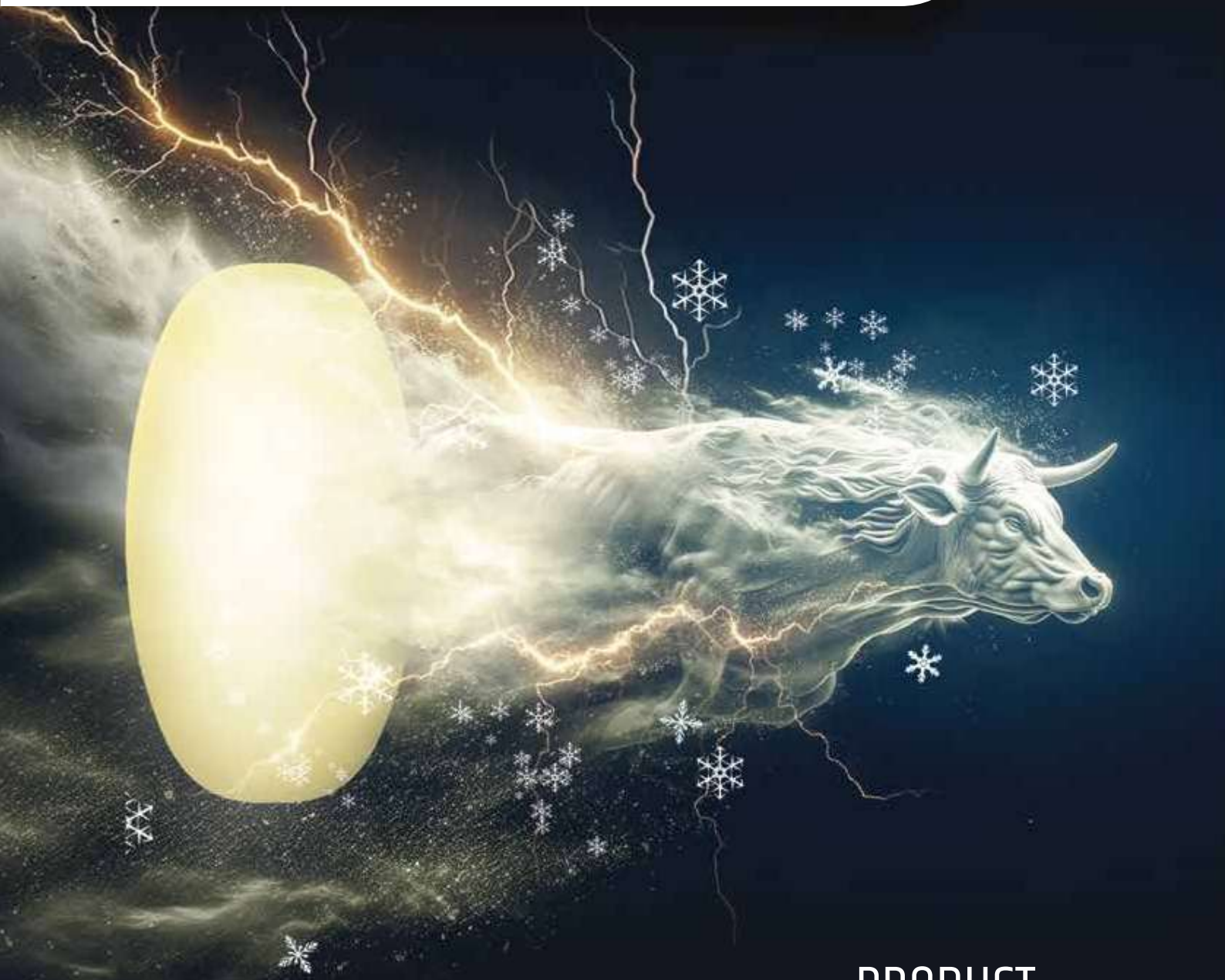
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Introduction

Acid-related diseases (ARDs), such as peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD), represent a major health-care concern.[1] They result from distinctive but overlapping pathogenic mechanisms that typically involve acid effects on diminished mucosal defence. Excessive acid exposure is considered as one of the possible mechanisms of injury in ARDs.[2] A peptic ulcer is histologically defined as a mucosal defect that extends to or beyond the muscularis mucosa, with mucosal damage due to pepsin and gastric acid secretion.[3] GERD is one of the most common acid-related disorder. It is defined based on both esophageal and extra-esophageal symptoms, and/or lesions resulting from the reflux of gastric contents into the esophagus.[4] GERD is defined as the presence of troublesome reflux or erosive complications in the esophagus due to retrograde reflux of gastric contents.[5] ARDs influence the quality of life and productivity of afflicted patients and are common and important causes of morbidity and mortality.[3]

Classification of GERD

Based on endoscopic and histopathologic appearance, GERD is classified into three different phenotypes: non-erosive reflux disease (NERD), erosive esophagitis (EE), and Barrett's esophagus (BE).[6]

Types of GERD
Non-erosive reflux disease **60 - 70%**
Erosive esophagitis **20 - 30%**
Barrett's esophagus **6 - 10%**

Epidemiology

Globally, prevalence of GERD is estimated to be around 15%. The overall prevalence in Asia is reported to be lower but there are regional variations, and India is among the nations with higher prevalence. Data from both community and hospital-based studies suggest that GERD is common in India irrespective of geographical or rural/urban location[7]. Prevalence of GERD in Indian population ranges from 5% to 28.5%.[8] Singh et al. reported the point prevalence of active peptic ulcer as 3.4%, and the lifetime prevalence as 8.8% in India. The duodenal-to-gastric ulcer ratio was 12:1. Helicobacter pylori was present in 84.6% subjects with peptic ulcer.[9]

Etiopathogenesis:[6]

The pathophysiology of GERD is multifactorial and is best explained by various mechanisms involved, including the influence of the tone of the lower esophageal sphincter, the presence of a hiatal hernia, esophageal mucosal defence against the refluxate and esophageal motility.

GERD Pathogenesis

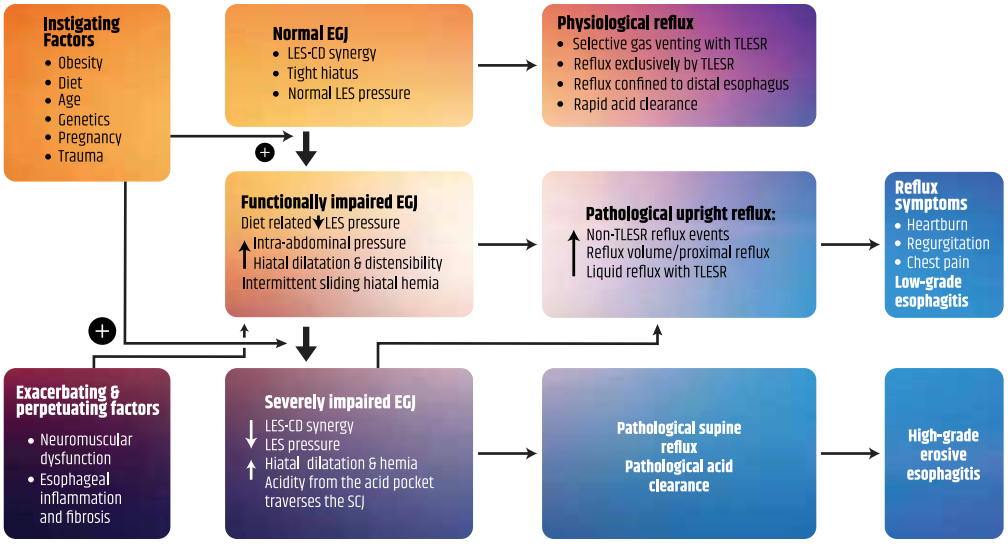


Figure 1: Pathogenesis of GERD[10]
The etiology of peptic ulcer disease is complex and multifactorial, comprising an imbalance between the protective and aggressive agents of the gastric mucosa.

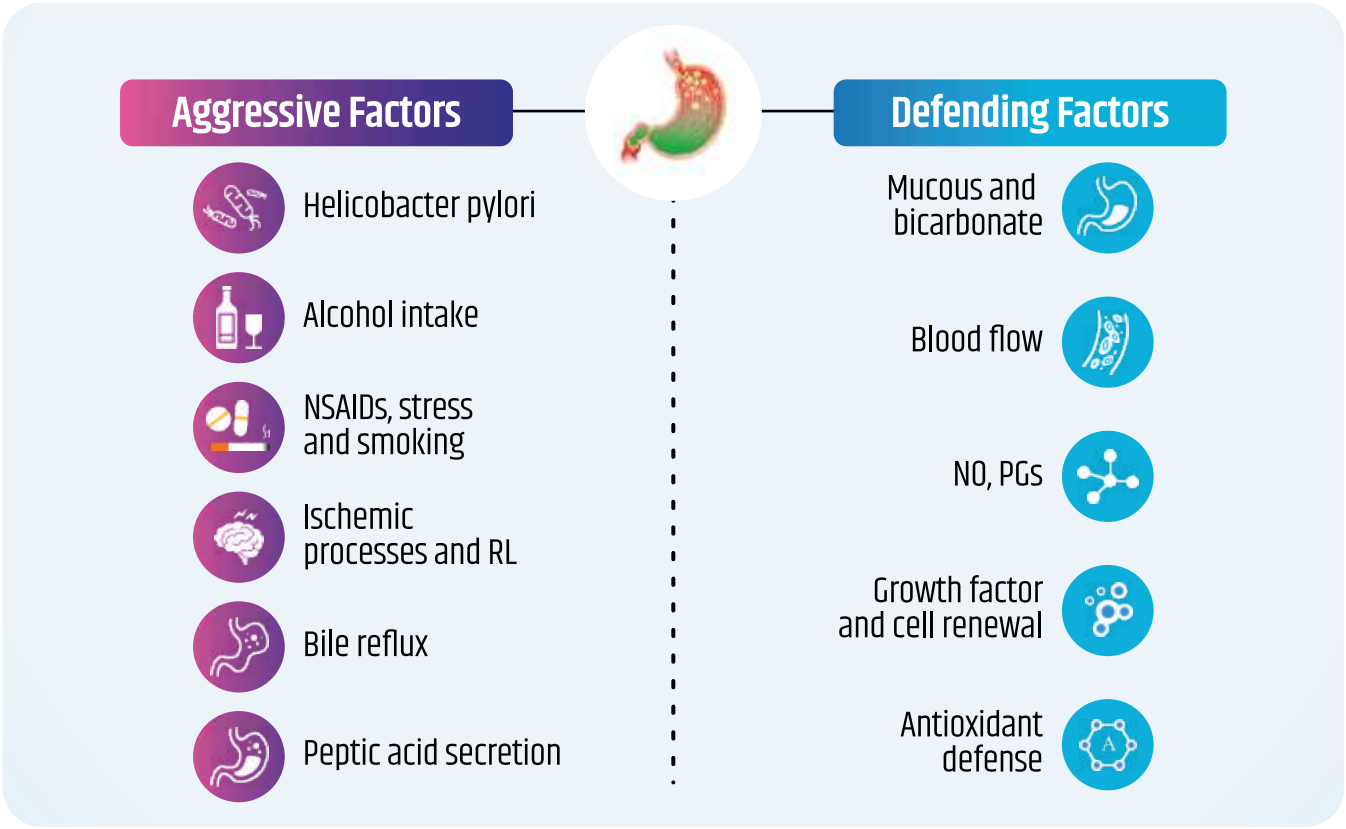


Figure 2: Etiopathogenesis of Peptic Ulcer[11]

Diagnosis of GERD and PUD

The diagnosis of GERD is usually based on symptoms and response to acid suppression. Typical symptoms of GERD are regurgitation and heartburn. Other symptoms of GERD include dyspepsia, nausea, bloating, sore throat, globus sensation, and epigastric pain. GERD is one of the common causes of non-cardiac chest pain. In GERD patients, dysphagia and odynophagia are alarm symptoms and require an upper endoscopy. Other alarm signs and symptoms include anemia, bleeding, and weight loss.[12,13,14]

Improvement in symptoms on a Proton Pump Inhibitor (PPI) trial has reasonable sensitivity and specificity to diagnose GERD. Patients with long-standing symptoms should undergo upper GI endoscopy to determine whether they have erosive esophagitis and to grade esophagitis, to look for complications of GERD such as peptic stricture, Barret's esophagus, and its extent. Grade of esophagitis is important for assessing treatment, patient response, complications, and prognosis.[15]

Due to its ease of use and very minor interindividual variability, the Los Angeles classification is commonly used for grading of esophagitis.

