non-Erosive Reflux Disease Patients on Vonoprazan Based on the Patient Assessment of Upper Gastrointestinal Symptom Severity Index



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Introduction

- Non-erosive reflux disease (NERD) patients commonly present with heartburn and/or regurgitation and normal endoscopy, making symptom relief a key therapeutic goal.^{1,2}
- Vonoprazan has demonstrated efficacy in reducing heartburn frequency in patients with symptomatic non-erosive reflux disease (NERD) in the Phalcon-NERD 301 phase 3 study. To date, the effect of vonoprazan on regurgitation symptoms has not been reported.³

Objective

- The aim of this exploratory analysis was to assess the effect of vonoprazan on regurgitation outcomes, as measured by the validated Patient Assessment of Upper Gastrointestinal Symptom Severity Index (PAGI-SYM), in patients with symptomatic NERD, and to explore the relationship between improvements in regurgitation and heartburn.

Methods

- Adults with symptomatic NERD were randomized to placebo, vonoprazan 10 mg, or vonoprazan 20 mg in a 4-week, double-blind, placebo-controlled, multicenter trial.
- Analyses were conducted in the intention-to-treat population (placebo: n = 258; vonoprazan 10 mg: n = 257; vonoprazan 20 mg: n = 257).
- Gastrointestinal symptoms were measured using PAGI-SYM, a validated 20-item instrument with six subscales assessing heartburn/regurgitation, postprandial fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain with a recall period of the past two weeks.
 - Items were rated on a 0-5 scale, with higher scores indicating more severe symptoms.
 - Participants completed the PAGI-SYM questionnaire at baseline and Week 4.
 - Total and subscale scores were calculated from questionnaire responses.
 - Subscale scores were calculated as the mean of all non-missing responses within that subscale. The total score was calculated as the mean of the subscale scores. A negative change indicated improvement.
 - Least-squares (LS) mean changes from baseline and group differences were obtained for total score, each subscale, and heartburn- and regurgitation-related questions separately.
 - The heartburn subscale score was defined as the mean of Q14 (heartburn during the day) and Q15 (heartburn when lying down).
 - The regurgitation subscale score was defined as the mean of Q18 (regurgitation during the day), Q19 (regurgitation when lying down), and Q20 (bitter, acid, or sour taste in the mouth).

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Results

- Baseline characteristics were well balanced across treatment groups (n = 257-258 each): age ~50 years, ~65-71% female, BMI ~30 kg/m², with similar race, lifestyle factors, prior PPI use, and heartburn frequency and severity.³
- At baseline, heartburn and regurgitation were strongly correlated (Pearson correlation, r = 0.70), with higher heartburn scores generally observed alongside higher regurgitation scores.
- At Week 4, LS mean change in PAGI-SYM total scores were -0.5 (placebo), -0.8 (vonoprazan 10 mg), and -0.6 (vonoprazan 20 mg) (Table 1).
- Subscale analysis showed improvements vs placebo (p < 0.05) in the heartburn/regurgitation domain for both vonoprazan 10 mg (-1.3) and 20 mg (-1.2) (Table 1).

