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Randomised clinical trial: Efficacy and safety of on-demand vonoprazan versus placebo for non-erosive reflux disease

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Summary

Background: Non-erosive reflux disease (NERD) symptoms are often episodic, making on-demand treatment an attractive treatment approach.

Aims: We compared the efficacy and safety of on-demand vonoprazan versus placebo in patients with NERD.

Methods: Patients with NERD, defined as heartburn for ≥6 months and for ≥4/7 consecutive days with normal endoscopy, received once-daily vonoprazan 20 mg during a 4-week run-in period. Patients without heartburn during the last 7 days and with ≥80% study drug and diary compliance were randomised 1:1:1:1 to vonoprazan 10, 20, 40 mg or placebo on-demand for 6 weeks. The primary endpoint was the percentage of evaluable heartburn episodes completely relieved within 3 h of on-demand dosing and sustained for 24 h.

Results: Of 458 patients in the run-in period, 207 entered the on-demand period. In the vonoprazan 10 mg group, 56.0% (201/359) of evaluable heartburn episodes met the criteria for complete and sustained relief; 60.6% (198/327) in the 20 mg group; and 70.0% (226/323) in the 40 mg group, compared with 27.3% (101/370) in the placebo group ($p < 0.0001$ versus placebo for each vonoprazan group). By 1 h post-dose, vonoprazan was associated with complete relief of significantly more heartburn episodes compared with placebo. No serious treatment-emergent adverse events were reported.

Conclusion: On-demand vonoprazan may be a potential alternative to continued daily acid suppression therapy for the relief of episodic heartburn in patients with NERD. Clinicaltrials.gov: NCT04799158.

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1 | INTRODUCTION

Non-erosive reflux disease (NERD), also known as symptomatic non-erosive gastro-oesophageal reflux disease (GERD), is characterised by episodic heartburn symptoms related to acid refluxate without endoscopically detectable damage to the oesophageal mucosa.[1,2] NERD affects 50%–70% of patients presenting with GERD-related symptoms and, as a chronic condition with recurring symptom episodes, it can have a profound effect on patients' well-being.[1,2] Patients with NERD have reported worse quality of life than those with erosive oesophagitis or Barrett's oesophagus, which may be related to limited response to anti-reflux treatment.[3] Pain and discomfort caused by heartburn episodes may limit participation in physical and social activities, and may negatively impact patients' sleep quality, leading to fatigue that further limits participation in daily activities.[4,5]

On-demand (i.e., as needed) treatment is an approach in which patients take medication only when symptoms occur.[6] Studies have demonstrated that patients favour on-demand treatment of GERD because of its convenience, the ability to exercise control over their treatment, reduced concerns about adverse effects of chronic medical therapy and lower costs.[7–10] On-demand treatment is particularly attractive for the management of NERD because, although episodic symptoms are common, there is minimal concern for progression to more severe and erosive forms of GERD.[1,7] Although proton pump inhibitors (PPIs) are approved by the United States Food and Drug Administration for continuous, once-daily use for the treatment of acid disorders, including NERD,[11,12] they are not approved for on-demand therapy. Furthermore, the pharmacokinetic and pharmacodynamic characteristics of PPIs limit their effectiveness for on-demand use because maximal acid suppression is generally not achieved until 3–5 days after starting PPI therapy.[13] Accordingly, the 2022 American College of Gastroenterology clinical guidelines highlight the fact that the evidence for on-demand PPI use is of low quality.[14] Thus, there is an unmet need for novel treatment options for NERD that can alleviate symptoms with on-demand use at the lowest effective dose.[7]

Vonoprazan, a potassium-competitive acid blocker (P-CAB), has been shown to provide greater and more prolonged acid suppression than PPIs in addition to a rapid onset of action.[15–17] The pharmacokinetic and pharmacodynamic properties of P-CABs such as vonoprazan suggest that they are very promising candidates for on-demand treatment of NERD.[13] Vonoprazan has previously been investigated in Asia, Europe and the United States for the healing and maintenance of healing in erosive oesophagitis and, in combination with antibiotics, for the eradication of *Helicobacter pylori* infection.[18–22]

The objective of the present double-blind, placebo-controlled trial was to evaluate the time to response and the duration of response to several doses of on-demand vonoprazan in patients with NERD who demonstrated complete symptom resolution as assessed during the last week of a 4-week course of daily vonoprazan therapy.

2 | MATERIALS AND METHODS

2.1 | Trial conduct and oversight

This was a randomised, placebo-controlled trial conducted at 54 study sites in the United States (NCT04799158). The institutional review board/independent ethics committee at each study location reviewed and approved the study protocol before the start of the study. The study was also performed in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided written informed consent before study entry. Data were collected by the investigators, analysed by statisticians funded by the sponsor and interpreted by the authors. All authors had access to the study data, and each author reviewed and approved the final manuscript.

2.2 | Study design and interventions

During the screening period (which lasted up to 5 weeks), patients underwent assessments to determine study eligibility, including high-definition white-light endoscopy to confirm the absence of erosive oesophagitis. Patients completed an electronic diary to record the presence and severity of heartburn symptoms, as well as their use of a study-supplied antacid as a symptomatic rescue medication. In addition, patients were instructed to refrain from extreme dietary changes, excessive alcohol consumption, excessive exercise and blood donation for the duration of the study.

During a 4-week open-label run-in period, all patients received 20 mg of oral vonoprazan daily. Subsequently, eligible patients (defined in Subsection 2.3 of Section 2) were randomised 1:1:1:1 to receive vonoprazan 10, 20, 40 mg or placebo in the 6-week on-demand period (Figure 1). The randomisation schedule was generated using SAS software Version 9.4, and an interactive response technology system was used to link sequential patient randomisation numbers to treatment codes. During the on-demand period, study drug was only taken in response to the onset of a heartburn episode, with only one dose allowed per 24-h period. There was a safety follow-up period lasting for 1 week after the 6-week on-demand period. During the screening, run-in, on-demand and safety follow-up periods, patients were provided with Gelusil® (WellSpring Pharmaceutical Corporation) as a rescue antacid. During the on-demand period, patients could take a rescue antacid starting no less than 3 h after study drug administration.