Table 1: Los Angeles classification of severity of reflux esophagitis[16]

Grade of Esophagitis	Description
Grade A	One or more esophageal mucosal breaks less than 5 mm in length
Grade B	One or more mucosal breaks greater than 5 mm but with continuity across mucosal folds
Grade C	Continuous mucosal breaks between the tops of two or more mucosal folds but involving less than 75% of the esophageal circumference
Grade D	Mucosal breaks involving more than 75% of the esophageal sphincter

Most common presenting symptom of peptic ulcer is epigastric pain, which may be associated with dyspepsia, bloating, abdominal fullness, nausea, and early satiety. Patient presenting with anemia, melena, hematemesis, dysphagia, or weight loss need to be further investigated for complications of PUD, predominantly bleeding, perforation, or cancer. Esophagogastroduodenoscopy (EGD) is considered as gold standard and most accurate diagnostic test with sensitivity and specificity up to 90% in diagnosing gastric and duodenal ulcers. H. pylori infection can be diagnosed through tests like urea breath test, stool antigen test, rapid urease test or histology of gastric biopsies taken at the time of upper endoscopy, and serologic test.[17,18]

Management of GERD and PUD

Lifestyle modifications is an important initial step in the management of GERD. Certain food items and habits may trigger reflux by altering the anti-reflux mechanism. Obesity is one of the most important risk factors of GERD, and evidence has shown that weight loss is associated with reduction in GERD symptoms. (ISG guideline) A meta-analysis found that GERD symptoms improved with weight loss and head elevation but not with dietary interventions.[19] Medical therapy is indicated in patients who do not respond to lifestyle modifications. Medical therapy includes of antacids, antisecretory agents like histamine (H2) receptor antagonists (H2RAs) or PPI therapy, and prokinetic agents.[6] PPI at standard dose for 4 weeks is the first line empirical therapy for patients of GERD in the absence of alarm symptoms. PPIs should be administered for 8 weeks in patients with erosive esophagitis, and twice-daily doses can be considered in patients with severe esophagitis.[15]

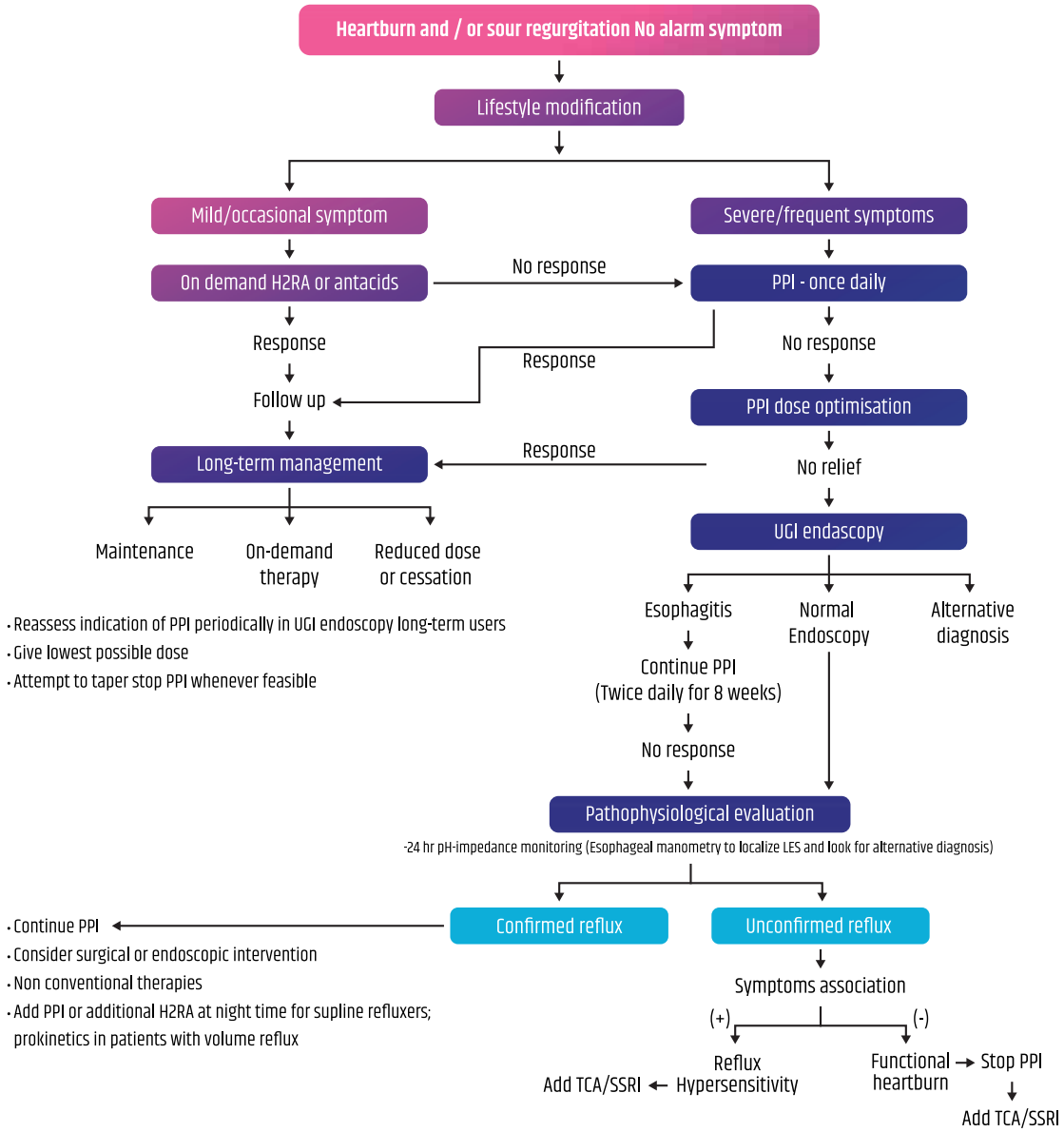


Figure 3: Algorithm for diagnostic and treatment of patients with symptoms suggestive of GERD[15]

In non-responder GERD patients, doubling the dose of PPI is commonly done. Other strategies for management of non-responder GERD patients include switching to other PPI, combining PPI with prokinetic agents, histamine receptor antagonist (H2RA), baclofen, etc.

Anti-reflux surgery can be considered for patients who either fail PPI therapy or have complications of reflux, such as severe esophagitis, stricture, or risk of aspiration. Surgery may also be appropriate for patients who cannot tolerate or comply with long-term pharmacotherapy.[20]

PPIs remain the mainstay of medical therapy for peptic ulcer disease. The length of PPI administration following the diagnosis of a peptic ulcer depends on the underlying ulcer etiology, location, and associated complications. The ultimate goal of therapy is to promote ulcer healing through acid suppression, while the underlying etiology of the ulcer is addressed. Positive H. pylori testing prompts treatment of the infection, while patients with NSAID induced ulcers are counselled to avoid the aggravating agents.[18]

Limitations of current therapy

Although PPIs are the most effective pharmacological therapy for acid suppression, GERD treatment a significant number of patients do not respond to once daily dosing of PPIs. Total or partial persistence of GERD symptoms occurs in 25% to 42% of patients using once-daily PPIs and in 10% to 20% of patients who use PPI twice-daily. Furthermore, up to 40% of patients with non-erosive reflux disease have symptoms despite long-term use of PPIs.[21,22]

Relapse

Relapse occurs within 6 months of initiating PPI therapy in 15%–23% of adult patients with Los Angeles (LA) grades A and B, and 24%–41% with grades C and D. A recent meta-analysis found that reflux symptoms are not adequately controlled after the first dose of a PPI in two-thirds of patients, and nearly 50% of patients are symptomatic even after 3 days. For the most part, once-daily PPIs are generally less effective for controlling nocturnal GERD.[22]

PPI failure

PPI failure is defined as an incomplete or unsatisfactory response to a full course of PPIs. Poor compliance with long-term therapy is one of the most common causes of refractory GERD symptoms. Dosing time is a critical factor underlying failure of, as most PPI must be taken 30–60 minutes before a meal in order to achieve maximal efficacy. Even with appropriate, once-daily dosing, PPIs are estimated to inhibit only 70% of active proton pumps. Proton pumps are active at different times, and ~25% are regenerated daily, with significant variation in turnover rate. The short half-life of PPIs (1–2 hours) prevents 24-hour control of gastric acid, which continues to be secreted by uninhibited or regenerated pumps. Increasing the once-daily dose of PPIs has shown only marginal benefit and does not increase the duration of acid control. Twice-daily PPI administration, either by splitting or doubling the dose, is reported to improve acid control but is associated with poorer compliance.[22]

Nocturnal Acid Breakthrough

Nocturnal acid-breakthrough (NAB) is defined as persistent reduction of intra-gastric pH below 4 for more than 60 minutes during the night. NAB occurs in 40% to 70% of patients with GERD while on proton pump inhibitors (PPIs).[23] Katz et al. have shown that an episode of gastro-oesophageal reflux coincident with NAB is seen in 31% of patients with GERD, 50% of patients with Barrett's oesophagus, and 9% of normal subjects.[24] NAB has been observed in 75% of all individuals (GERD patients as well as healthy subjects) taking PPI twice a day.[25] Among patients on PPI twice a day, 39.1% patients had to increase the dose due to poor symptom control at night.[26]

PPI pharmacokinetics

PPI have pKa of about 4.0, which enables their accumulation only in the acidic secretory canaliculus of the stimulated parietal cell, where they are converted into thiophilic intermediates that bind to cysteine sulfhydryl groups on the luminal aspect of the proton pump to form covalent disulfide bonds.

This covalent inhibition of the enzyme by the thiophilic sulfenamide results in a specific and long-lasting impairment of gastric acid secretion. The antisecretory effect of the drugs reflects their short plasma half-life (ranging from 1 to 1.5 h), the number of active pumps during that time, and the recovery of pumps following biosynthesis and reversal of inhibition.[27]

Inter-individual variability of pharmacodynamics and clinical activity due to cytochrome polymorphism

PPIs are affected by marked inter-individual variability of pharmacodynamics and clinical activity due to the existence of cytochrome polymorphism. They are mainly metabolized in the liver by cytochrome P450 2C19 (CYP2C19) which has a large ethnic difference in the frequency of genetic polymorphism. As a result of genetic polymorphisms, CYP2C19 exists as three possible genotype groups with varying metabolic activity:

- Homozygous extensive metabolizers (carrying two mutated alleles)
- Heterozygous extensive metabolizers (carrying one mutant and one wild-type allele)
- Poor metabolizers (carrying two wild-type allele)[28]

A recent meta-analysis found that PPI response rate in GERD among rapid metabolizers, intermediate metabolizers, and poor metabolizers was 52.2%, 56.7%, and 61.3%, respectively.[29]

Delayed absorption and antisecretory effect

PPIs are acid-labile weak bases formulated as delayed-release enteric-coated preparations. An enteric coating protects PPIs from premature acid degradation in the stomach so that absorption can occur in the proximal small intestine. Because of that, there is a delay in absorption and onset of their antisecretory effect.

Only 30% of patients achieve early and complete heartburn relief for the entire day after their first PPI dose. Although PPIs might provide benefit from the first day of therapy, most patients will not have symptom relief with 1 or 2 days of PPI therapy. Effectiveness of a PPI is also dependent on food timing and food intake. As gastric acid secretion is maximally stimulated by food ingestion, maximal PPI efficacy should be achieved when they are taken before a meal.[27]

Moreover, it has been well documented that achieving complete symptomatic relief with PPI is more difficult than simply healing mucosal breaks. The reasons for the lack of efficacy of PPIs were suggested to be the mechanism of action requiring acid activation, rapid elimination, nocturnal increase in gastric acid and they are slow to achieve steady state inhibition of gastric acid secretion, typically taking 3 to 5 days to achieve maximum effect. About one third of patients with GERD are dissatisfied with current therapy. For GERD patients, more complete and faster relief of symptoms is still needed. For patients receiving NSAIDs, PPI co-therapy reduces, but does not eliminate the risk of GI ulcers and complications. There are still a significant number of patients that have persistent dyspeptic symptoms and a decreased QoL despite the use of PPIs. There is still lack of complete control of acid secretion with oral PPI administration in the management of patients with gastroesophageal symptoms, nonvariceal upper gastrointestinal bleeding, NSAID gastrointestinal injury and H. pylori. Hence, there are definite unmet needs for more efficient therapies for managing GERD and acid related disorders.[24-30]

Potassium-competitive acid blockers (PCABs)

Potassium-competitive acid blockers (PCABs) represent a novel class of acid suppressants that have shown tremendous promise to enhance care of acid peptic disorders. PCAB's characteristics are distinct from those of proton pump inhibitors—such as acid stability with dosing independent of food consumption, rapid onset of action, less variability with CYP2C19 polymorphisms, and extended half-lives. PCABs now have data beyond Asian populations and expanding regulatory approvals. Of these, vonoprazan is the most extensively studied PCAB.[31]

Vonoprazan

Vonoprazan is a novel orally active, pyrrole derivative, potassium-competitive acid blocker (P-CAB). It was approved in Japan in December 2014 for the treatment of adult patients with acid-related diseases, including gastric ulcer, duodenal ulcer, reflux oesophagitis, and for the prevention of recurrence of gastric or duodenal ulcer during low-dose aspirin or non-steroidal anti-inflammatory drug (NSAID) administration.[32] It is also approved as an adjunct to H. pylori eradication. Vonoprazan was approved by US FDA in November 2023 for treatment of erosive GERD and for relief of heartburn associated with erosive GERD in adults. It is also approved for treatment of H. pylori infection when used in combination with amoxicillin or amoxicillin and clarithromycin.[33] Vonoprazan was approved in India in May 2024 for reflux esophagitis and acid-peptic disorders.[34]

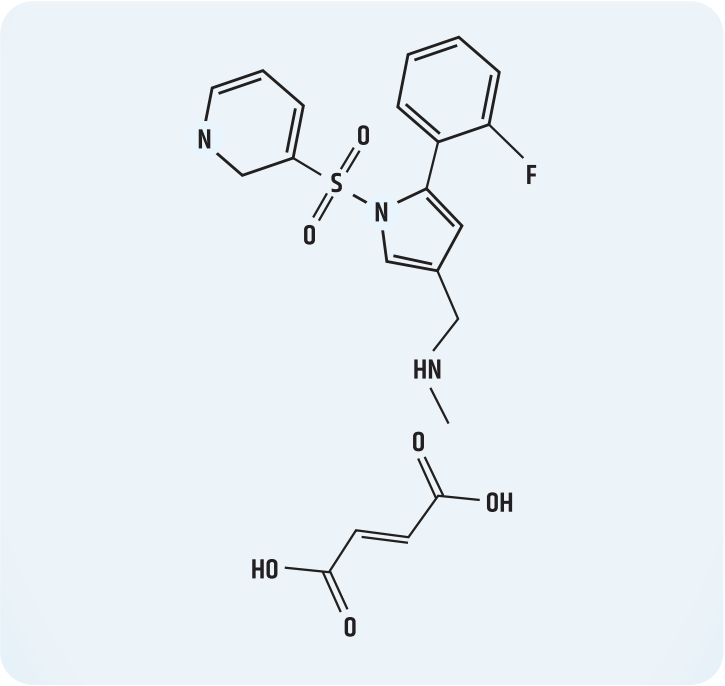


Figure 4: Chemical Structure of Vonoprazan
(1-[5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine monofumarate)

Mechanism of Action

P-CABs act at the H+/K+ ATPase transporter on the luminal membrane of gastric parietal cells, the same proton pump targeted by PPIs. After systemic absorption, P-CABs concentrate in parietal cell canaliculi, bind to H+/K+ ATPase transporters ionically and prevent acidifying proton secretion. P-CABs are characterized as weak bases, and their protonated form block the K+ exchange channel of H+/ K+-ATPase in the proton pump. Since, vonoprazan has a high pKa of 9.3, it is protonated easily and exerts its inhibitory action.