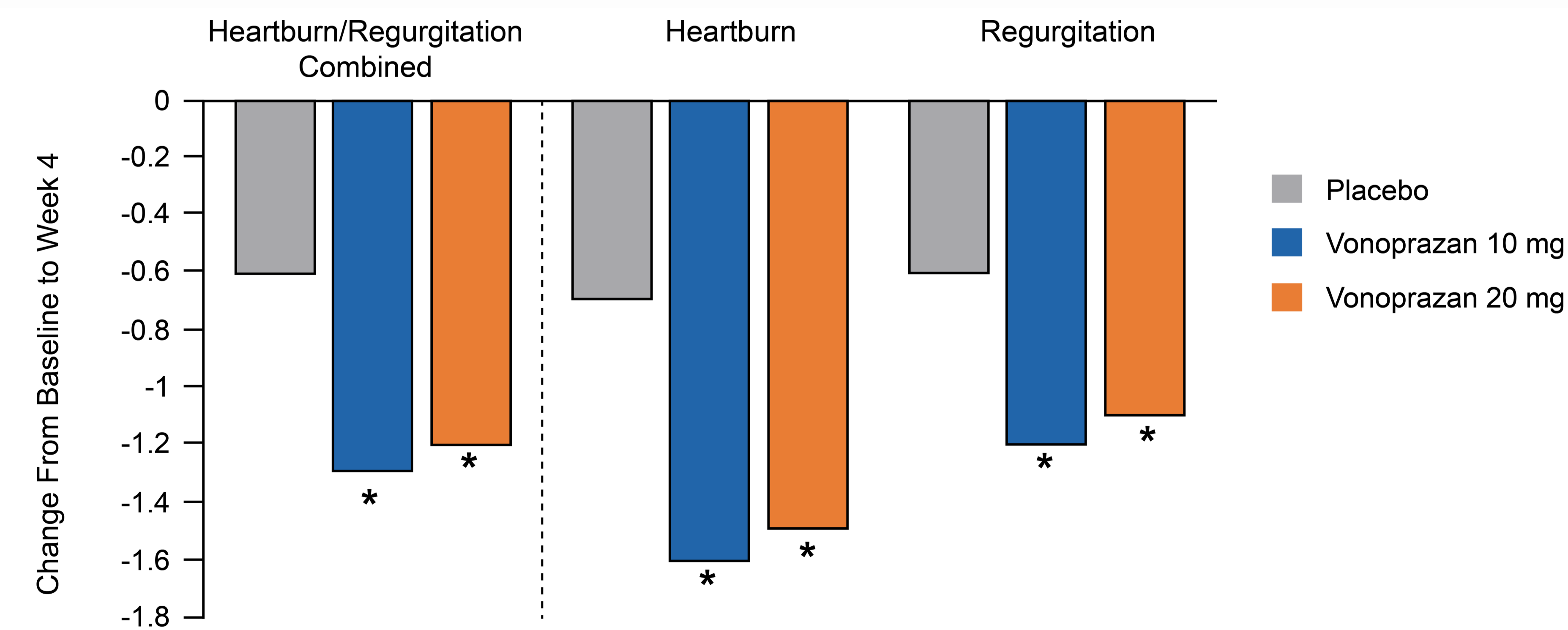
Table 1. Comparison of average PAGI-SYM scores between baseline and Week 4 in placebo and vonoprazan groups

	Placebo		Vonoprazan 10 mg		Vonoprazan 20 mg	
	Baseline (n = 257)	Change (n = 241)	Baseline (n = 255)	Change (n = 238)	Baseline (n = 256)	Change (n = 230)
Total Score	1.52	-0.5	1.57	-0.8*	1.58	-0.6
Heartburn/Regurgitation	2.16	-0.6	2.20	-1.3*	2.24	-1.2*
Nausea/Vomiting	0.84	-0.3	0.91	-0.5*	0.80	-0.2
Fullness/Early Satiety	1.63	-0.4	1.65	-0.6*	1.72	-0.5
Bloating	1.89	-0.5	2.02	-0.8*	2.01	-0.6
Upper Abdominal Pain	1.59	-0.6	1.56	-0.8	1.64	-0.7
Lower Abdominal Pain	1.04	-0.4	1.08	-0.5	1.05	-0.4

*Asterisks indicate p < 0.05 vs placebo. Least-squares (LS) means shown for change from baseline coming from a general linear model with treatment group as a factor and severity and frequency of symptoms at baseline as covariates.

- When analyzed separately, improvements (p < 0.05) over placebo were also noted in both heartburn and regurgitation components, regardless of vonoprazan dose (Figure 1).