2.3 | Patients

Patients eligible for entry into the run-in period were at least 18 years old with a history of heartburn episodes for 6 months or longer at a frequency of at least 4 days of heartburn during any

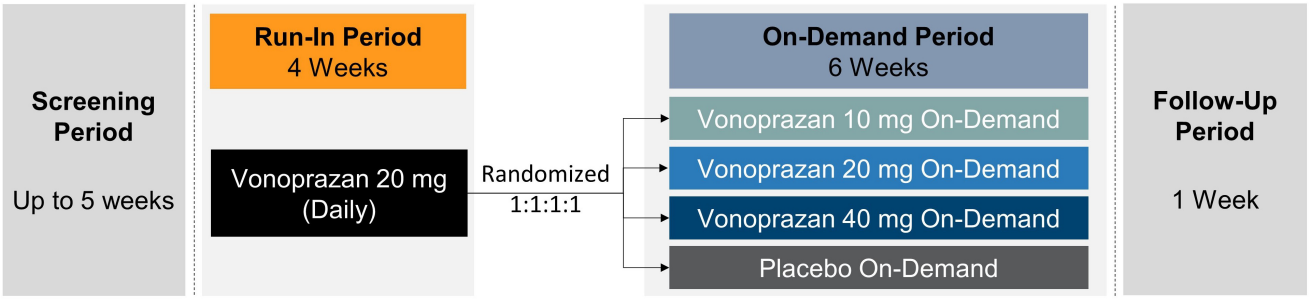

FIGURE 1 Study design. During the screening period, patients underwent assessment for entrance criteria, including endoscopy to rule out erosive oesophagitis. Following the run-in period, patients were eligible for the randomised on-demand period if they had at least 80% compliance with study drug and electronic-diary requirements and reported no heartburn within the last 7 days of the run-in period.

seven consecutive days of the screening period. Patients underwent endoscopic evaluation (performed any time during the screening period after the patient had fulfilled all other eligibility criteria) and were excluded if erosive oesophagitis (any grade by Los Angeles classification), Barrett's oesophagus (>1 cm of columnar-lined oesophagus) or any other mucosal abnormalities were present in the oesophagus. Rome IV Criteria were used to identify patients with functional heartburn and functional dyspepsia for exclusion.[23] However, reflux monitoring was not performed, as current consensus definitions of NERD do not require reflux testing for diagnosis.[2,24] Without reflux monitoring, it is possible that some patients with functional heartburn or functional dyspepsia were not excluded.

Patients with any other condition affecting the oesophagus (eosinophilic oesophagitis, oesophageal varices, oesophageal stricture, viral or fungal infection, history of caustic or physiochemical trauma, history of radiation therapy to the oesophagus) were also excluded. Patients who completed the run-in period with at least 80% compliance with study drug and electronic diary requirements and who reported no heartburn during the last 7 days of the run-in period were eligible for entry into the on-demand period. For full inclusion and exclusion criteria, please see Appendix S1.

2.4 | Study assessments

Patients were given an electronic diary on the first day of the screening period. During the screening, run-in and safety follow-up periods, patients recorded the presence and severity of heartburn symptoms twice daily (daytime and night-time), as well as any antacid use. Heartburn severity was rated as mild, moderate, severe or very severe, depending on its duration and impact on daily routine or sleep. Mild heartburn was defined as occasional heartburn that could be ignored and did not influence daily routine or sleep. Moderate heartburn was defined as heartburn that could not be ignored and/or occasionally influenced daily routine or sleep. Severe heartburn was defined as heartburn that was present most of the day and/or regularly influenced daily routine or sleep. Very severe heartburn was defined as heartburn that was constant and/or markedly influenced daily routine or sleep.

During the on-demand period, patients documented heartburn episodes and the use of study medication as they occurred. When a heartburn episode was recorded, patients were prompted to take the study drug. Then, the diary assessed symptoms at 0.5, 1, 1.5, 2 and 3 h after the study drug was taken to determine the timing of symptom relief. Patients were instructed not to take additional study drug for 24 h. Patients also continued recording rescue antacid use, including the time and number of tablets taken. On days when patients had not yet reported an episode of heartburn, they received reminders in the morning and evening to either record any unrecorded heartburn episodes (no earlier than the previous day) or to document that they had not had any heartburn episodes.

Safety assessments included physical and laboratory examinations and vital sign monitoring. Treatment-emergent adverse events (TEAEs) were recorded as any adverse event (AE) that occurred, or any event present at baseline that worsened, after the first dose of study drug. The severity of AEs was classified as mild, moderate or severe.

2.5 | Clinical endpoints

The primary efficacy endpoint was the percentage of evaluable heartburn episodes completely relieved within 3 h and with no further heartburn for 24 h after study drug use. An evaluable episode was defined as an episode for which study drug was taken and at least one entry in the heartburn episode diary was completed. To meet the definition of 'completely relieved', patients could not have taken rescue antacid within 3 h of taking study drug.

Secondary endpoints included the percentage of evaluable heartburn episodes completely relieved within 3 h of taking study drug without the requirement for 24 h of relief; the percentage of evaluable heartburn episodes per patient completely relieved within 3 h and sustained for 24 h; the mean number of tablets of rescue antacid taken per day in the on-demand period; the percentage of patients with complete relief of heartburn within 3 h after the first evaluable episode and with no further heartburn

reported for 24 h after taking study drug; the percentage of days study drug was taken during the on-demand period; and the percentage of 24-h heartburn-free days during the on-demand period. Pre-defined exploratory endpoints included the percentage of evaluable episodes completely relieved within 0.5, 1, 1.5 or 2 h with no further heartburn reported for 24 h after taking study drug.

The safety endpoints included AEs, laboratory test values (haematology, serum chemistry, urinalysis, serum gastrin and pepsinogen I/II levels), electrocardiograms and vital signs.

2.6 | Statistical analysis

The sample size for the on-demand period was calculated based on the assumption that each patient would experience at least four evaluable heartburn episodes and that there would be a clinically relevant and absolute difference of 15% between each vonoprazan dose and placebo for the primary endpoint; the comparison between each vonoprazan dose and placebo was performed using Fisher's exact test. A sample size of 200 heartburn episodes (50 patients with at least four heartburn episodes each) per treatment group was calculated to provide at least 80% statistical power at the significance level of 0.05. Assuming 60% of patients at the end of the run-in period would not meet the eligibility criteria for the on-demand period, it was determined that approximately 500 patients would be needed for the run-in period with final enrolment dependent on the actual rate of eligible patients entering the on-demand period to achieve the target of 200 patients.