P-CABs are acid-stable and thus do not require enteric coating or optimal dosing administration 30 minutes prior to meals. Additionally, they are not prodrugs and act immediately at the proton pump. Vonoprazan accumulates in parietal cells under both acidic and neutral conditions. It does not require an acidic environment for activation, has long-term stability at the site of action. P-CABs have beneficial effects including rapid, long-lasting, and reversible inhibition of the gastric H+/K+ ATPase, the proton pump of the stomach.[31-35]

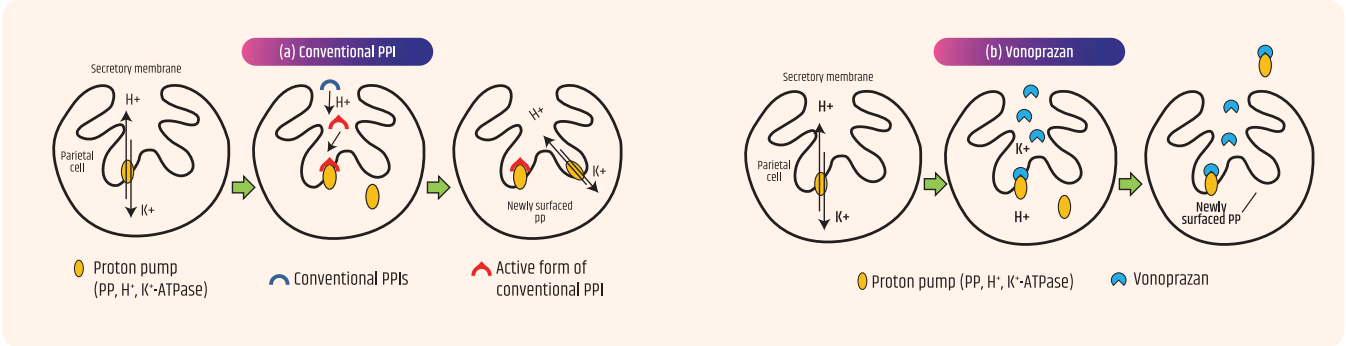


Figure 5: Mechanism of Action of P-CABs and PPIs[36]

Table 2: Difference between Vonoprazan and PPIs[31,35]

Characteristic	Vonoprazan	PPIs
Pro-drug	No	Yes
Acid stability	Yes	No
Action	Acts directly (after protonation)	Transformation to the active form (sulphenamide) is needed
H+, K+-ATPase binding	Binds competitively to the K+ binding site of H+, K+-ATPase	Sulphenamide binds covalently to H+, K+-ATPase
Binding to the proton pump	Reversible	Irreversible
Maximal acid suppression after dosing	1 day	3-5 days
Antisecretory activity	Meal independent	Meal dependent
Half-life	6-9 hours	1-2 hours
Significantly affected by CYP2C19 polymorphism	No	Yes
Optimal dosing administration	Independent of mealtimes (before or after meals)	30-60 minutes prior to mealtimes (for most PPIs)

Pharmacokinetics

Vonoprazan is rapidly absorbed and reaches to the maximum plasma level (Cmax) within 2 hours. It has plasma half-life ($t_{1/2}$) about 7 h with 20 mg of vonoprazan taken on fasting while conventional PPIs have much shorter half-lives ($t_{1/2}$ = 1–2 h). Vonoprazan stays in the blood longer and can block acid secretion continuously. Since it does not require acid-catalyzed activation, acid suppression with vonoprazan is equally efficacious irrespective of the administration before or after breakfast. Vonoprazan exhibits potent, long-lasting acid suppression starting from the first day of administration which is dose-dependent and further increases in 7 days.[30]

Vonoprazan is mainly metabolized by CYP3A4. The data from clinical studies on healthy volunteers and GERD patients showed limited influence by CYP2C19 polymorphisms on Vonoprazan metabolism. The effects of clarithromycin, a potent CYP3A4 inhibitor, on the pharmacokinetics of vonoprazan were evaluated and no significant pharmacokinetic interactions were observed.[37,38]

Pharmacodynamics

Vonoprazan is effectively absorbed and quickly accumulates in parietal cells. Conventional PPIs require 3 to 5 days to achieve maximal and steady-state inhibition of acid secretion. The effect after the first dose of vonoprazan is more pronounced compared to conventional PPIs. A single dose of 20 mg vonoprazan can increase intragastric pH to nearly 7 in as little as 4 hours. Dose dependent mean 24-h intragastric pH >4 holding time ratio [HTR (%)] during the 24-h dosing interval and during the night-time period after vonoprazan administration is shown in table 3.[37,38]

Table 3: Dose Response relationship for mean 24-h intragastric- pH >4 holding time ratio (HTR %)[38]

Characteristic	Vonoprazan 20 mg	Vonoprazan 40 mg
Japanese study		
24-h pH >4 HTR (%)		
Day 1	63.3 ± 17.9	85.3 ± 8.3
Day 7	83.4 ± 16.7	100.0 ± 0.0
Night-time pH >4 HTR (12–24 h post-dose) (%)		
Day 1	61.1 ± 29.3	86.5 ± 15.5
Day 7	73.0 ± 26.5	100 ± 0.1
UK study		
24-h pH >4 HTR (%)		
Day 1	62.7 ± 16.8	85.6 ± 7.4
Day 4	82.9 ± 14.7	94.0 ± 9.1
Day 7	85.2 ± 12.3	93.2 ± 10.5
Night-time pH >4 HTR (20:00–08:00 hours) (%)		
Day 1	57.3 ± 23.2	87.7 ± 11.4
Day 4	73.8 ± 22.4	91.0 ± 14.5
Day 7	75.4 ± 20.6	90.4 ± 14.8

(Data obtained from healthy male subjects)

Table 4: pH > 4 holding time (%) with proton-pump inhibitors and potassium-competitive acid blockers[30]

PPI/P-CAB	Dose (mg)	Study participants	Single-dose studies pH>4 holding time (%)	Multiple-dose studies pH>4 holding time (%)
Omeprazole	20		30.4	48.7 ± 20.5
Esomeprazole	20		32.5 ± 9.2	56.3 ± 7.4
	40		43.1 ± 17.8	64.6 ± 15.2
Lansoprazole	15		28.1 ± 10	45.9 ± 14.3
	30		39.1 ± 12.8	55.1 ± 14.4
Rabeprazole	10		29.8 ± 13.2	51.2 ± 13.1
	20		42.8 ± 15.9	57.7 ± 14.2
Vonoprazan	20	JP	63.3 ± 17.9	83.4 ± 16.7
		UK	62.7 ± 16.8	85.2 ± 12.3
	40	JP	85.3 ± 8.3	100 ± 00
		UK	85.6 ± 7.4	93.2 ± 10.5

(Data is obtained from healthy volunteers, JP, Japanese; UK, the United Kingdom)

Acid-inhibitory effects of Vonoprazan compared to PPI: Clinical evidence

A randomised, open-label, two-period, cross-over study was conducted to examine the acid-inhibitory effects of vonoprazan compared with esomeprazole (Study V vs. E) or rabeprazole (Study V vs. R)[39]

Study Design

The study was conducted in healthy Japanese adult male volunteers aged 20–45 years. Each study group was comprised of two treatment sequences. Subjects were randomly and equally allocated to the two treatment sequences within each study group (Fig 6) Total 20 subjects received the study drug.

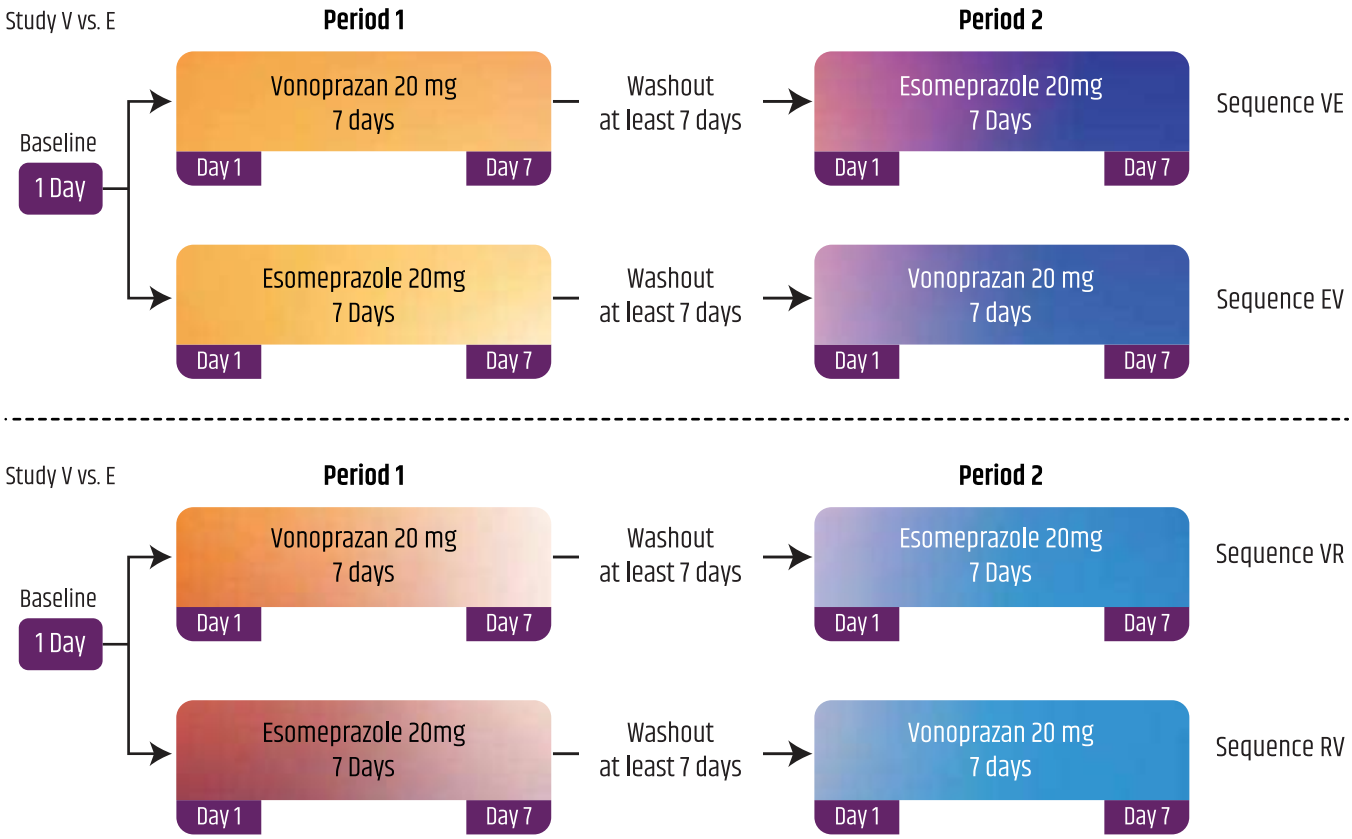


Figure 6: Study Design

Results

Pharmacodynamic effects

Time course of gastric pH over 24-h:

The time courses of gastric pH indicate that gastric pH tended to be higher after administration of vonoprazan than after administration of esomeprazole or rabeprazole (Figure 7 and 8) This difference was noticeable 2 h after administration of study drugs and the trend continued until Day 7.