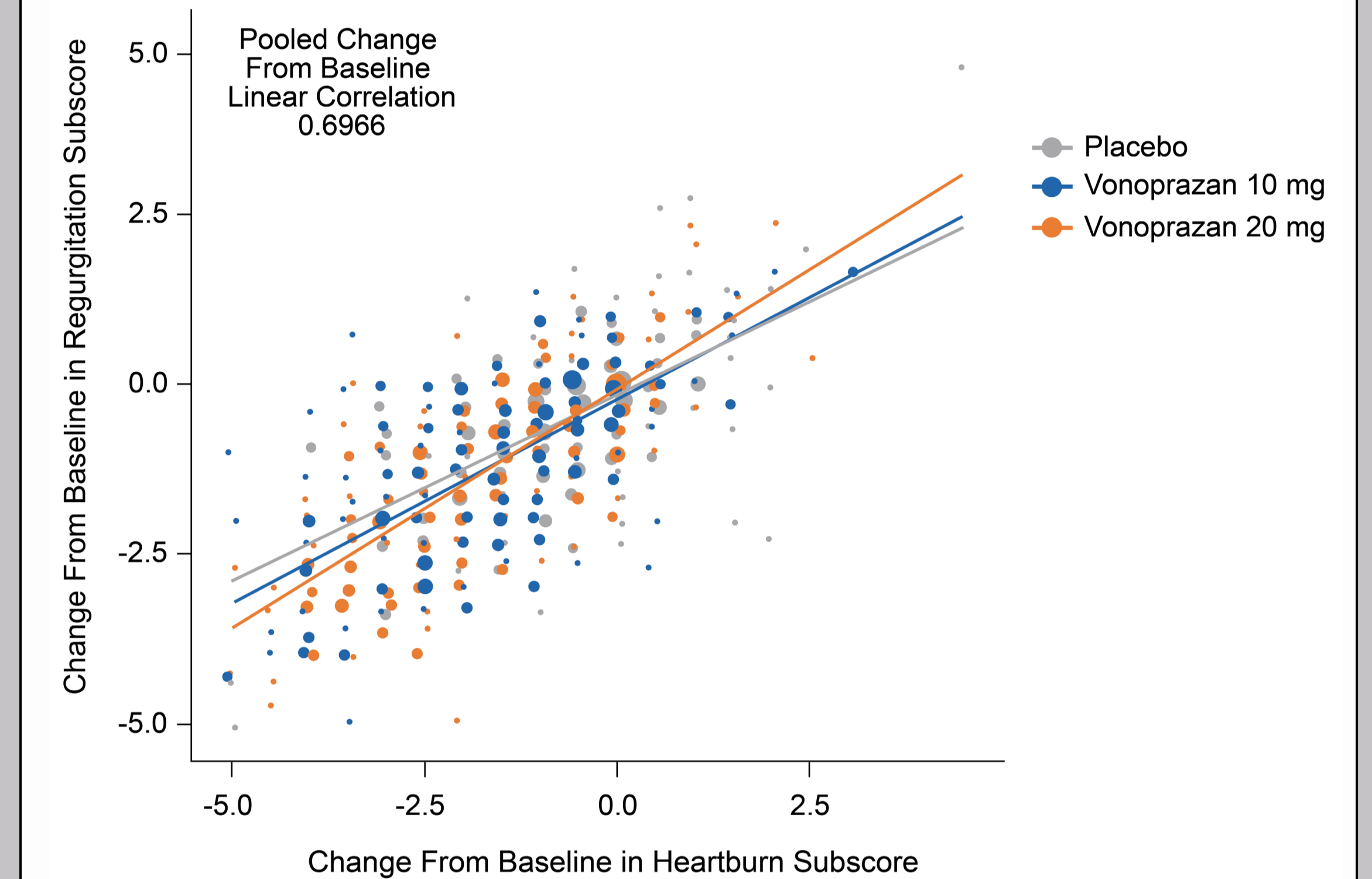
Figure 1. Comparison of average change in PAGI-SYM scores at Week 4 for the combined domains heartburn/regurgitation, and separated domains heartburn and regurgitation between placebo and vonoprazan



LS mean for change from baseline presented. * p < 0.05 for comparison to placebo

- Examination of the relationship between the change from baseline in heartburn and regurgitation scores revealed a strong correlation (Pearson correlation, r = 0.70), with most subjects demonstrating decreases in both heartburn and regurgitation symptoms (Figure 2).

Figure 2. Correlation between change from baseline in heartburn and regurgitation PAGI-SYM subscores



Dot size represents number of subjects per value (larger dot = more subjects). Minor jitter was applied to reduce overlap due to discrete PAGI-SYM scoring.

Limitations

- This analysis is limited by reliance on patient-reported outcomes, potential conceptual overlap between heartburn and regurgitation subscales, and the absence of adjustment for multiplicity.

Conclusions

- Vonoprazan, regardless of dose, improved regurgitation symptoms compared with placebo in this exploratory analysis, with consistent improvements also observed for heartburn as measured by the PAGI-SYM instrument.
- The observed treatment difference in the PAGI-SYM heartburn/regurgitation subscale represents a potentially clinically meaningful improvement and aligns with previously reported heartburn outcomes in NERD.
- These findings suggest that vonoprazan may improve regurgitation symptoms in patients with symptomatic NERD and highlight the relationship between improvements in regurgitation and heartburn as captured by PAGI-SYM.