Efficacy analyses were performed in the on-demand intent-to-treat (ITT) set, which included all patients in the safety run-in set who were randomised and completed at least one heartburn episode diary during the on-demand period. Safety analyses were performed in the safety on-demand set, which included all patients in the safety run-in set who were randomised and treated at least one heartburn episode with randomised treatment during the on-demand period. The primary endpoint was assessed by comparing each vonoprazan dose with placebo using Fisher's exact test.

The secondary endpoints were also assessed by comparison of each vonoprazan dose with placebo, using either Fisher's exact test (the percentage of evaluable heartburn episodes completely relieved within 3 h of taking study drug, and the percentage of patients with complete relief of the first heartburn episode within 3 h of taking study drug with no further heartburn reported for 24 h) or a Wilcoxon rank-sum test (all other endpoints).

An exploratory analysis of the primary endpoint using a generalised linear model with the generalised estimating equation method was also performed for this correlated binary data. Results were presented for the odds ratio (back-transformed log-odds) for the comparisons between each dose of vonoprazan and placebo along with the associated 95% CI and two-sided *p*-value.

No correction for multiplicity was done for this Phase 2 study. All statistical analyses were performed using SAS software version 9.4.

3 | RESULTS

3.1 | Patient disposition and baseline characteristics

Of the 1115 patients screened for the study, 458 (41.1%) were enrolled into the run-in period. The majority of screen failures (578/657; 88%) were due to not meeting the entrance criteria (Figure 2). Of the 458 patients enrolled, 251 (54.8%) were considered run-in failures. The most frequent reason for run-in failure was not meeting on-demand eligibility criteria (226/458; 49.3%). The two most common reasons for not meeting eligibility criteria were not completing at least 80% of diary entries (125/458; 27.3%) and the presence of heartburn episodes within the last 7 days of the run-in period (116/458; 25.3%). One patient did not receive any study drug during the run-in period and therefore was not included in the analyses.

Subsequently, 207 patients were randomised into the on-demand period; all but seven completed the study, and all were included in efficacy analyses. There were also 14 patients (three in each vonoprazan group and five in the placebo group) who did not take any dose of the study drug and were not included in the on-demand safety analysis. The four treatment arms in the on-demand period had similar numbers of evaluable heartburn episodes: 359 in the vonoprazan 10 mg group ($n = 52$), 327 in the vonoprazan 20 mg group ($n = 52$), 323 in the vonoprazan 40 mg group ($n = 51$) and 370 in the placebo group ($n = 52$).

Patients entering the study (run-in period) were mostly female (296/457; 64.8%), white (310/457; 67.8%) and had a mean age of 52.0 years (Table 1). The mean body mass index was 30.4 kg/m^2. Most patients (410/457; 89.7%) had a baseline serum gastrin level of <200 pg/mL. Most patients (142/207; 68.6%) had a history of treatment with at least 1 PPI, and the majority of those patients (92/142; 64.8%) had experienced symptom relief with a PPI. The mean severity of daytime or night-time heartburn in the last 7 days before the run-in period was moderate in 214/457 (46.8%), severe in 108/457 (23.6%) and mild in 100/457 (21.9%) of patients. In the last 7 days before the run-in period, the majority of patients had heartburn for 6–7 days (292/457; 63.9%), and patients took an average of 3.2 antacid tablets per day. Baseline disease characteristics and demographics were similar between the group entering the run-in period and patients who qualified for the on-demand period. Characteristics and demographics were generally similar between treatment groups in the on-demand period.

3.2 | Primary endpoint

In all three vonoprazan groups, significantly more evaluable heartburn episodes were completely relieved within 3 h with sustained relief for 24 h compared with placebo (vonoprazan 10 mg 201/359 [56.0%]; 20 mg 198/327 [60.6%]; 40 mg 226/323 [70.0%]; vs. placebo 101/370 [27.3%], $p < 0.0001$ for all comparisons; Figure 3).

In an additional analysis using a model that accounted for the correlation between episodes from the same patient, the odds ratios