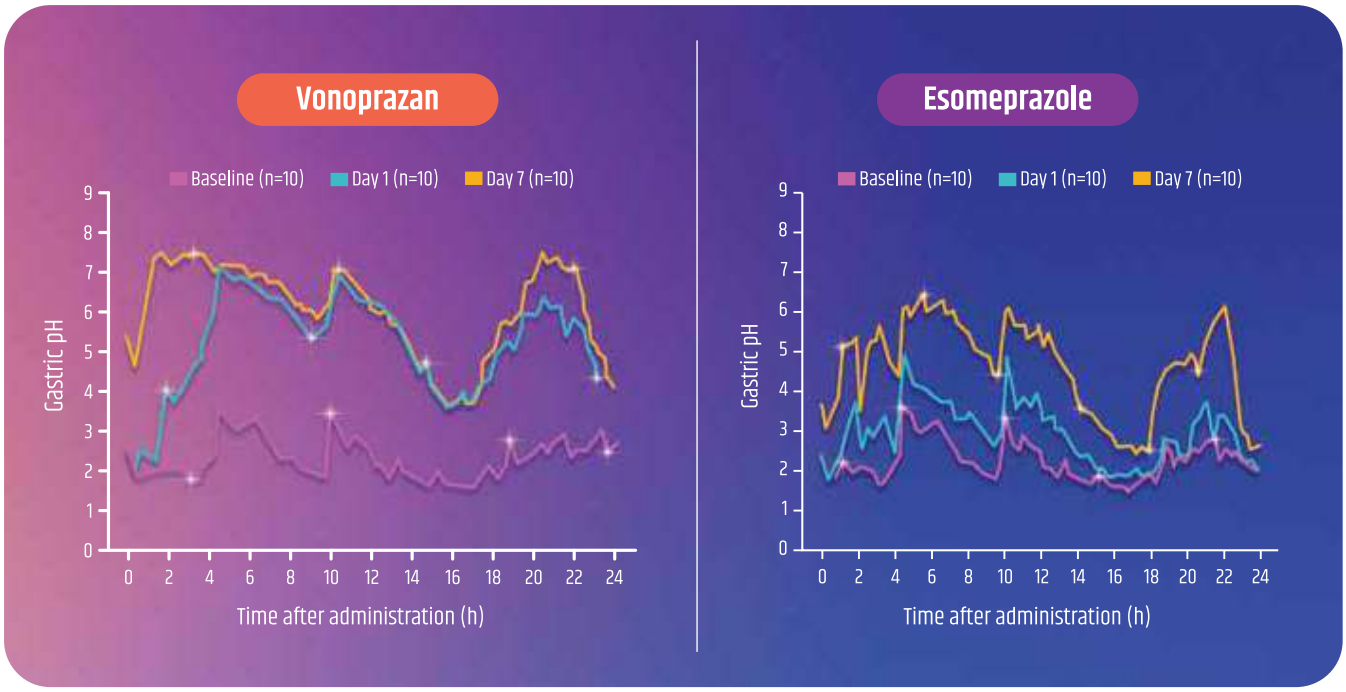


Figure 7: Time courses of gastric pH over 24 h for (a) vonoprazan and (b) esomeprazole at baseline, on Days 1 and 7 for Study V vs. E

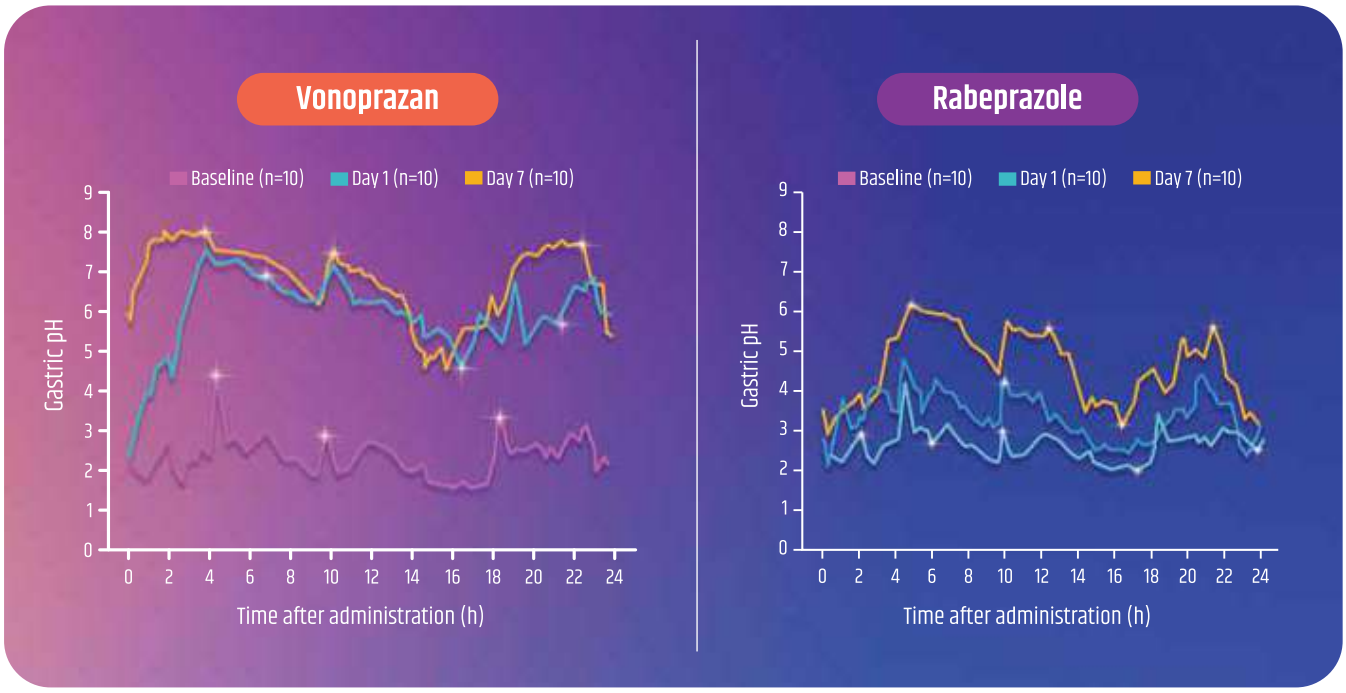


Figure 8: Time courses of gastric pH over 24 h for (a) vonoprazan and (b) rabeprazole at baseline, on Days 1 and 7 for Study V vs. R

Gastric pH 4 HTR

A greater acid-inhibitory effect of vonoprazan compared with both esomeprazole and rabeprazole was observed. The means of 0–24 h, 0–12 h (daytime) and 12–24 h (night-time) pH 4 HTRs on Days 1 and 7 were higher after administration of vonoprazan than after administration of esomeprazole (Table 5) or rabeprazole (Table 6).

Table 5: pH 4 HTRs (mean ± s.d.) and differences (95% CIs) between vonoprazan and esomeprazole for Study V vs. E

0-24 h pH 4 HTR (%)			
Visit	**Treatment**	**Mean ± s.d.***	**Difference (95% CIs)**
Baseline†	Vonoprazan	10.6 ± 7.4	
	Esomeprazole	10.6 ± 7.4	
Day 1	Vonoprazan	71.4 ± 17.0	47.5 (35.5-59.4)
	Esomeprazole	23.9 ± 16.9	
Day 7	Vonoprazan	85.8 ± 14.7	24.6 (16.2-33.1)
	Esomeprazole	61.2 ± 17.1	

0-12 h pH 4 HTR (%)‡			
Visit	**Treatment**	**Mean ± s.d.***	**Difference (95% CIs)**
Baseline†	Vonoprazan	13.0 ± 11.1	
	Esomeprazole	13.0 ± 11.1	
Day 1	Vonoprazan	74.8 ± 9.7	39.9 (22.0-57.9)
	Esomeprazole	34.9 ± 24.6	
Day 7	Vonoprazan	96.5 ± 4.4	18.8 (7.8-29.8)
	Esomeprazole	77.6 ± 17.3	

12-24 h pH 4 HTR (%)§			
Visit	**Treatment**	**Mean ± s.d.***	**Difference (95% CIs)**
Baseline†	Vonoprazan	8.2 ± 13.7	
	Esomeprazole	8.2 ± 13.7	
Day 1	Vonoprazan	67.9 ± 28.3	54.9 (36.3-73.6)
	Esomeprazole	12.9 ± 10.9	
Day 7	Vonoprazan	75.2 ± 26.4	30.4 (16.2-44.6)
	Esomeprazole	44.8 ± 17.3	

pH 4 HTR, percentage of time pH≥4; CI, confidence interval; s.d., standard deviation

*The 0-12 h means are based on daytime pH values, while 12-24 h means are based on night-time pH values.

Table 6: pH 4 HTRs (mean ± s.d.) and differences (95% CIs) between vonoprazan and rabeprazole for Study V vs. R

0-24 h pH 4 HTR (%)			
Visit	**Treatment**	**Mean ± s.d.***	**Difference (95% CIs)**
Baseline†	Vonoprazan	8.9 ± 6.5	
	Rabeprazole	8.9 ± 6.5	
Day 1	Vonoprazan	84.2 ± 12.4	58.2 (43.6-72.9)
	Rabeprazole	26.3 ± 13.4	
Day 7	Vonoprazan	93.8 ± 7.3	28.8 (17.2-40.4)
	Rabeprazole	65.1 ± 14.2	

0-12 h pH 4 HTR (%)‡			
Visit	**Treatment**	**Mean ± s.d.***	**Difference (95% CIs)**
Baseline†	Vonoprazan	8.0 ± 5.7	
	Rabeprazole	8.0 ± 5.7	
Day 1	Vonoprazan	84.0 ± 7.8	47.4 (24.2-70.5)
	Rabeprazole	37.3 ± 20.4	
Day 7	Vonoprazan	98.8 ± 3.0	22.7 (13.9-31.5)
	Rabeprazole	76.1 ± 9.6	

12-24 h pH 4 HTR (%)§			
Visit	**Treatment**	**Mean ± s.d.***	**Difference (95% CIs)**
Baseline†	Vonoprazan	9.8 ± 14.1	
	Rabeprazole	9.8 ± 14.1	
Day 1	Vonoprazan	84.3 ± 20.3	69.1 (50.5-87.7)
	Rabeprazole	15.3 ± 13.3	
Day 7	Vonoprazan	88.8 ± 14.4	34.9 (13.2-56.6)
	Rabeprazole	54.1 ± 25.3	

pH 4 HTR, percentage of time pH≥4; CI, confidence interval; s.d., standard deviation

*The 0-12 h means are based on daytime pH values, while 12-24 h means are based on night-time pH values.

Mean gastric pH

The mean 0–24 h mean gastric pH was higher after administration of vonoprazan on day 1 and day 7 than after administration of esomeprazole or rabeprazole (Table 7 and 8).

Table 7: 0-24 h mean gastric pH on day 1 and day 7 in study V vs E

0-24 h mean gastric pH	Vonoprazan	Esomeprazole
Day 1	5.2	3.0
Day 7	6.1	4.7

Table 8: 0-24 h mean gastric pH on day 1 and day 7 in study V vs R

0-24 h mean gastric pH	Vonoprazan	Rabeprazole
Day 1	5.8	3.3
Day 7	6.5	4.8

No serious adverse events were reported during the study and vonoprazan was generally well tolerated.

Study Conclusion:

This study demonstrated a more rapid and sustained acid-inhibitory effect of vonoprazan 20 mg vs. esomeprazole 20 mg or rabeprazole 10 mg.

Phase III clinical trials

Vonoprazan has been evaluated in various phase 3 clinical trials to assess its efficacy and safety in patients of non-erosive GERD, erosive esophagitis, gastric and duodenal ulcers, and also for prevention of recurrent gastric and duodenal ulcers.

Trials in patients with Erosive esophagitis

Study 1:

Randomised clinical trial of vonoprazan, a novel potassium competitive acid blocker vs. lansoprazole for the healing of erosive esophagitis in Japan (EE).[40]

Study Design:

This was an 8-week multicentre, randomised, double-blind, parallel-group comparison study conducted in Japan to verify the non-inferiority of vonoprazan (VPZ) 20 mg to lansoprazole (LPZ) 30 mg in patients with endoscopically confirmed EE [Los Angeles (LA) Classification Grades A–D].

Patients who achieved endoscopically healed EE by week 8 in the comparison study were re-randomised into a second sequential randomised, single-blind, multicentre, parallel-group, long-term maintenance study to evaluate the safety and efficacy of vonoprazan 10 or 20 mg in patients with healed EE for 52 weeks.

Study End-points:

Comparison study:

The primary endpoint was the proportion of healed EE patients up to week 8.
The secondary endpoints were the proportions of healed EE patients at week 2 and up to week 4.
Other endpoints included subjective symptoms of EE (daytime and night-time heartburn and regurgitation as reported in patient diaries) and safety endpoints.

Long-term maintenance study:
The primary endpoint was the incidence of treatment emergent adverse events (TEAEs). The secondary endpoints were clinical laboratory test values, ECG findings, vital signs and serum gastrin and pepsinogen I/II levels. An additional secondary endpoint was the proportion of patients with EE recurrence.

Results:
The proportion of patients with healed erosive esophagitis up to 8 weeks (primary endpoint), and at week 2 and up to week 4 (secondary endpoint) are shown in table 9.

Table 9: Proportion of patients with healed erosive esophagitis up to 8 weeks (primary endpoint), and at week 2 and up to week 4 (secondary endpoint)

Time point	Treatment	% Patients healed (n/N) [95% CIs]	Difference [95% CIs] (VPZ - LPZ)	P-value non-inferiority*	P-value Fisher's exact test†
Week 8	VPZ 20 mg	99.0 (203/205) [96.5-99.9]	3.5 [0.36-6.73]	<0.0001	0.03
	LPZ 30 mg	95.5 (190/199) [91.6-97.9]			
Week 2	VPZ 20 mg	90.7 (185/204) [85.8-94.3]	8.8 [2.11-15.45]	<0.0001	0.01
	LPZ 30 mg	81.9 (163/199) [75.9-87.0]			
Week 4	VPZ 20 mg	96.6 (198/205) [93.1-98.6]	4.1 [-0.31-8.55]	<0.0001	0.08
	LPZ 30 mg	92.5 (184/199) [87.9-95.7]			

*Farrington and Marning test with a non-inferiority margin of 10%.
†Post-hoc analysis.

Erosive oesophagitis symptoms of heartburn and regurgitation recorded in patient diaries improved in both the vonoprazan and lansoprazole groups, with no notable differences between them.

Safety:
Overall, both treatments were well-tolerated during the comparison study. The majority of treatment emergent adverse events (TEAEs) were mild in intensity (114 of 123). Nasopharyngitis was the most frequently reported TEAE in both groups and was the only TEAE with an incidence of ≥2% in the vonoprazan group during the comparison study.

Long-term maintenance study:
A total of 135 (87.7%) patients in vonoprazan 10 mg and 129 (85.4%) in vonoprazan 20 mg completed the 52 weeks of treatment. The details of TEAEs are mentioned in table 10.

Most of the TEAEs were mild in intensity and there was no obvious trend towards an increase in incidence over time in the two treatment groups.

