# Vonoprazan Improves Nocturnal Gastroesophageal Reflux Symptoms in Non-Erosive Reflux Disease

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## Background

- Nocturnal symptoms are common among patients with gastroesophageal reflux disease (GERD) but are infrequently investigated in therapeutic studies.
- The Nocturnal Gastro-esophageal Reflux Disease Symptom Severity and Impact Questionnaire (N-GSSIQ) has been developed to better characterize nocturnal symptoms. It assesses the severity, morning impact, and the patient's concerns about nocturnal GERD over the past two weeks.[1]
- Vonoprazan, a potassium-competitive acid blocker, has documented efficacy in the treatment of erosive esophagitis and non-erosive reflux disease (NERD), but its effects on nocturnal symptoms have remained unexplored.

## Objective

- **To evaluate the efficacy of vonoprazan for nocturnal GERD symptoms in patients with NERD using daily electronic symptom diaries and the N-GSSIQ.**

## Methods

- Efficacy of vonoprazan for nocturnal symptoms was assessed as an exploratory endpoint in a double-blind, placebo-controlled trial.
- Inclusion criteria: Adult patients with heartburn ≥4 days in any consecutive 7-day period during screening, without erosive esophagitis or visible Barrett's esophagus on endoscopy.
- Patients randomized to placebo, vonoprazan 10mg, or vonoprazan 20mg once daily for 4 weeks.
- Electronic diaries were completed twice daily for presence and severity of daytime and nighttime heartburn. N-GSSIQ was completed at baseline and week 4. N-GSSIQ comprises 20 items covering 3 subscales with higher scores representing greater severity of symptoms. The ranges of anchor-based estimates of minimal important differences (MID) are 0.3-0.5 for N-GSSIQ total scores; 0.4-0.6 for Nocturnal Symptoms; 0.1-0.4 for Morning Impact; and 0.1-0.4 for Concern subscales.
- Outcome Measures: Heartburn-free nights, N-GSSIQ total score and subscales.

## Results

**Table 1.** Selected Baseline Characteristics of Treatment Groups in Placebo-Controlled Period

| | Placebo (N=258) | Vonoprazan 10mg (N=257) | Vonoprazan 20mg (N=257) |
|---|---|---|---|
| Age, mean (SD) years | 51.5 (14.7) | 51.0 (14.0) | 50.4 (14.4) |
| Female sex (%) | 179 (69.4) | 182 (70.8) | 166 (64.6) |
| Race | | | |
| White (%) | 205 (79.5) | 186 (72.4) | 185 (72.0) |
| Black (%) | 33 (12.8) | 38 (14.8) | 52 (20.2) |
| Asian (%) | 12 (4.7) | 22 (8.6) | 11 (4.3) |
| Other/unknown (%) | 8 (3.1) | 11 (4.3) | 9 (3.5) |
| Latin ethnicity (%) | 77 (29.8) | 87 (33.9) | 80 (31.1) |
| BMI, mean (SD) Kg/m$^2$ | 30.4 (6.9) | 30.5 (6.5) | 29.9 (6.7) |
| Current smoker (%) | 35 (13.6) | 29 (11.3) | 34 (13.2) |
| Any alcohol use (%) | 133 (51.6) | 136 (52.9) | 135 (52.5) |
| Prior proton pump inhibitor use (%) | 164 (63.6) | 182 (70.8) | 162 (63.0) |
| Mean (SD) nighttime heartburn severity score (0-4)[a] | 1.3 (0.9) | 1.3 (0.9) | 1.3 (0.9) |
| Days without heartburn symptoms (%), mean (SD) | 11.9 (15.8) | 11.4 (17.6) | 13.6 (17.3) |
| Days without nighttime heartburn (%), mean (SD) | 29.6 (27.0) | 25.8 (27.4) | 31.1 (28.3) |

[a] Baseline heartburn severity based on diary entries from the 7 days before randomization

## Results

**Figure 1.** N-GSSIQ: LS Mean Change From Baseline Scores at Week 4 in the Placebo-Controlled Period

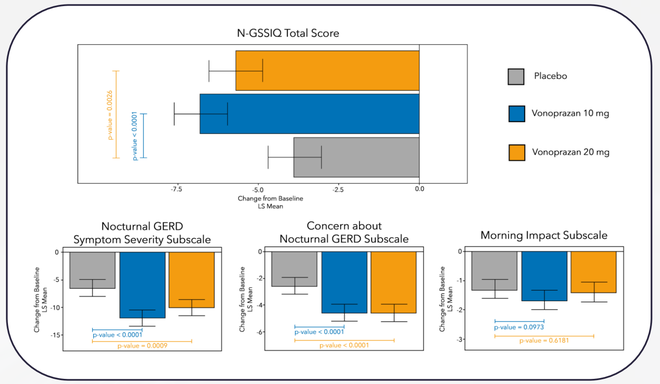


**Figure 2.** Percentage of Subjects with Heartburn-Free Nights on Each Day of the Last Week of the Screening and Placebo-Controlled Period.