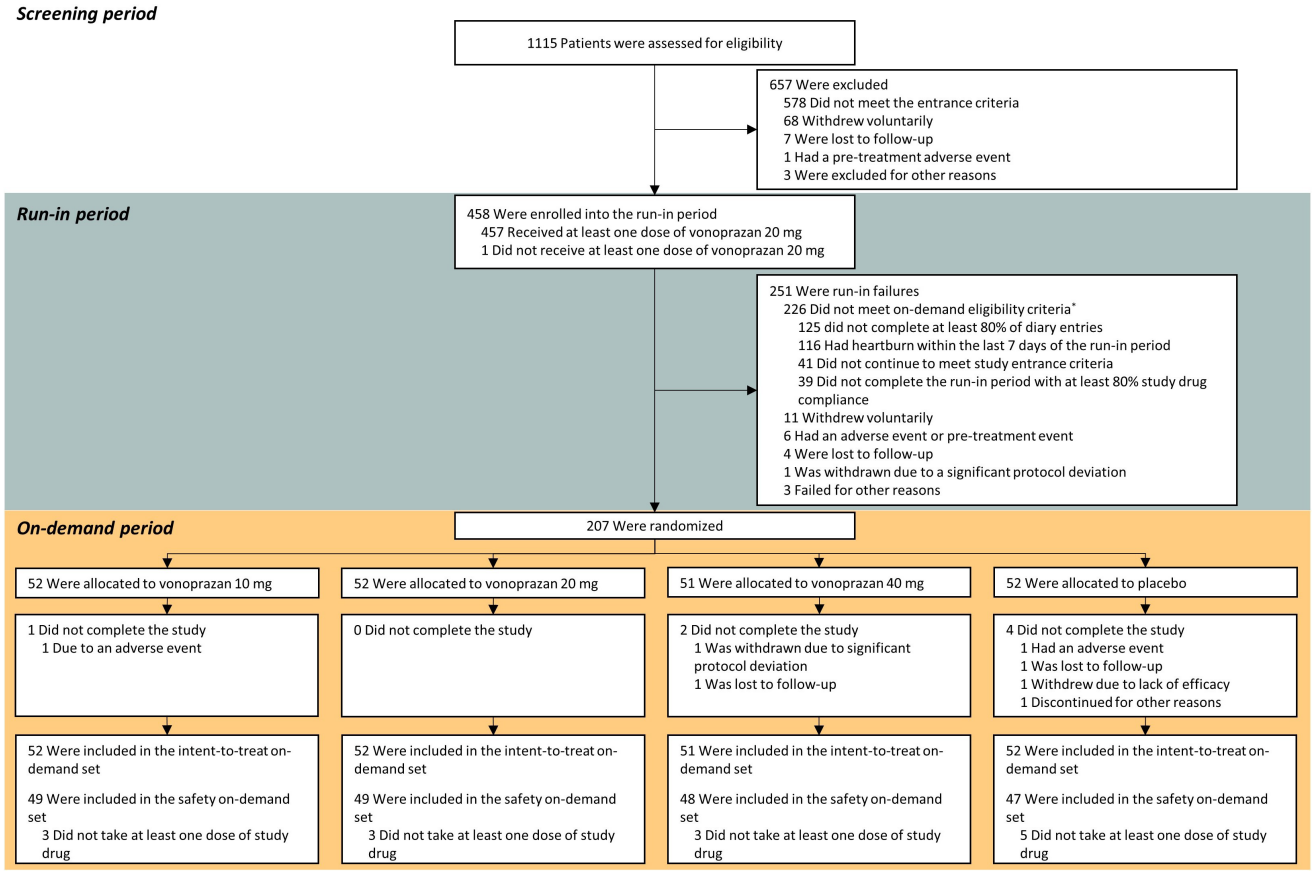

FIGURE 2 Patient flow diagram. 1115 patients were screened, and 458 were eligible and enrolled into the run-in period (one did not receive a study drug dose during this period and was excluded from analysis). Two hundred and seven patients were subsequently randomised to on-demand treatment. *Patients might have not met more than one criterion.

(95% CI; *p*-value) of achieving complete and sustained relief in all three vonoprazan groups compared with placebo were 1.9 (1.00–3.62; $p=0.0517$), 2.2 (1.14–4.15; $p=0.0189$) and 3.2 (1.73–5.92; $p=0.0002$) for the 10, 20 and 40 mg doses, respectively.

Furthermore, an exploratory analysis showed that there were significantly more heartburn episodes with complete and sustained relief compared with placebo by the 1-h post-dose timepoint in all vonoprazan treatment arms (Figure 3): 101/359 [28.1%] for vonoprazan 10 mg (95% CI: 10.54–21.94; $p<0.0001$); 63/327 [19.3%] for 20 mg (95% CI: 1.98–12.77; $p=0.0083$); and 74/323 [22.9%] for 40 mg (95% CI: 5.37–16.66; $p=0.0002$); *p*-values provided are in comparison with placebo 44/370 [11.9%].

3.3 | Secondary endpoints

Complete relief of heartburn episodes within 3 h without the additional requirement of sustained relief was also assessed. Significantly more evaluable heartburn episodes were completely relieved within 3 h in all vonoprazan groups compared with placebo (Figure 4): 259/359 [72.1%] for vonoprazan 10 mg; 215/327 [65.7%] for vonoprazan 20 mg; and 257/323 [79.6%] for vonoprazan 40 mg; $p<0.0001$ vs. placebo 155/370 [41.9%] for all vonoprazan doses. Within 1 h of study drug administration, significantly more heartburn episodes were completely relieved (without the additional requirement of sustained relief) with vonoprazan 10 mg (129/359; 35.9%) and vonoprazan 40 mg (86/323; 26.6%) compared with placebo (67/370; 18.1%; $p<0.0001$ and $p<0.01$ for vonoprazan dose vs. placebo comparisons, respectively). At 1 h post drug administration, 22.0% (72/327) of heartburn episodes in patients who took vonoprazan 20 mg had achieved complete relief compared with placebo (67/370; 18.1%); $p>0.05$ versus placebo. In the vonoprazan 20 mg group, significance was achieved by 1.5 h post administration (115/327 [35.2%] vs. 101/370 [27.3%]; $p<0.05$ versus placebo).

The mean (standard deviation, SD) percentage of evaluable episodes per patient that were relieved within 3 h and sustained for 24 h was 60.1% (38.5%) for vonoprazan 10 mg, 60.8% (37.5%) for vonoprazan 20 mg and 72.0% (28.9%) for vonoprazan 40 mg compared with 47.8% (41.0%) for placebo (vonoprazan 40 mg vs. placebo $p<0.01$; $p>0.05$ for all other comparisons) (Appendix S2). The median percentage of evaluable episodes per patient that were relieved was 69.7%, 68.3% and 75.0% for the vonoprazan groups (10, 20 and 40 mg, respectively) and 50.0% for placebo. When only the first evaluable heartburn episode during the on-demand period was assessed, the percentage of patients who experienced

TABLE 1 Baseline characteristics and demographics.