Table 10: Treatment Emergent Adverse Effects in Long Term Maintenance study

	Vonoprazan 10 mg	Vonoprazan 20 mg
Overall TEAEs	**76.6%**	**78.8%**
Drug -related TEAEs	9.7%	16.6%
TEAEs leading to treatment discontinuation	5.2%	7.9%
Moderate to Severe TEAEs	12.3%	11.3%
Serious AEs	5.2%	7.3%
Serious drug- related AEs	0.6%	1.3%

There were few recurrences of EE during the maintenance treatment. (Table 11)

Table 11: Recurrence of EE during maintenance study

Recurrence of EE	Vonoprazan 10 mg	Vonoprazan 20 mg
Recurrence at week 24	6%	9.4%
	4.1%	9%

Study Conclusion:

Comparison study demonstrated the non-inferiority of vonoprazan compared with lansoprazole, and demonstrated that the novel P-CAB is highly effective for the treatment of patients with EE, more notably for patients with more severe EE (LA Classification Grades C/D). During the long-term maintenance (52 weeks) treatment, there were few cases (<10%) of recurrence with vonoprazan 10 or 20 mg once daily. Overall, vonoprazan was well-tolerated for up to 52 weeks with few patients discontinuing treatment.

Study 2:

This was a randomized, double-blind, parallel-group trial conducted with 2 doses of vonoprazan comparing with the approved doses of the PPI lansoprazole for healing and maintenance of healing in patients with erosive esophagitis from the US and Europe. Modification due to the potential impact of COVID-19 was incorporated into the study after the advent of the pandemic. Statistical analysis plan was adjusted to impute missing data for subjects without a postbaseline endoscopy at a visit due to COVID-19–related reasons.[41]

Study Design:

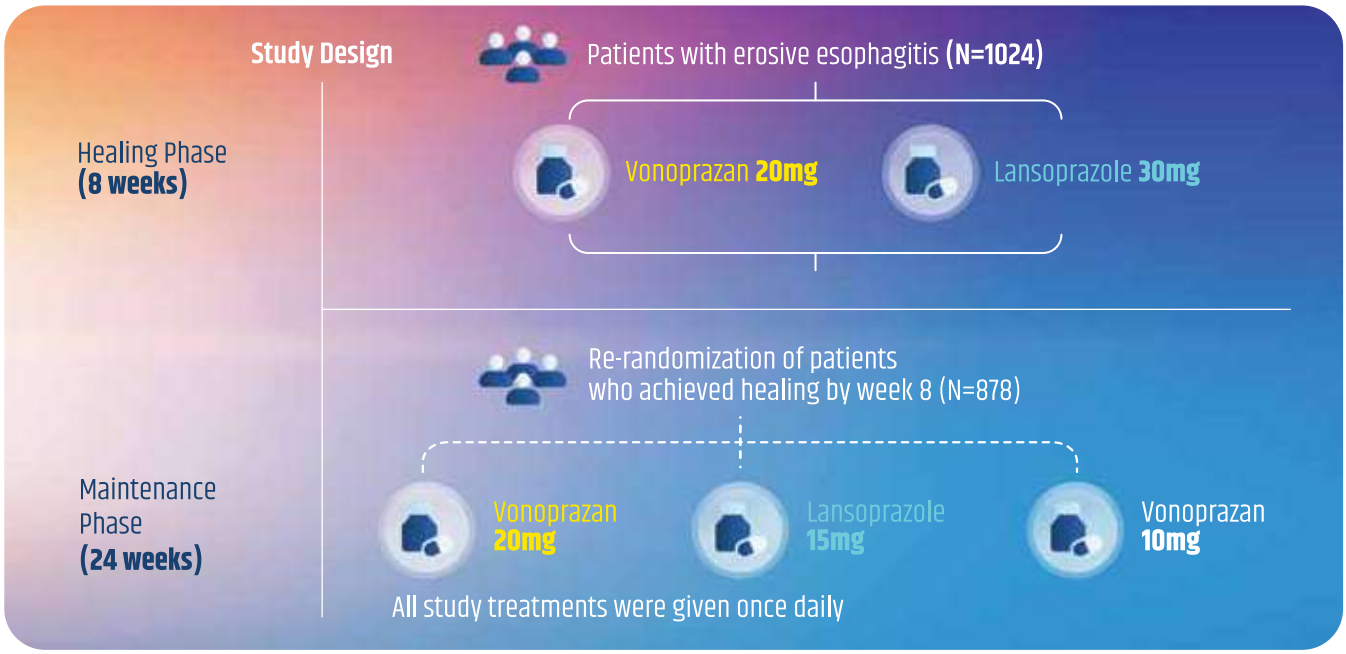


Figure 9: Study Design

Study End-point:

Healing phase of trial:
The primary end point was the percentage of subjects with healing by week 8.

Secondary end points:
- Subjects with healing at week 2
- Subjects with baseline LA Grade C/D esophagitis with healing at week 2 and week 8
- 24-hour heartburn-free days
- Subjects with onset of sustained heartburn resolution (≥ 7 consecutive days without heartburn) by day 3

Endpoints for maintenance phase of trial:
The primary end point was the percentage of subjects who maintained healing after 24 weeks.
Secondary end points included the percentage of subjects with baseline LA Grade C/D erosive esophagitis who maintained healing after 24 weeks and of 24-hour heartburn-free days over the maintenance phase.

Study Results:

Healing Phase:
The primary analysis of healing by week 8 showed vonoprazan was noninferior to lansoprazole with noninferiority maintained in sensitivity analyses with differing imputation methods. Vonoprazan was also superior on the predefined exploratory analysis.

Table 12: Primary and Secondary Efficacy End Points in Predefined Fixed-Sequence Analyses for Healing Phase

Efficacy End Point	Vonoprazan 20 mg (n=514)	Lansoprazole 30 mg (n=510)	Difference (95% CI)
Healing by week 8, %	92.9	84.6	8.3 (4.5-12.2), P= 0.0001*
24-hour heartburn-free days, mean (SD), %	66.8 (34.6)	64.1 (35.5)	2.7 (-1.6 to 7.0)
Healing at week 2 in LA Grade C/D, %	70.2	52.6	17.6 (7.4-27.4), P=0.0008#
Onset of sustained resolution of heartburn by day 3, n (%)	177 (34.4)	164 (32.2)	2.3 (-3.5 to 8.0), P=0.44
Healing by week 8 in LA Grade C/D, %	91.7	72	19.6 (11.8–27.6)
Healing at week 2, %	74.3	68.2	6.1 (0.5-11.6)

(*P for noninferiority 0.0001, #P = 0.0008 for superiority in predefined fixed-sequence analysis of the secondary end point)

Secondary end points assessed in fixed-sequence analyses revealed vonoprazan was noninferior to lansoprazole in mean 24 hour heartburn-free days, was superior in healing at week 2 for LA Grade C/D esophagitis and was not superior in sustained resolution of heartburn by day 3.

Maintenance Phase:
The primary analysis of maintenance of healing at week 24 showed both doses of vonoprazan were noninferior to lansoprazole. Treatment effect was generally comparable across different subgroup analyses. Fixed-sequence analyses of secondary end points showed both doses of vonoprazan were superior to lansoprazole for maintenance of healing in LA Grade C/D esophagitis (Table 13).

Table 13: Primary and Secondary Efficacy End Points in Predefined Fixed-Sequence Analyses for Maintenance Phase

Efficacy End Point	Vonoprazan 20 mg (n=291)	Vonoprazan 10 mg (n=293)	Lansoprazole 15 mg (n=294)	Difference (95% CI) vonoprazan, 20 mg, vs lansoprazole, 15 mg	Difference (95% CI) vonoprazan, 10 mg, vs lansoprazole 15 mg
Healing maintained, %	80.7	79.2	72	8.7 (1.8–15.5), P= 0.0001*	7.2 (0.2-14.1), P= 0.0001*
Healing maintained in LA Grade C/D, %	77.2	74.7	61.5	15.7 (2.5 - 28.4), P = 0.020#	13.3 (0.02-26.1) P = 0.049#
24-hour heartburn-free days, mean (SD), %	80.6 (30)	80.9 (28.6)	78.6 (27.5)	2 (-2.6 to 6.7)	2.3 (-2.3 to 6.8)

*P for noninferiority 0.0001, #P values for superiority

Post hoc analysis revealed maintenance of healing for LA Grade A/B esophagitis of 82.3% for vonoprazan 20 mg, 81.3% for vonoprazan 10 mg, and 77.1% for lansoprazole (difference vs 20 mg, 5.3%; 95% CI, -2.7% to 13.2%; difference vs 10 mg, 4.3%; 95% CI, -3.8% to 12.3%).

Predefined exploratory analysis showed higher distributions of percentage of heartburn-free days for vonoprazan (Table 14).

Table 14: Predefined exploratory analysis of percentage of heartburn-free days

Efficacy End Point	Vonoprazan 20 mg (n=291)	Vonoprazan 10 mg (n=293)	Lansoprazole 15 mg (n=294)	P value, vonoprazan, 20 mg, vs. lansoprazole, 15 mg	P value, vonoprazan, 10 mg, vs. lansoprazole 15 mg
Heartburn-free days, median, %	95.2	94.6	89.3	P= 0.002	P= 0.026
Heartburn-free days in LA Grade A/B, median, %	94.3	94	87.8		
Heartburn-free days in LA Grade C/D patients, median, %	97.6	95.4	90.5		

The most common adverse events reported in the healing phase was diarrhea and in the maintenance phase was COVID-19.

Study Conclusion:

Vonoprazan was noninferior and superior to the PPI lansoprazole in healing and maintenance of healing of erosive esophagitis in patients negative for H pylori infection from the US and Europe. Differences in favor of vonoprazan were greater in patients with LA Grade C/D esophagitis than in those with LA Grade A/B esophagitis. Prespecified analyses indicated superiority for vonoprazan in patients with LA Grade C/D esophagitis.

Study 3:

This was a phase III, randomised, double-blind, multicentre trial for assessment of efficacy and safety of vonoprazan compared with lansoprazole in 56 sites across Asia in patients with endoscopically confirmed erosive esophagitis.[42]

Study design:

This was a randomised, double-blind, double-dummy, parallel-group, multicentre study conducted in 56 sites across Asia. Patients with endoscopically confirmed erosive esophagitis were stratified according to the LA classification grade A/B or C/D and randomised 1:1 to receive vonoprazan 20 mg or lansoprazole 30 mg, once daily for up to 8 weeks.

Study endpoints:

- The primary efficacy endpoint was EE healing rate at 8 weeks
- The secondary efficacy endpoints were EE healing rates at 2 and 4 weeks of treatment
- Additional efficacy endpoints included the subjective symptoms of EE as recorded in patient diaries (eg, heart burn, gastric acid regurgitation), health related quality of life (HRQoL) over 8 weeks and the percentage of days without rescue medication during treatment

Results:

Non-inferiority of vonoprazan compared with lansoprazole in terms of EE healing rate at 8 weeks was demonstrated. Rate of healing at 2 weeks, 4 weeks and 8 weeks is shown in Figure 10.

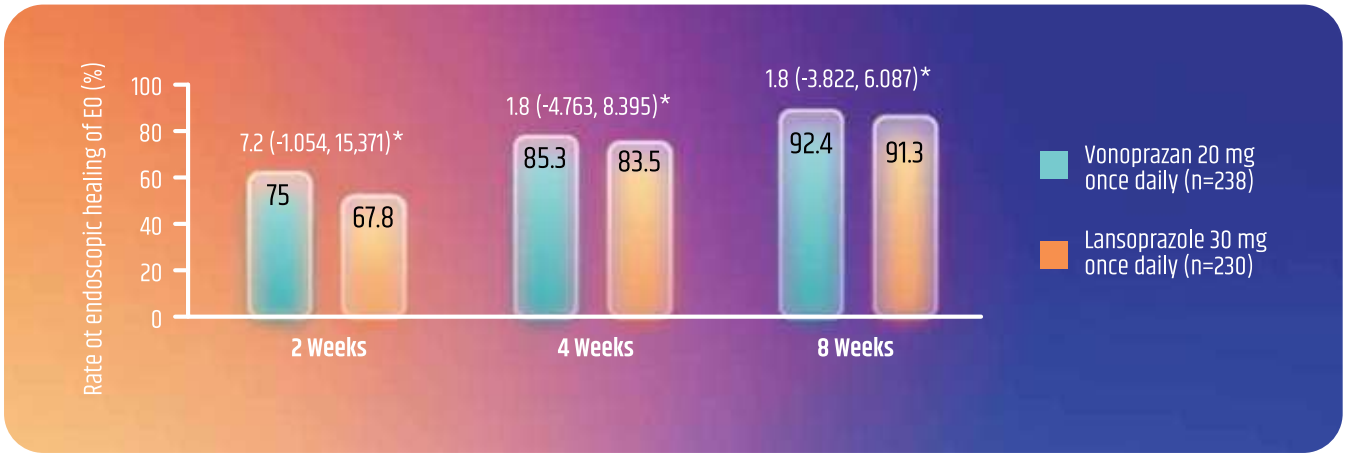


Figure 10: Rate of endoscopic healing of EE at 2, 4, 8-week treatment period for full analysis set

In patients with baseline LA classification grade C/D, 2-week, 4-week and 8-week EE healing rates were numerically higher with vonoprazan versus lansoprazole (Figure 11).