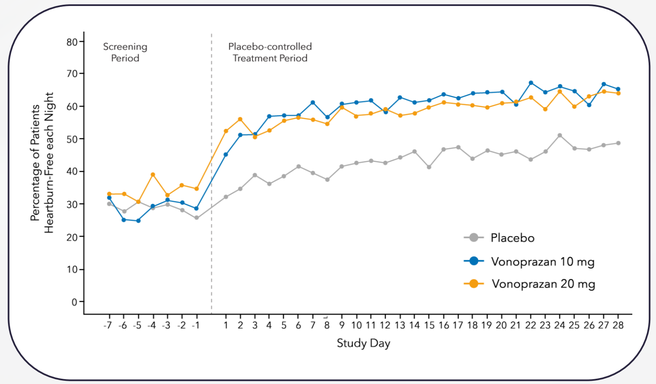


**Table 2.** Heartburn-Free Nights (%) During Placebo-Controlled Period, Intent-to-Treat Set

| | Placebo (N=258) | Vonoprazan 10mg (N=257) | Vonoprazan 20mg (N=257) |
|---|---|---|---|
| LS Mean (SE)[a] | **43.3 (1.9)** | **59.9 (1.9)** | **56.4 (1.9)** |
| Median (Q1, Q3) | 45.5 (8.0, 71.4) | 70.4 (25.0, 92.3) | 71.0 (13.8, 92.9) |
| LS Mean Difference vs Placebo (SE)[a] | - | 16.5 (2.6) | 13.1 (2.7) |
| P-value vs Placebo[a] | - | <0.0001 | <0.0001 |

[a] LS Mean and SE obtained from a general linear model with treatment group as a factor and severity and frequency of heartburn during the last seven nights of the screening period as covariates.

**Key Results:**

- Total N-GSSIQ Score at week 4, LS mean change from baseline: -3.9 (placebo), -6.8 (vonoprazan 10mg), -5.7 (vonoprazan 20mg). (Figure 1)
- N-GSSIQ Score at week 4, LS mean change from baseline compared to placebo:
  - Total score: -2.9 (vonoprazan 10mg, p<0.0001), -1.8 (vonoprazan 20mg, p=0.0026).
  - Nocturnal GERD Severity Sub-score: -5.4 (vonoprazan 10mg, p<0.0001), -3.5 (vonoprazan 20mg, p=0.0009).
  - Concern about Nocturnal GERD Sub-score: -2 (vonoprazan 10mg, p<0.0001), -2 (vonoprazan 20mg, p<0.0001).
  - Morning Impact Sub-score: -0.4 (vonoprazan 10mg, p=0.0973), -0.1 (vonoprazan 20mg, p=0.6181).
- The effect on heartburn-free nights remained positive during each day of the placebo-controlled trial. (Figure 2)
- LS Mean % heartburn-free nights at week 4: 43.3% (placebo), 59.9% (vonoprazan 10mg), 56.4% (vonoprazan 20mg). (Table 2)

## Conclusions

- **Analysis suggests that treatment with vonoprazan leads to a meaningful reduction in nighttime heartburn symptoms in patients with NERD.**
- **Treatment with vonoprazan resulted in a reduction in nocturnal symptoms severity and patient's concern about nocturnal GERD as evidenced by the N-GSSIQ total score and subscales.**
- **The effect on heartburn-free nights was noticeable from the initiation of therapy and sustained over the entire 4-week treatment period.**

## Disclosures

CA: consultant for Phathom Pharmaceuticals; GG: consultant for Phathom Pharmaceuticals; PK: consultant for Phathom Pharmaceuticals and Sebella; RY: advisory committee for RJS Mediagnostix, consultant for Braintree Pharmaceuticals, Phathom Pharmaceuticals, Reckitt Beckiser Healthcare Ltd, Medtronic, StatLinkMD, research support from Ironwood Pharmaceuticals: EL, TH, and HG are employees of Phathom Pharmaceuticals; LL: consultant for Phathom Pharmaceuticals.

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**Reference:** [1]Spiegal BM et al. The development and validation of a nocturnal gastro-esophageal reflux disease symptom severity and impact questionnaire for adults. *Aliment Pharmacol Ther*. 2010. 32(4):591-602. doi: 10.1111/j.1365-2036.2010.04385.x.