	Run-in period	On-demand period			
	Vonoprazan 20 mg (*n* = 457)	Vonoprazan 10 mg QD (*n* = 52)	Vonoprazan 20 mg QD (*n* = 52)	Vonoprazan 40 mg QD (*n* = 51)	Placebo (*n* = 52)
Age, mean (SD), years	52.0 (14.4)	53.8 (11.6)	55.1 (13.0)	52.5 (14.6)	53.1 (15.2)
Sex, *n* (%)					
Male	161 (35.2)	24 (46.2)	17 (32.7)	24 (47.1)	17 (32.7)
Female	296 (64.8)	28 (53.8)	35 (67.3)	27 (52.9)	35 (67.3)
Race, *n* (%)					
White	310 (67.8)	34 (65.4)	38 (73.1)	42 (82.4)	31 (59.6)
Black or African American	85 (18.6)	8 (15.4)	6 (11.5)	6 (11.8)	13 (25.0)
Asian	46 (10.1)	8 (15.4)	6 (11.5)	3 (5.9)	7 (13.5)
American Indian or Alaska Native	2 (0.4)	0	1 (1.9)	0	0
Native Hawaiian or other Pacific Islander	1 (0.2)	0	0	0	0
Other	6 (1.3)	0	0	0	0
Unknown	7 (1.5)	2 (3.8)	1 (1.9)	0	1 (1.9)
Ethnicity					
Latinx	146 (31.9)	18 (34.6)	19 (36.5)	16 (31.4)	14 (26.9)
Not Latinx	307 (67.2)	34 (65.4)	33 (63.5)	35 (98.9)	38 (73.1)
Unknown	4 (0.9)	0	0	0	0
BMI, mean (SD), kg/m^2	30.4 (6.7)	29.3 (7.9)	31.1 (7.3)	31.5 (6.7)	32.0 (7.6)
Serum gastrin (pg/mL), *n* (%)					
<200	410 (89.7)	49 (94.2)	46 (88.5)	45 (88.2)	48 (92.3)
≥200	28 (6.1)	2 (2.8)	5 (9.6)	3 (5.9)	3 (5.8)
Missing	19 (4.2)	1 (1.9)	1 (1.9)	3 (5.9)	1 (1.9)
Pepsinogen I/II ratio, *n* (%)					
≤2	3 (0.7)	0	1 (1.9)	0	0
>2–≤3	7 (1.5)	0	0	2 (3.9)	0
>3	430 (94.1)	52 (100)	50 (96.2)	46 (90.2)	50 (96.2)
Missing	17 (3.7)	0	1 (1.9)	3 (5.9)	2 (3.8)
Severity of daytime or night-time heartburn, mean (SD)	1.78 (0.743)	1.49 (0.786)	1.81 (0.697)	1.66 (0.748)	1.68 (0.749)
Severity of daytime heartburn, mean (SD)	1.59 (0.826)	1.30 (0.805)	1.57 (0.751)	1.37 (0.749)	1.46 (0.788)
Severity of night-time heartburn, mean (SD)	1.25 (0.847)	1.14 (0.847)	1.41 (0.844)	1.26 (0.854)	1.27 (0.847)
Number of days with the use of rescue antacid					
≥0–≤3	159 (34.8)	17 (32.7)	18 (34.6)	15 (29.4)	17 (32.7)
>3–≤5	98 (21.4)	15 (28.8)	6 (11.5)	17 (33.3)	15 (28.8)
>5–≤7	200 (43.8)	20 (38.5)	28 (53.8)	19 (37.3)	20 (38.5)
Number of rescue antacid tablets taken per day, mean (SD)	3.2 (4.04)	2.5 (2.0)	3.4 (3.0)	3.5 (5.0)	2.7 (2.1)

Note: Baseline characteristics and demographics were similar among patients in the safety run-in set and the ITT on-demand set.

Abbreviations: BMI, body mass index; ITT, intention-to-treat; QD, once daily; SD, standard deviation.

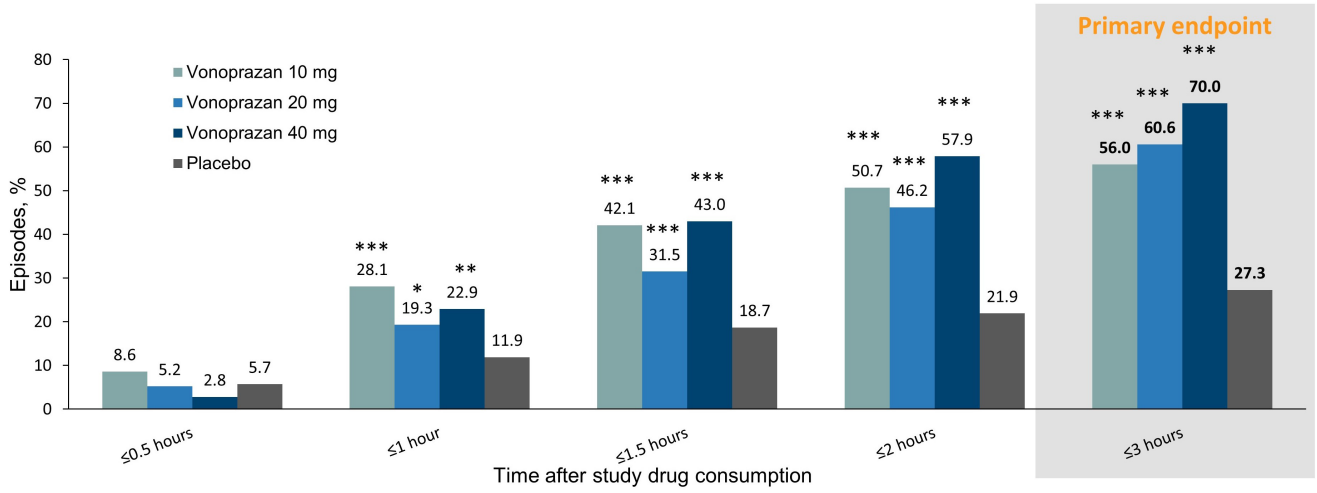

FIGURE 3 Percentage of evaluable episodes relieved within 3 h and with no further heartburn reported for 24 h. In all three vonoprazan groups, significantly more evaluable heartburn episodes were completely relieved within 3 h with sustained relief for 24 h compared with placebo. $^{*}p < 0.01$, $^{**}p < 0.001$, $^{***}p < 0.0001$ compared with placebo.

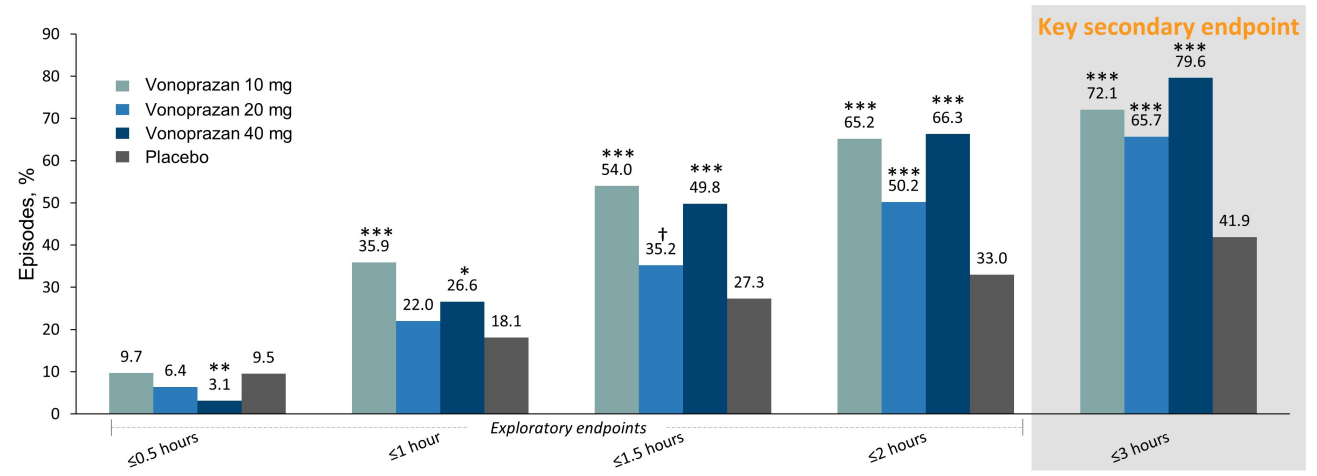

FIGURE 4 Percentage of evaluable episodes relieved within 3 h. Significantly more evaluable heartburn episodes were completely relieved within 3 h at all vonoprazan doses compared with placebo. $\dagger p < 0.05$, $^{*}p < 0.01$, $^{***}p < 0.0001$ compared with placebo.