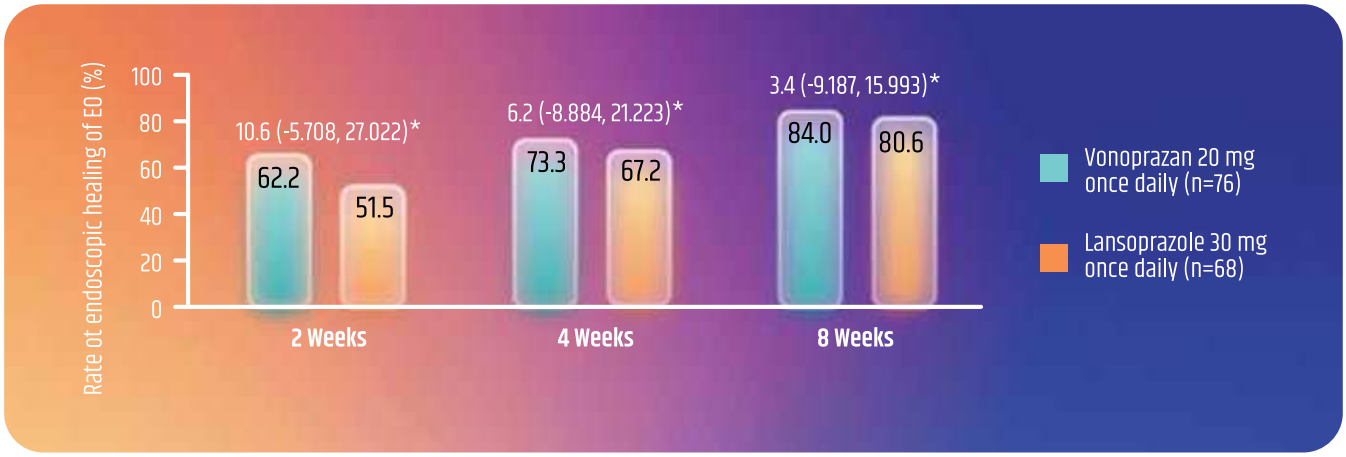


Figure 11: Rate of endoscopic healing of EE at 2, 4, 8-week treatment period in patients with LA classification C/D

For the additional efficacy endpoints (subjective symptoms, HRQoL and days without rescue medication), there were no statistically significant differences between the treatment arms.
The proportion of patients without heart burn at week 8 was numerically higher in the vonoprazan group at 70.5% compared with 66.0% in the lansoprazole group.
The incidence of TEAEs was similar between the two arms: 38.1% (93/244) in the vonoprazan group and 36.6% (86/235) in the lansoprazole group, respectively.

Study Conclusion:
Vonoprazan 20 mg once daily was non-inferior to lansoprazole 30 mg once daily for healing EE at 8 weeks and was well tolerated, thus indicating that vonoprazan is effective for the treatment of EE.

Trial in patients with duodenal or gastric ulcers

Study 1:
Two phase 3, non-inferiority, randomized, double-blind, double-dummy, multicentre, parallel-group trials were conducted to evaluate the non-inferiority of vonoprazan vs. lansoprazole, a proton pump inhibitor, for the treatment of gastric ulcer (GU) or duodenal ulcer (DU).[43]

Study Design:
OPD patients aged ≥ 20 years were eligible for inclusion if they had at least 1 endoscopically confirmed GU or DU with a white coating at least 5 mm wide at the start of the treatment period. Study patients were randomly assigned at a 1:1 ratio to receive either vonoprazan 20 mg or lansoprazole 30 mg once daily after eating breakfast for 8 weeks (GU) or 6 weeks (DU).

The follow-up period began when healing of GU or DU was endoscopically confirmed (the white ulcer coating was not visible), or at Week 8 (GU) or Week 6 (DU). After healing was endoscopically confirmed, follow- up continued for 8 weeks (GU), 6 weeks (DU), or until recovery of the baseline serum gastrin level.

Each patient who had endoscopically confirmed GU or DU healing at Week 2, 4 or 8 (GU), and at Week 2, 4 or 6 (DU) was discontinued from the study medication and the patient was considered to be a completed case.

Study Endpoints:
- Primary endpoint: proportion of patients with endoscopically confirmed GU or DU healing at Week 8 (GU) or Week 6 (DU)
- Secondary endpoints: the proportion of patients with endoscopically confirmed GU and DU healing at Weeks 2 and 4 and the resolution of gastrointestinal symptoms related to GU or DU during the treatment

Results:
- **For GU study**
  - 93.5% (216/231) of vonoprazan-treated patients and 93.8% (211/225) of lansoprazole-treated patients achieved healed GU; non-inferiority of vonoprazan to lansoprazole was confirmed [difference = -0.3% (95% CI-4.750, 4.208); P = 0.0011].
  - The resolution of heartburn was higher in the vonoprazan group compared with the lansoprazole group (difference: 14.5%; 95% CI: 2.820, 26.162

- **For DU study**
  - 95.5% (170/178) of vonoprazan-treated patients and 98.3% (177/180) of lansoprazole-treated patients achieved healed DU; non-inferiority to lansoprazole was not confirmed [difference = -2.8% (95% CI
  - 6.400, 0.745); P = 0.0654]. However, more than 95% of patients in both the vonoprazan and lansoprazole groups experienced DU healing.
  - In DU study, the resolution of symptoms during the study was similar between groups with the exception of heartburn and anorexia, which had numerically higher resolution rates in the vonoprazan group compared with the lansoprazole group.

• Most treatment-emergent adverse events (TEAEs) were mild in severity, and few drug-related TEAEs were reported. Overall, vonoprazan was well tolerated in Japanese patients with GU or DU for up to 8 weeks of treatment.

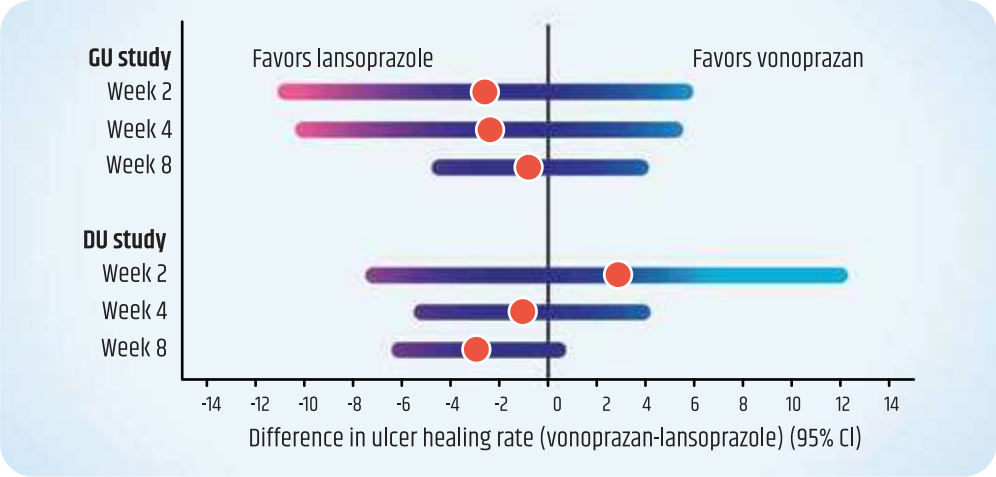


Figure 12: Difference in the proportions of patients with healed GU or DU between treatment groups [vonoprazan-lansoprazole (95% CI)].
Data are calculated using the full analysis set. CI, confidence interval; DU, duodenal ulcer; GU, gastric ulcer.

Table 15: Resolution of ulcer-related symptoms in study patients in the gastric ulcer and duodenal ulcer studies

Symptom	GU study			DU study		
	Vonoprazan	Lansoprazole	Difference (Von.—Lan.)	Vonoprazan	Lansoprazole	Difference (Von.—Lan.)
Epigastric pain (postprandial)						
N	77	65		56	61	
Resolved, n (%)	70 (90.9)	61 (93.8)	−2.9	47 (83.9)	53 (86.9)	−3.0
95% CI, lower, upper	82.2, 96.2	84.9, 98.3	−11.6, 5.7	71.7, 92.4	75.8, 94.1	−15.8, 9.7
Epigastric pain (fasting/nocturnal)						
N	120	118		116	123	
Resolved, n (%)	109 (90.8)	106 (89.8)	1.0	98 (84.5)	107 (87.0)	−2.5
95% CI, lower, upper	84.2, 95.3	82.9, 94.6	−6.5, 8.5	76.6, 90.5	79.7, 92.4	−11.4, 6.4
Abdominal distension						
N	42	44		59	38	
Resolved, n (%)	39 (92.9)	39 (88.6)	4.2	48 (81.4)	32 (84.2)	−2.9
95% CI, lower, upper	80.5, 98.5	75.4, 96.2	−7.9, 16.4	69.1, 90.3	68.7, 93.9	−18.1, 12.4
Nausea						
N	44	41		39	36	
Resolved, n (%)	41 (93.2)	37 (90.2)	2.9	36 (92.3)	34 (94.4)	−2.1
95% CI, lower, upper	81.3, 98.6	76.9, 97.3	−8.8, 14.7	79.1, 98.4	81.3, 99.3	−13.3, 9.1
Heartburn						
N	57	50		50	38	
Resolved, n (%)	55 (96.5)	41 (82.0)	14.5	44 (88.0)	33 (86.8)	1.2
95% CI, lower, upper	87.9, 99.6	68.6, 91.4	2.8, 26.2	75.7, 95.5	71.9, 95.6	−12.9, 15.2
Anorexia						
N	56	51		38	41	
Resolved, n (%)	53 (94.6)	43 (84.3)	10.3	35 (92.1)	36 (87.1)	4.3
95% CI, lower, upper	85.1, 98.9	71.4, 92.9	−1.3, 21.9	78.6, 98.3	73.8, 95.9	−8.9, 17.4

Study Conclusion:

Vonoprazan 20 mg has a similar tolerability profile to lansoprazole 30 mg and is non-inferior with respect to GU healing and has similar efficacy for DU healing.

Trial in patients with low dose aspirin therapy:

Study 1:

Double-blind, randomised, non-inferiority study was conducted to compare efficacy and safety of vonoprazan and lansoprazole for secondary prevention of low-dose aspirin (LDA)-associated peptic ulcers in a 24-week study and long-term extension therapy was evaluated in separate study.[44]

Study Design:

Double-blind, randomized, non-inferiority study; single-blind extension study at 104 Japanese sites, including 621 patients (439 in extension) with a history of peptic ulcers who required long-term LDA therapy. Randomized (1:1:1, computer-generated) patients received lansoprazole 15 mg (n=217), vonoprazan 10 mg (n=202) or vonoprazan 20 mg (n=202) once daily for 24 weeks (double-blind), and ≤2 years (extension).

Study Endpoints:

For double blind study:

Primary endpoint: Rate of peptic ulcer recurrence during the 24-week treatment period

Secondary endpoints: Rate of peptic ulcer recurrence within 12 weeks, the rate of occurrence of bleeding in the stomach or duodenum (based on modified Forrest classification,18 cases classified as I or II were reported as bleedings), and the time to peptic ulcer recurrence

Safety endpoints: Safety was assessed based on treatment-emergent adverse events (TEAEs), laboratory test results, ECG findings, vital signs, serum gastrin concentrations, and serum pepsinogen I and II concentrations by RI/PEG method

For single blind extension study:

Primary endpoint: Incidence of TEAEs

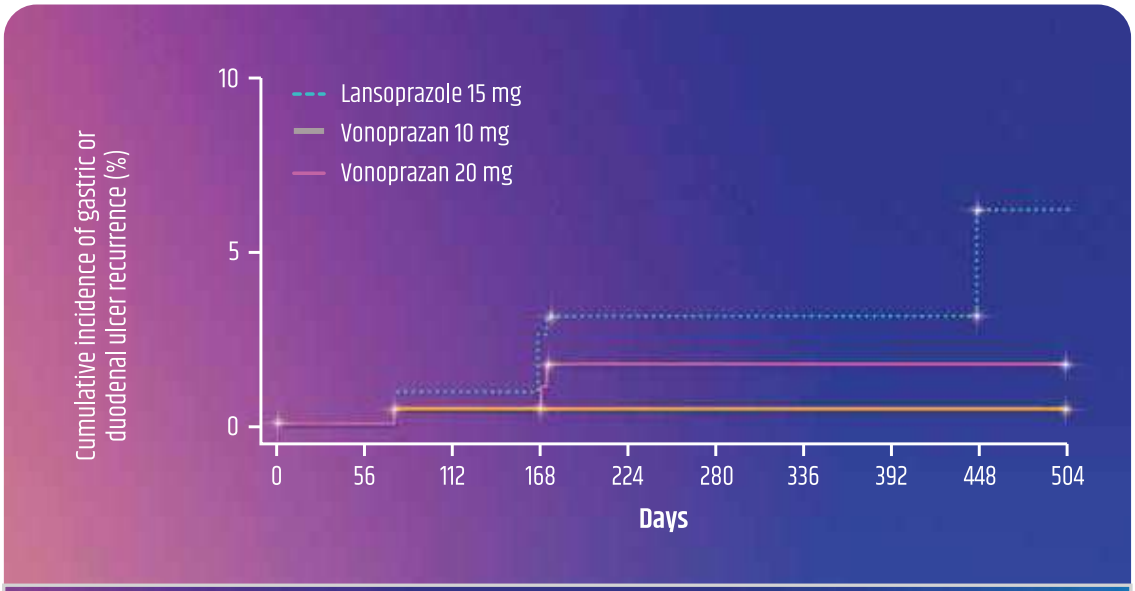
Secondary efficacy endpoint: Rate of peptic ulcer recurrence

Additional secondary endpoints: Rate of occurrence of bleeding in the stomach or duodenum and the time to peptic ulcer recurrence

Results:

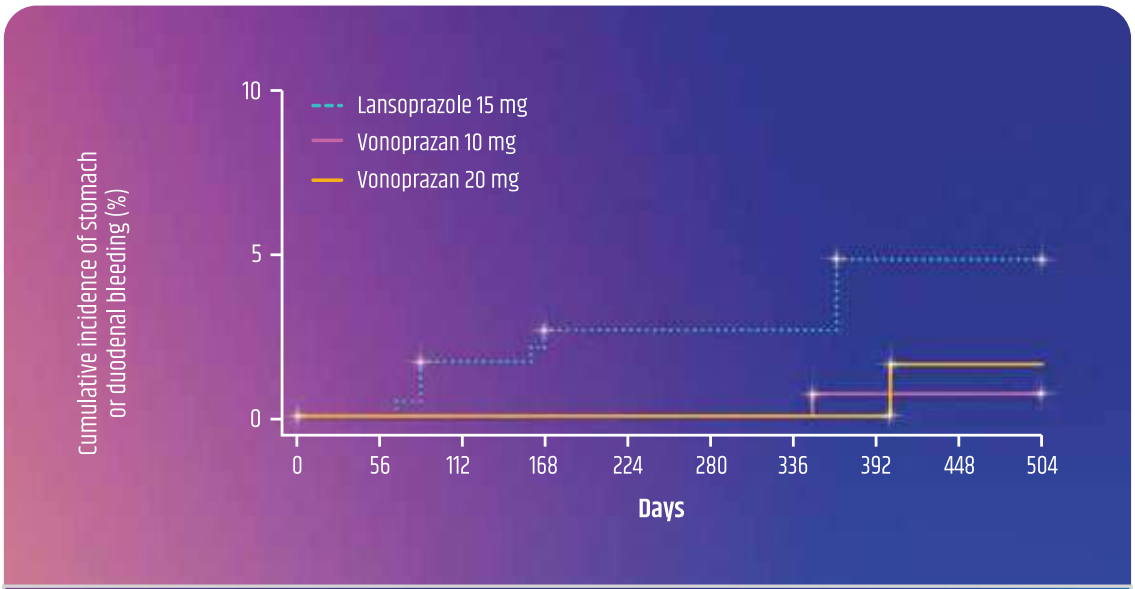
The 24-week peptic ulcer recurrence rate was 2.8%, 0.5%, and 1.5% in the lansoprazole 15 mg, vonoprazan 10 mg and vonoprazan 20 mg groups, respectively. Vonoprazan was non-inferior (Farrington and Manning test: margin 8.7%, significance level 2.5%) to lansoprazole.