complete relief that was sustained for 24 h was similar between treatment groups (vonoprazan 10 mg 26/46 [56.5%], vonoprazan 20 mg 26/42 [61.9%] and vonoprazan 40 mg 27/43 [62.8%] vs. placebo 26/43 [60.5%]; $p > 0.05$ for all vonoprazan doses vs. placebo) (Appendix S3).

The mean (SD) percentage of days that study drug was taken did not differ between groups (Appendix S4): 22.0 (19.2) for vonoprazan 10 mg, 20.8 (17.0) for 20 mg and 21.0 (17.3) for 40 mg versus 22.2 (23.3) for placebo. The median percentage of days that study drug was taken was 16.7, 16.1 and 16.3 for the vonoprazan 10, 20 and 40 mg groups, respectively, and 12.8 for the placebo group. Similarly, the mean (SD) percentage of heartburn-free days was not different in each of the vonoprazan groups compared with the placebo group (Appendix S4): 75.0 (21.4) for vonoprazan 10 mg, 73.6 (21.5) for vonoprazan 20 mg and 74.0 (22.3) for vonoprazan 40 mg versus 71.2 (29.0) for placebo. The median percentage of heartburn-free days was 80.7, 78.6 and 81.0 for the vonoprazan 10, 20 and 40 mg groups, respectively, and 80.1 for the placebo group. The mean (SD) number of rescue antacid tablets taken per day was numerically higher in the placebo group than in the vonoprazan groups (Appendix S5); however, this difference did not reach statistical significance (vonoprazan 10 mg 0.1 [0.2], 20 mg 0.2 [0.3] and 40 mg 0.1 [0.3] vs. placebo 0.5 [0.9]). The median number of rescue antacid tablets taken per day in the vonoprazan 10, 20 and 40 mg groups was 0.03, 0.05 and 0, respectively, versus 0.04 for placebo. The mean number of rescue antacid tablets taken per day was reduced during the on-demand period compared with the screening period across all study arms. However, only one patient in each vonoprazan dose arm, compared with eight patients in the placebo arm, required an average of ≥1 rescue antacid per day during the on-demand period.

3.4 | Open-label run-in treatment period

The mean (SD) percentage of 24-h heartburn-free days during the run-in period (where patients received vonoprazan 20 mg once daily) was 65.4% (32.4%), and the median was 76.0% (Appendix S6). The mean severity of heartburn was 0.47 (0.64), with similar mean severity for daytime (0.49 [0.67]) and night-time (0.44 [0.64]) heartburn. The mean (SD) percentage of days without rescue antacid use was 78.7% (26.7%), and the mean (SD) number of rescue antacid tablets taken per day was 0.70 (2.53).

At the end of the run-in period, 77.6% of patients rated their overall heartburn symptoms as much better, 16.0% as a little improved, 4.6% as unchanged, 1.0% as a little worse and 0.8% as much worse (based on patient-impression question). During the last week of the run-in period, 64.6% of patients had no heartburn symptoms, while 23.4% had mild heartburn, 9.4% had moderate heartburn, 2.0% had severe heartburn and 0.5% had very severe heartburn (based on patient-impression question). During the last 7 days of the run-in period, 69.1% of patients did not have heartburn.

3.5 | Safety

In the run-in period, when vonoprazan 20 mg was given once daily, 13.1% (60/457) of patients reported ≥1 TEAEs. In total, 16/457 (3.5%) reported ≥1 TEAEs that were considered to have been related to the study drug, including one serious TEAE of anaphylaxis that occurred within a couple of hours of the first vonoprazan dose during the run-in period. The most common TEAEs (>1% of patients) were diarrhoea (1.5%), abdominal distension (1.3%) and nausea (1.3%) (Table 2). In the on-demand period, 10/47 (21.3%) of patients administered placebo reported a TEAE compared with 8/49 (16.3%), 9/49 (18.4%) and 8/48 (16.7%) receiving vonoprazan 10, 20 and 40 mg, respectively. No individual TEAE was reported by >1 patient per group, and no serious TEAEs were reported. One patient (vonoprazan 10 mg) reported non-serious TEAEs of abdominal pain and nausea, which were considered to have been related to the study drug.

The mean baseline serum gastrin level was 54.2 pg/mL (SD: 136.5 pg/mL and median: 19.5 pg/mL). The mean baseline serum pepsinogen I and pepsinogen II levels were 87.4 μg/L (SD: 60.2 μg/L and median: 72.5 μg/L) and 7.9 μg/L (SD: 6.2 μg/L and median: 6.0 μg/L), respectively. At the end of the 4-week run-in period, the mean serum gastrin level was 193.6 pg/mL (SD: 203.4 pg/mL and median: 128.5 pg/mL). The mean serum pepsinogen I and pepsinogen II levels at the end of the run-in period were 254.9 μg/L (SD: 131.8 μg/L and median: 269.0 μg/L) and 32.5 μg/mL (SD: 24.5 μg/L and median: 26.0 μg/L), respectively; the mean change in pepsinogen I/pepsinogen II was −3.02 (SD: 4.8 and median: −2.4). During the on-demand and follow-up periods, seven patients (one vonoprazan 10 mg, two vonoprazan 20 mg, three vonoprazan 40 mg and one placebo) had serum gastrin levels >500 pg/mL. Three of these seven patients (one vonoprazan 20 mg, one vonoprazan 40 mg and one placebo) had elevated serum gastrin levels at the run-in baseline and safety follow-up visit (Table 3).

4 | DISCUSSION

Because NERD (symptomatic non-erosive GERD) is a chronic, episodic condition, on-demand (as needed) treatment that rapidly relieves symptoms is an attractive alternative to daily maintenance therapy. In this study, on-demand treatment with vonoprazan achieved the primary endpoint: a significantly greater proportion of evaluable heartburn episodes completely relieved within 3 h of on-demand use, accompanied by sustained relief for 24 h, in all active treatment groups compared with placebo. The differences between vonoprazan and placebo were statistically significant within 1 h of on-demand use. Overall, vonoprazan was associated with a rate of heartburn relief at least two times greater than that of the placebo.

In the absence of a consensus definition of a standardised endpoint for on-demand trials in symptomatic GERD, various endpoints

TABLE 2 Safety during the run-in and on-demand periods.

	Run-in period	On-demand period			
n/N, (%)	Vonoprazan 20 mg	Vonoprazan 10 mg	Vonoprazan 20 mg	Vonoprazan 40 mg	Placebo
Any TEAE	60/457 (13.1)	8/49 (16.3)	9/49 (18.4)	8/48 (16.7)	10/47 (21.3)
Mild	23/457 (5.0)	6/49 (12.2)	5/49 (10.2)	2/48 (4.2)	6/47 (12.8)
Moderate	31/457 (6.8)	1/49 (2.0)	4/49 (8.2)	6/48 (12.5)	4/47 (8.5)
Severe	6/457 (1.3)	1/49 (2.0)	0	0	0
Any serious TEAE	4/457 (0.9)	0	0	0	0
Any study drug–related TEAE	16/457 (3.5)	1/49 (2.0)	0	0	0
Any TEAE leading to discontinuation of study	9/457 (2.0)	1/49 (1.0)	0	0	1/47 (2.1)
Any TEAE leading to death	0	0	0	0	0

Note: TEAEs were generally mild or moderate and safety was similar across treatment groups in the on-demand period.
Abbreviation: TEAE, treatment-emergent adverse event.

TABLE 3 Serum gastrin levels during the run-in and on-demand periods.

	Vonoprazan 10 mg	Vonoprazan 20 mg	Vonoprazan 40 mg	Placebo
Run-in period baseline, median (min, max), pg/mL	15.5 (10, 1855)	19.0 (10, 779)	18.0 (10, 789)	20.0 (10, 294)
On-demand period baseline, median (min, max), pg/mL	172.0 (10, 915)	169.0 (10, 1283)	124.0 (10, 651)	109.0 (12, 689)
End of on-demand period, median (min, max), pg/mL	23.0 (10, 747)	38.0 (10, 785)	43.5 (10, 808)	22.0 (10, 575)

Note: Median serum gastrin levels at the beginning of the on-demand period were elevated compared to the run-in period baseline (before 4 weeks of daily vonoprazan 20 mg therapy) but normalised by the end of the 6-week on-demand period.

related to the relief of heartburn were explored in addition to the primary endpoint. The analysis of the first heartburn episode suggests a carryover effect of the run-in period treatment as evidenced by a higher placebo response rate for the first evaluable heartburn episode compared with the placebo response rate across all evaluable episodes. Approximately 60% of patients in all four treatment groups experienced complete and sustained relief of the first evaluable heartburn episode in the on-demand period. Although the study was not powered for analysis at the patient level, numerical trends suggested that vonoprazan resulted in a 12%–24% increase in the percentage of heartburn episodes resolved per patient compared with placebo.

On-demand vonoprazan was also generally well-tolerated, with similar proportions of patients on each dose experiencing TEAEs. One serious TEAE of anaphylaxis related to vonoprazan was reported during the study; the patient developed symptoms a couple of hours after the first dose of vonoprazan 20 mg. Hypergastrinaemia is a potential consequence of acid suppression therapy. In this study, mean gastrin levels increased during the run-in period in all treatment groups but normalised by the end of the on-demand period.

The favourable efficacy and safety profile of on-demand vonoprazan for the treatment of NERD once symptom control is achieved with daily therapy is promising, as both patients and providers may have concerns regarding the risks of long-term, continuous acid suppression.[7,14] Observational studies have noted modest associations between long-term PPI therapy and a variety of conditions, including *Clostridium difficile* colitis, bone fractures and community-acquired pneumonia.[7] Although there is a lack of evidence to support a causal relationship between PPIs and these AEs, in a survey of 437 physicians, many believed that PPIs increased the risk of bone loss or fracture (88%), *C. difficile* infection (82%) and pneumonia (70%).[24] Because these concerns influence prescribing habits and may lead to premature PPI deprescribing, alternative therapies are worth considering.[25]

Additionally, current guidelines recommend using the lowest effective dose of PPIs and discontinuing daily therapy when disease control is achieved.[10,14,24] In the present study, patients received daily vonoprazan for 4 weeks before entering a 6-week on-demand period to simulate the clinical transitioning of patients from continuous to on-demand treatment after achieving disease control. However, with abrupt discontinuation of acid suppression therapy, there is a theoretical risk of rebound acid hypersecretion and increased reflux symptoms, which is the rationale for recommendations to taper PPI doses—an approach that may prolong the transition to on-demand use.[14] In the present study, there was no evidence of increased reflux symptoms or rebound acid hypersecretion after patients stopped daily treatment and entered the on-demand period.

While there are some prior studies of PPIs that have explored on-demand therapy, no published studies have evaluated the ability of PPIs to rapidly relieve acute heartburn episodes. PPI studies suggest that continuous therapy in NERD offers no benefit over on-demand therapy.[8,26,27] For example, one study found no significant differences in symptom relief between continuous and on-demand omeprazole in the last 7 weeks of a 24-week period of maintenance therapy.[26] Another study found on-demand treatment with esomeprazole to be non-inferior to continuous treatment as measured by the proportion of patients discontinuing because of dissatisfaction with treatment, with similar safety profiles.[27] However, a meta-analysis of studies comparing on-demand and daily PPIs found that patients with NERD and mild erosive oesophagitis were more likely to adhere to on-demand treatment.[8] Because previous studies of on-demand heartburn treatment used different outcome measures, they cannot readily be compared with the results of the present study. In addition, to the best of our knowledge, there are currently no studies that have examined on-demand P-CAB treatment of heartburn episodes. The present study adds to the body of evidence for the treatment of NERD by showing that vonoprazan is efficacious, rapidly relieving heartburn symptoms with on-demand dosing.