In the post hoc analyses of the extension study, peptic ulcer recurrence rates were significantly lower with vonoprazan 10 mg (log-rank test, P=0.039), but not vonoprazan 20 mg (P=0.260), compared with lansoprazole 15 mg. GI bleeding rates were higher with lansoprazole compared with two doses of vonoprazan in both 24-week study and extension study.



Number at risk										
Lansoprazole 15 mg	213	212	198	187	145	144	142	51	43	15
Vonoprazan 10 m	197	195	189	174	147	146	145	63	54	16
Vonoprazan 20 mg	196	194	184	169	128	128	126	56	44	12

Figure 13: Kaplan-Meier estimates of the cumulative incidence of peptic ulcer recurrence in patients treated with lansoprazole 15 mg (dotted line), vonoprazan 10 mg (solid line), or vonoprazan 20 mg (thick solid line)



Number at risk										
Lansoprazole 15 mg	213	212	198	187	145	144	142	51	43	15
Vonoprazan 10 m	197	195	189	174	147	146	145	63	54	16
Vonoprazan 20 mg	196	194	184	169	128	128	126	56	44	12

Figure 14: Kaplan-Meier estimates of bleeding in the stomach or duodenum in patients treated with lansoprazole 15 mg (dotted line), vonoprazan 10 mg (solid line) or vonoprazan 20 mg (thick solid line)

The most common TEAEs reported in patients occurred at similar rates in each group in both studies. There were no cardiovascular events in the 120 patients who concomitantly received clopidogrel and LDA. No clinically significant changes were observed in vital signs, haematology tests, serum chemistry, or urinalysis before and after treatment for any group.

Study Conclusion:

Vonoprazan (10 and 20 mg) was as effective as lansoprazole (15 mg) in preventing peptic ulcer recurrence during LDA therapy, had a similar long-term safety profile, and was well tolerated.

Trial in patients with long term NSAIDs therapy:

Non-inferiority of vonoprazan to lansoprazole was evaluated for secondary prevention of non-steroidal anti-inflammatory drug (NSAID)-induced peptic ulcer (PU) and the safety of vonoprazan was evaluated during extended use.[45]

Study Design:

A phase 3, 24-week, multicenter, randomised, double-blind (DB), active-controlled study, followed by a phase 3, ≥28 week, multicenter, single-blind, parallel-group extension study (EXT) in outpatients (n=642) receiving long-term NSAID therapy who are at risk of PU recurrence was conducted. The patients received vonoprazan (10 mg or 20 mg) or lansoprazole 15 mg once daily for 24 weeks.

Subjects who completed the non-inferiority study were eligible for enrolment in the phase 3, multicenter, single-blind, parallel-group extension study to evaluate safety and ulcer recurrence during longer-term exposure. Patients were enrolled into the extension study on the day following the final visit of the preceding study and were required to complete a minimum of 28 weeks of follow-up up to a maximum of 80 weeks follow-up.

Study Endpoints:

For double-blind study:

Primary endpoint:

- Proportion of patients with recurrent peptic ulcer during 24 weeks of treatment

Secondary endpoints:

- Proportions of patients with recurrent peptic ulcer up to 12 weeks
- Proportion of patients with endoscopically proven bleeding in the stomach or duodenum evaluated according to the cases classified as I or II by modified Forrest classification at week 12 and at week 24
- Time to event of peptic ulcer

Single blind extension study:

Primary endpoint:

- Incidence of TEAEs

Secondary efficacy endpoints:

- Proportion of patients with recurrent peptic ulcer
- Proportion of patients with bleeding in the stomach or duodenum
- Time to event of peptic ulcer

Results:

The proportion of patients with endoscopically confirmed recurrent peptic ulcers within 24 weeks was lower for the vonoprazan 10 mg (3.3%) and 20 mg (3.4%) groups compared with the lansoprazole 15 mg group (5.5%). The non-inferiority of vonoprazan 10 mg and 20 mg to lansoprazole was verified because the percentage difference between treatment groups was <8.3% (percentage difference −2.2%, 95% CI −6.2% to 1.8%, p<0.001; −2.1%, 95% CI −6.1% to 2.0%, p<0.001, respectively).

At each evaluation time point from weeks 12 to 104, the proportion of patients with recurrent peptic ulcer was lower with vonoprazan 10 mg and 20 mg compared with lansoprazole 15 mg, but the differences between the treatment groups were not statistically significant

The proportion of patients with bleeding in the stomach or duodenum was consistently lower with vonoprazan 10 mg and 20 mg compared with lansoprazole 15 mg at all evaluation time points from weeks 12 to 104, and the differences versus lansoprazole were not statistically significant

Across both studies, the incidence of any TEAE was similar among treatment groups without any apparent dose-dependent increase between vonoprazan 10 mg and 20 mg

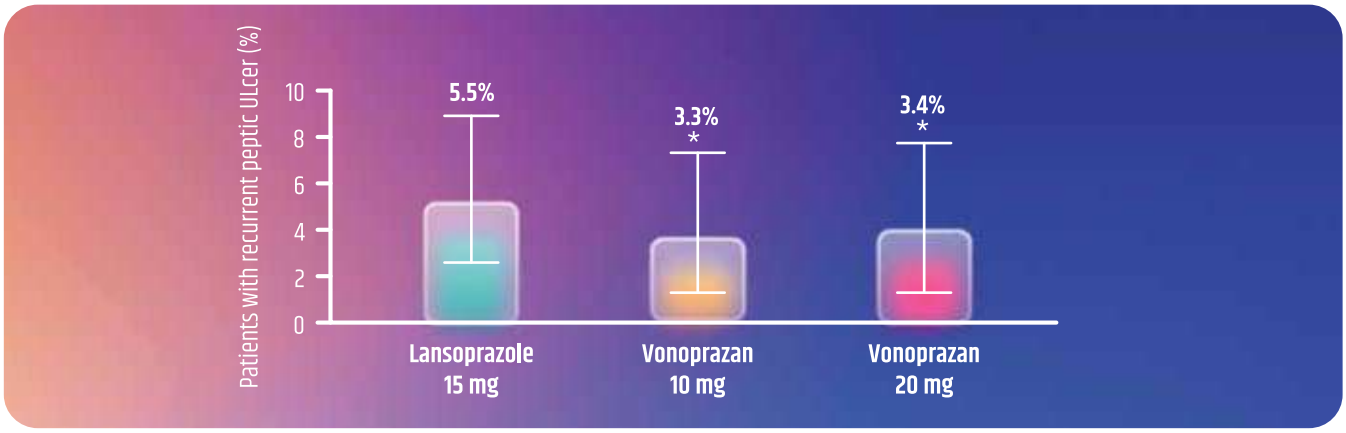


Figure 15: Peptic ulcer recurrence at week 24. The proportion of patients in the full analysis set population with endoscopically confirmed recurrent peptic ulcers within 24 weeks was lower for the vonoprazan 10 mg and 20 mg groups compared with the lansoprazole 15 mg group. *Non-inferiority p<0.001 versus lansoprazole 15 mg. Error bars indicate 95% CIs.

Study Conclusion:
The non-inferiority of vonoprazan (10 and 20 mg) was verified in patients receiving long-term NSAIDs; it was effective and well tolerated in extension study for longer than 1 year, with a safety profile similar to lansoprazole (15 mg).

Trial for Helicobacter pylori eradication

A randomized, double-blind, multicentre, parallel-group study was conducted to assess the efficacy, safety, and tolerability of vonoprazan, as a component of Helicobacter pylori eradication therapy and to verify the noninferiority of Vonoprazan 20 mg to lansoprazole 30 mg as part of first-line triple therapy (with amoxicillin (AMX) 750 mg and clarithromycin (CLR) 200 or 400 mg) in H pylori positive patients with gastric or duodenal ulcer history.[46]

Study Design:
Male or female H pylori-positive patients aged ≥20 years with gastric or duodenal ulcer history were eligible for inclusion in the study. Subjects were randomised in a 1:1:1:1 ratio to receive first-line triple therapy with vonoprazan 20 mg or lansoprazole 30 mg in combination with AMX 750 mg plus CLR 200 or 400 mg. The first 50 subjects who failed their allocated vonoprazan-based or lansoprazole-based first-line triple therapy but who also had good compliance received second-line triple therapy with vonoprazan 20 mg (in combination with AMX 750 mg and MTZ 250 mg) as an open-label treatment. All treatments were administered orally twice daily for 7 days.

Study Endpoints:

Primary endpoint: First-line H pylori eradication rate

Secondary endpoint: Second-line H pylori eradication rate among those who failed first-line eradication therapy

Results:

Of the 650 subjects randomly allocated to either first-line triple therapy, 641 subjects completed first-line therapy, and 50 subjects completed second-line therapy

- The first-line eradication rate was 92.6% with vonoprazan-based triple therapy and 75.9% with lansoprazole-based triple therapy with difference of 16.7% (95% CI 11.2% to 22.1%) which was statistically significant difference in favour of vonoprazan.
- Vonoprazan was shown to be non-inferior to lansoprazole with a non-inferiority margin of 10%.
- The second-line eradication rate was 98.0% in those who received second-line therapy.
- Post hoc analyses showed that first-line eradication rates were significantly higher with vonoprazan than with lansoprazole in various subgroups, including age, gender, CLR dose, CYP2C19 extensive metabolizers, and susceptibility to AMX and CLR.
- Both first-line and second-line triple therapies were well tolerated with no notable differences.

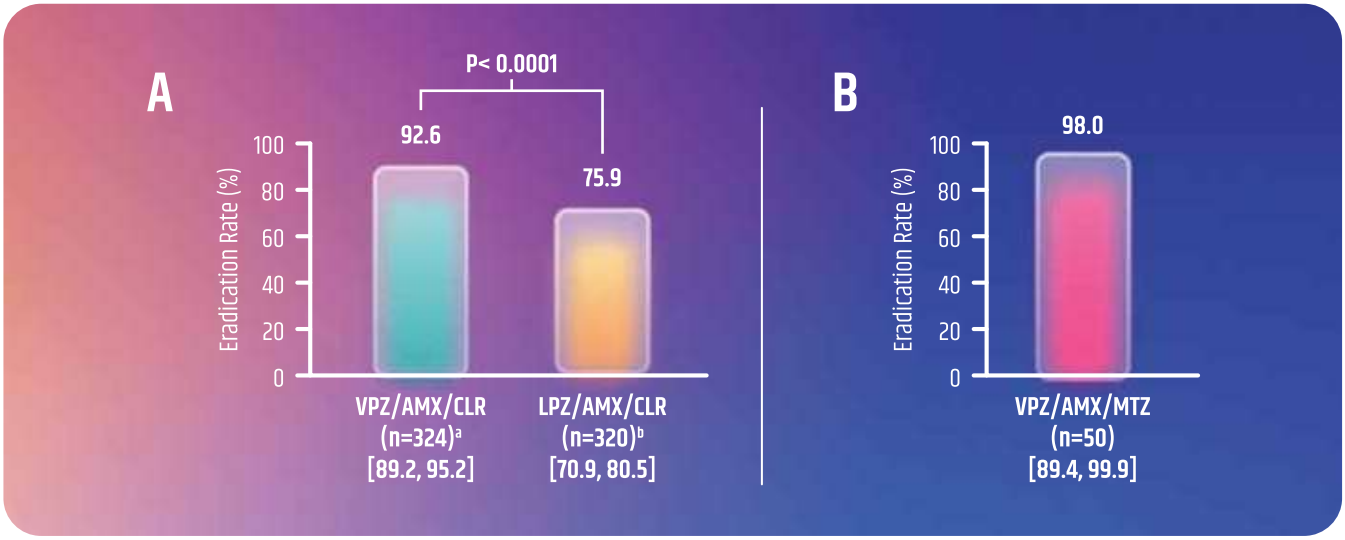


Figure 16: Helicobacter pylori eradication rates (full analysis set) in (A) first-line triple therapy and (B) second-line triple therapy (95% CIs shown in brackets) are shown. AMX, amoxicillin; CLR, clarithromycin; LPZ, lansoprazole; MTZ, metronidazole; VPZ, vonoprazan.

Study Conclusion:

Vonoprazan is effective as part of first-line triple therapy and as part of second-line triple therapy in H pylori-positive patients with a history of gastric or duodenal ulcer.

Phase 4 Clinical Trial

Study 1:

Vonoprazan study In patients with erosive esophagitis to evaluate long-term safety (VISION):

VISION is a 5-year, randomised, open-label, parallel-group, multicentre, phase 4 study conducted in Japan to evaluate the long-term safety and efficacy of vonoprazan 10 mg or 20 mg in patients receiving maintenance treatment for recurrent/reactivated erosive esophagitis, compared with lansoprazole. Results of the prespecified 3-year interim analysis have been reported.[47]

Patients with endoscopically diagnosed erosive esophagitis were randomised 2:1 to once-daily vonoprazan 20 mg or lansoprazole 30 mg, for a 4- to 8-week healing phase. Patients with endoscopically confirmed healing entered a 260-week maintenance phase with a once-daily starting dose of vonoprazan 10 mg or lansoprazole 15 mg.

A total of 202 patients entered the maintenance phase and 167 (82.7%) completed over 1008 days of maintenance treatment and were included in the 3-year interim analysis. Histopathological evaluation of the gastric mucosa showed no neoplastic changes in either group. Incidences of the majority of gastritis parameters in the greater curvature of the antrum and middle gastric body were similar between vonoprazan and lansoprazole groups at week 156.

AEs were reported in 89.6% of patients in the vonoprazan group and 95.5% of patients in the lansoprazole group. AEs were mostly mild or moderate in severity, and the majority of AEs were not considered to be related to the vonoprazan or lansoprazole.

Three-year interim analysis of VISION study reported pathological examination of gastric biopsy specimens and showed no neoplastic/dysplastic alteration of epithelial cells, no gastric neuroendocrine tumours, no exacerbation of gastritis.

Indication[34]

Vonoprazan is indicated in

- Treatment of reflux esophagitis(RE)
- Treatment of gastric ulcer (GU)
- Treatment of duodenal ulcer(DU)
- Prevention of recurrence of gastric ulcer or duodenal ulcer during lowdose aspirin administration.
- Prevention of recurrence of gastric ulcer or duodenal ulcer during NSAIDs administration.
- Adjunct to Helicobacter pylori eradication associated with: Gastric ulcer, Duodenal ulcer, gastric MALT lymphoma, idiopathic thrombocytopenic purpura, the stomach after endoscopic resection of early-stage cancer, or Helicobacter pylori gastritis

Dosage and Administration

- **Reflux esophagitis:**

The usual dose is 20mg of vonoprazan once a day. Administration should be limited to 4 weeks. However, when the effect is insufficient, treatment may be continued for up to 8 weeks.

- **Gastric Ulcer:** The usual dose is 20mg of vonoprazan once a day. Administration should be limited to 8 weeks.
- **Duodenal Ulcer:** The usual dose is 20mg vonoprazan once a day. Administration should be limited to 6 weeks.
- **Prevention of recurrence of gastric ulcer or duodenal ulcer during low-dose aspirin administration:**

The usual dose is 10mg of vonoprazan once a day

- **Adjunct to H. pylori eradication:**

Usually, the following 3 drugs are orally administered at the same time twice daily for 7 days:
20 mg vonoprazan, 750 mg amoxicillin hydrate, and 200 mg clarithromycin. The dose of clarithromycin may be appropriately increased as required, however, the upper limit is 400mg twice daily or physician judgement. When H. pylori eradication treatment with 3 drugs consisting of a proton pump inhibitor, amoxicillin hydrate, and clarithromycin fails, alternative treatment with the following 3 drugs is recommended; 20 mg vonoprazan, 750 mg amoxicillin hydrate, and 250 mg metronidazole, orally administered at the same time twice daily for 7 days. The doses of antibiotic should follow the respective label recommendations for H. pylori eradication.

Method of Administration

Vonoprazan can be taken without regard to food or timing of food.

Contraindications

Hypersensitivity to the active ingredients or to any of the excipients.

Specific warnings and precautions for use

Hepatotoxicity

Hepatic function abnormalities including liver injury have been reported in clinical studies. Post marketing reports have also been received in patients treated with vonoprazan, many of which occurred shortly after initiation of treatment Discontinuation of vonoprazan is recommended in patients who have evidence of liver function abnormalities or if they develop signs or symptoms suggestive of liver dysfunction.

Elevation of intragastric pH

Administration of vonoprazan results in elevation of intragastric pH and is therefore not recommended to be taken with drugs for which absorption is dependent on acidic intragastric pH.

Masking of Symptoms Associated with Gastric Malignancy

Gastric malignancy may present with symptoms associated with acid-related disorders which initially respond to drugs that elevate intragastric pH. A symptomatic response to vonoprazan does not exclude the presence of gastric malignancy.

Clostridium difficile associated diarrhea, including pseudomembranous colitis

Drugs that elevate intragastric pH may be associated with an increased risk of Clostridium difficile gastrointestinal infection. Pseudomembranous colitis may be due to antibiotics used for Helicobacter pylori eradication in combination with vonoprazan. If abdominal pain and frequent diarrhea occur, appropriate measures, including discontinuation of the treatment, should be taken.

Bone Fracture

An increased risk for osteoporosis-related fractures of the hip, wrist, or spine, predominantly in the elderly or in presence of other recognized risk factors, has been reported with the use of proton pump inhibitors, especially with use of high doses over a long-term period (>1 year). The mechanism is not clear and is likely to be multifactorial.

Drug Interactions

Administration of vonoprazan results in elevation of intragastric pH, suggesting that it may interfere with the absorption of drugs where gastric pH is an important determinant of oral bioavailability. Use of vonoprazan is therefore not recommended with some of these drugs for which absorption is dependent on acidic intragastric pH such as atazanavir and nelfinavir, due to significant reduction in their bioavailability.

Vonoprazan is metabolized mainly by hepatic drug-metabolizing enzyme CYP3A4 and partially by CYP2B6, CYP2C19 and CYP2D6.

With strong CYP3A4 inhibitors, e.g., clarithromycin, blood concentration of vonoprazan may increase. It has been reported that blood concentration of vonoprazan increased in concomitant use with clarithromycin by 1.5- fold, but no dose adjustment of vonoprazan is considered necessary. Coadministration of vonoprazan with the antibiotic regimen clarithromycin and amoxicillin increased concentrations of vonoprazan by up to 1.9-fold. No increase was observed with the antibiotic regimen of metronidazole and amoxicillin. No dose adjustment of vonoprazan is considered necessary. There were no clinically significance effects of low-dose aspirin or NSAIDs on the pharmacokinetics of vonoprazan, and no clinically significance effects of vonoprazan on the pharmacokinetics of low-dose aspirin or NSAIDs. The effect on platelet-aggregating inhibitory activity of low-dose aspirin was not considered clinically meaningful.

Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy and Lactation

Pregnancy

No clinical studies have been conducted to date to evaluate vonoprazan in subjects who are pregnant. In a rat toxicology study, embryo-foetal toxicity was observed following exposure of more than approximately 28 times of the exposure (AUC) at the maximum clinical dose (40mg/day) of vonoprazan. As a precaution, vonoprazan should not be administered to women who are or may be pregnant, unless the expected therapeutic benefit is thought to outweigh any possible risk.

Lactation

No clinical studies have been conducted to date to evaluate vonoprazan in subjects who are lactating. It is unknown whether vonoprazan is excreted in human milk. In animal studies it has been shown that vonoprazan was excreted in milk. During treatment with vonoprazan, nursing should be avoided if the administration of this drug is necessary for the mother.

Effects on ability to drive and use machines

The influence of vonoprazan on the ability to drive or use machines is unknown.

Undesirable effects

Clinical Trials

Clinical trial data for expected adverse events is based on pooled safety analysis from the following studies: EE healing (CCT-001 and CCT-002), EE maintenance therapy (CCT-003 and OCT-001), GU healing (CCT-101), DU healing (CCT-102), prevention of recurrence of peptic ulcer associated with NSAID use (CCT-301, OCT-301 and OCT-303), prevention of recurrence of peptic ulcer associated with LDA use (CCT-302, OCT-302 and OCT-304) and treatment of non-erosive reflux disease (NERD; CCT- 201). Although the study in patients with NERD has the placebo arm and is considered as the best data, the number of patients (N=449 and 278 for TAK-438 and placebo, respectively) is relatively small compared to the number of patients of all other active-comparator studies combined (N=3162 and 1392) for TAK-438 and AG-1749 [Lansoprazole], respectively). Therefore, the pooled safety data of active-comparator studies are used for the primary analysis. The safety data of CCT-201 study are analysed separately. (Note: AG-1749 (Lansoprazole) is the only comparator used in the comparator studies.)
The following convention is used for the classification of the frequency of an adverse drug reaction (ADR) and is based on the Council for International Organizations of Medical Sciences (CIOMS) guidelines: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table 16: Adverse reaction with Vonoprazan in clinical studies

Frequency/ System Organ Class*	Common	Uncommon
Gastrointestinal Disorder	Diarrhoea Constipation	Nausea, Abdominal distension
Investigation		Gamma-Glutamyl transferase increased aspartame aminotransferase, increased Liver function test abnormal Alanine aminotransferase increased.

*ADRs included as preferred terms are based on MedDRA version 21.0.

Post-marketing: Following is a list of ADRs which have been observed in post-marketing (Frequency unknown):

Table 17: Adverse reactions with vonoprazan in post-marketing setting

System Organ Class	Preferred Term
Immune system disorders	Drug hypersensitivity (including anaphylactic shock), Drug eruption Urticaria
Hepatobiliary disorders	Hepatotoxicity Jaundice
Skin and subcutaneous tissue disorders	Rash Erythema multiforme Stevens-Johnson syndrome, Toxic epidermal necrolysis

Overdose

There is no experience of overdose with vonoprazan. Vonoprazan is not removed from the circulation by hemodialysis. If overdose occurs, treatment should be symptomatic and supportive.

Drug Abuse and Dependence

Vonoprazan has no known potential for abuse or dependence.

Guideline Recommendation

Japanese Society of Gastroenterology Evidence-based Clinical Practice Guidelines for Gastroesophageal Reflux Disease 2021 [48]

Severe reflux esophagitis (RE):

- Vonoprazan at 20 mg once daily for 4 weeks is proposed as the initial treatment of patients with severe reflux esophagitis. (Weak recommendation, Evidence level: C, 100% agreed)
- Vonoprazan at 10 mg once daily is proposed for the long-term management of severe RE due to the low endoscopic relapse rate. (Weak recommendation, Evidence level C, 93% agreed)

Mild RE:

- PPI and P-CAB both achieve esophageal mucosal healing in the initial treatment of mild RE. Both medications are recommended as a first-line treatment for patients with mild RE. (Strong recommendation, Evidence level B, 100% agreed).
- P-CAB is proposed for the long-term maintenance of mild RE. (Weak recommendation, Evidence level C, 86% agreed)

When the effect of a PPI is insufficient at the standard dose:

- Patient develops severe symptoms despite standard PPI treatment, a change to the standard dose of PPI twice daily or vonoprazan 20 mg once daily is recommended. (Strong recommendation, Evidence level B, 93% agreed)

Thailand guideline 2020 for medical management of gastroesophageal reflux disease[49]

- PCAB is effective and noninferior to PPIs for healing and maintenance of healed EE. In addition, PCABs have a trend toward higher healing rates than PPIs in patients with severe EE.
- Level of evidence: High
- Grade of recommendation: Conditional recommendation

2020 Seoul Consensus on the Diagnosis and Management of Gastroesophageal Reflux Disease[50]

- The efficacy of potassium-competitive acid blockers is comparable to proton pump inhibitors; hence they are recommended as an initial treatment of gastroesophageal reflux disease.
- Level of evidence: Moderate
- Strength of recommendation: strong

Summary

- Acid peptic disease is a common cause of morbidity in India. GERD is common irrespective of geographical location with prevalence ranging from 5% to 28.5% while the prevalence of peptic ulcer is 8.8% .
- A significant number of patients have persistent dyspeptic symptoms and a decreased QoL despite the use of PPIs due to limitations of PPI which include mechanism of action requiring acid activation, rapid elimination, nocturnal increase in gastric acid taking 3 to 5 days to achieve maximum effect.
- Vonoprazan is a novel orally active potassium-competitive acid blocker (P-CAB) which binds to H+/K+ ATPase transporters ionically and prevent acidifying proton secretion.
- It has rapid onset of action, long duration of acid suppression, fewer interindividual variations in terms of acid suppression, and minimum dietary influence on its action.
- Vonoprazan causes potent, long-lasting acid suppression starting from the first day of administration.
- Clinical trials have shown that vonoprazan is highly effective for the treatment of patients with erosive esophagitis, more notably for patients with more severe EE (LA Classification Grades C/D).
- It has shown to be effective for gastric and duodenal ulcer healing, preventing peptic ulcer recurrence during LDA therapy, in patients receiving long-term NSAIDs, also as part of first-line triple therapy and second-line triple therapy in H pylori-positive patients with a history of gastric or duodenal ulcer.
- In clinical trials generally it has been well tolerated for up to 52 weeks.
- Vonoprazan has been recommended by the Japanese Society of Gastroenterology evidence-based clinical practice guidelines for gastroesophageal reflux disease 2021, Thailand guideline 2020 and 2020 Seoul Consensus on the Diagnosis and Management of Gastroesophageal Reflux Disease for medical management of gastroesophageal reflux disease.
- Vonoprazan can be considered as a suitable treatment option in management of GERD, treatment and prevention of gastric and duodenal ulcers and as a part of H. pylori eradication therapy.

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