The experience of patients in this study further highlights the usefulness of on-demand (or as-needed) treatment. During the on-demand period, only a small proportion of patients (14/207; 6.8%) did not experience episodes of heartburn or require on-demand dosing. This suggests that a substantial number of patients with NERD may experience recurrence of heartburn episodes within 6 weeks of discontinuing daily acid suppression therapy (represented in this study by the run-in period). For those patients who did experience heartburn during the on-demand period, episodes were relatively infrequent compared with baseline, with no differences in episode frequency and therefore no differences in the number of doses of study drug administered between treatment groups. Overall, this supports the idea that on-demand dosing can be a viable approach to treatment after patients initially get their symptoms under control. However, the relatively short duration of this study precludes the assessment of long-term outcomes with on-demand vonoprazan, such as the duration and frequency of dosing over time. Because NERD is a chronic condition and acid suppression does not address its underlying causes, patients may require on-demand treatment

for extended periods. Further investigation would be required to assess both the efficacy and tolerability of on-demand vonoprazan for long-term users.

Capturing a representative population of patients with NERD is a challenge, as the clinical presentation overlaps with other acid-related and functional gastrointestinal disorders.[14,28] Therefore, a population of patients with NERD without ambulatory testing is considered heterogeneous as it likely includes patients with functional heartburn or reflux hypersensitivity.[14,29,30] This study was specifically designed to limit the inclusion of patients with functional heartburn and reflux hypersensitivity while recognising that reflux testing would have impeded recruitment and is often not performed in routine clinical practice. To reduce the likelihood of including patients with functional oesophageal disorders, we enrolled patients with heartburn as their predominant symptom, normal endoscopy and complete symptom resolution during the last 7 days of the run-in period before they could enter the on-demand period. Patients with functional heartburn are unlikely to demonstrate complete symptomatic response to daily treatment of vonoprazan. While reflux hypersensitivity patients do demonstrate response to anti-reflux treatment, their response is relatively limited; therefore it is unlikely that many patients with reflux hypersensitivity were included among the patients achieving complete symptom resolution during the run-in period. Therefore, it is expected that the number of patients with functional heartburn or reflux hypersensitivity in the on-demand period would have been very small and would have had very limited effect, if any, on the results of the study. This study design allows for inclusion in the on-demand period of a patient population representative of those with NERD and initial response to daily therapy in real-world clinical practice. In comparison, all pivotal trials using PPIs required only a normal endoscopy and the presence of heartburn to establish a diagnosis of NERD.[29]

While the on-demand period only included vonoprazan responders, this is likely representative of a majority of patients with NERD, not just a subset of the population. The rate of response to PPIs in patients with NERD is similar to that in patients with erosive oesophagitis.[31] As PPI trials in patients with erosive oesophagitis have reported that 72% to >80% of the patients achieved complete symptom resolution, we expected a similar response rate among our study population.[31–33]

A limitation of this study was that the number of patients in each group was relatively small, and that the study was powered to detect differences in the proportion of heartburn episodes relieved between the different treatment groups. Therefore, insights provided by secondary patient-level analyses were limited. Furthermore, this study did not account for non-evaluable heartburn episodes experienced by patients, which occurred when patients did not complete the timed assessments in the electronic diary after taking the study drug. The study included only highly symptomatic NERD patients, which may have excluded some patients with less frequent symptoms that did not warrant daily dosing (which may have accounted for the 88% screen failure rate). However, this was necessary in order to demonstrate a therapeutic effect in an on-demand study that randomised patients with episodic heartburn to either placebo or a medication (vonoprazan). Inclusion of NERD patients with low symptom burden, even if they responded to on-demand vonoprazan, would have significantly increased the placebo effect.

In conclusion, our study demonstrated that the treatment of patients with NERD (defined as endoscopy-negative, P-CAB-responsive heartburn) with on-demand vonoprazan is efficacious and well-tolerated, resulting in a greater proportion of heartburn episodes with complete and sustained relief (within 3 h and with no further heartburn reported for 24 h after taking study drug) compared with placebo. On-demand (as-needed) vonoprazan treatment may be a reasonable alternative to continued daily therapy for patients with heartburn, completely relieving heartburn symptoms within 1 h of use in some patients. The results of this study support further investigation of on-demand vonoprazan for the treatment of NERD symptoms in larger clinical trials.

AUTHOR CONTRIBUTIONS

Ronnie Fass: Conceptualization (equal); formal analysis (supporting); methodology (equal); visualization (lead); writing – original draft (equal); writing – review and editing (equal). **Michael Vaezi:** Conceptualization (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Prateek Sharma:** Conceptualization (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Rena Yadlapati:** Conceptualization (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Barbara Hunt:** Conceptualization (equal); formal analysis (lead); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Tom Harris:** Conceptualization (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Neila Smith:** Conceptualization (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Eckhard Leifke:** Conceptualization (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **David Armstrong:** Conceptualization (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

Ronnie Fass has served as a consultant for Phathom Pharmaceuticals, Takeda, Daewoong, Clexio and Viatris; as a speaker for AstraZeneca, Takeda, Johnson & Johnson, Eisai Pharmaceuticals, GI Supply/Laborie, Medicamenta and Adcock Ingram. Michael Vaezi has served as a consultant for Phathom Pharmaceuticals, ISOThrive, Sanofi and Bayer Pharmaceuticals; and owns a patent on Mucosal Integrity Testing and has engaged in consultation in litigations relating to acid suppression therapy for Diversatek Healthcare. Prateek Sharma has served as a consultant for Phathom Pharmaceuticals. Rena Yadlapati has served as a consultant for Medtronic, Phathom Pharmaceuticals, Ironwood Pharmaceuticals, StatLinkMD and RJS Mediagnostix; and has received research funding from Ironwood Pharmaceuticals. Barbara Hunt is an employee of Phathom Pharmaceuticals. Tom Harris is an employee of Phathom Pharmaceuticals. Neila Smith is an employee of Phathom Pharmaceuticals. Eckhard Leifke is an employee of Phathom Pharmaceuticals. David Armstrong has served as a consultant for Canadian Partnership Against Cancer, Phathom Pharmaceuticals, Cinclus Pharma and Takeda; has served as a speaker for Fresenius Kabi, Viatris and Takeda; is a co-founder of A.I. VALI Inc; has a patent pending for Medical Image Processing and has received research funding from Nestlé Health Sciences, the Canadian Association of Gastroenterology and Weston Family Foundation.

PATIENT CONSENT STATEMENT

All patients provided written informed consent before study entry.

AUTHORSHIP

Ronnie Fass is the submission's guarantor. All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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