Report on the Deliberation Results

November 26, 2014

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Takecab Tablets 10 mg, Takecab Tablets 20 mg
[Non-proprietary name]	Vonoprazan Fumarate (JAN*)
[Applicant]	Takeda Pharmaceutical Company Limited
[Date of application]	February 28, 2014

[Results of deliberation]
In the meeting held on November 21, 2014, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 8 years, and the drug substance is classified as a powerful drug, but the drug product is not classified as a poisonous drug or a powerful drug. The product is not classified as a biological product or a specified biological product.

[Conditions for approval]
The applicant is required to develop a risk management plan and implement it appropriately.

**Japanese Accepted Name (modified INN)*

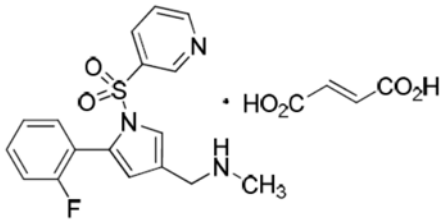
Review Report

November 11, 2014
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Takecab Tablets 10 mg, Takecab Tablets 20 mg
[Non-proprietary name]	Vonoprazan Fumarate
[Name of applicant]	Takeda Pharmaceutical Company Limited
[Date of application]	February 28, 2014
[Dosage form/Strength]	Each tablet contains Vonoprazan Fumarate equivalent to 10 or 20 mg of vonoprazan.
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



Molecular formula: $C_{17}H_{16}FN_3O_2S \bullet C_4H_4O_4$

Molecular weight: 461.46

Chemical name:
1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine monofumarate

[Items warranting special mention]	None
[Reviewing office]	Office of New Drug I

Review Results

November 11, 2014

[Brand name] Takecab Tablets 10 mg, Takecab Tablets 20 mg
[Non-proprietary name] Vonoprazan Fumarate
[Name of applicant] Takeda Pharmaceutical Company Limited
[Date of application] February 28, 2014
[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the following has been demonstrated and its safety is acceptable in view of its observed benefits: the treatment of gastric ulcer, duodenal ulcer, or reflux esophagitis; the prevention of recurrent gastric or duodenal ulcer associated with low-dose aspirin administration; the prevention of recurrent gastric or duodenal ulcer associated with non-steroidal anti-inflammatory drug administration; as well as adjunct therapy to *Helicobacter pylori* eradication in gastric ulcer, duodenal ulcer, gastric mucosa-associated lymphatic tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, the stomach after endoscopic resection of early stage gastric cancer, or *Helicobacter pylori* gastritis.

As a result of its review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the indications and the dosage and administration as shown below, with the following conditions.

[Indications]
- Treatment of gastric ulcer, duodenal ulcer, or reflux esophagitis; prevention of recurrent gastric or duodenal ulcer associated with low-dose aspirin administration; and prevention of recurrent gastric or duodenal ulcer associated with non-steroidal anti-inflammatory drug administration

- Adjunct therapy to *Helicobacter pylori* eradication in the following:
  Gastric or duodenal ulcer, gastric mucosa-associated lymphatic tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, the stomach after endoscopic resection of early stage gastric cancer, or *Helicobacter pylori* gastritis

[Dosage and administration]
- Treatment of gastric ulcer and duodenal ulcer:
  The usual adult dosage is 20 mg of vonoprazan administered orally once daily. The usual treatment period should be up to 8 weeks for gastric ulcer and up to 6 weeks for duodenal ulcer.

- Treatment of reflux esophagitis:
  The usual adult dosage is 20 mg of vonoprazan administered orally once daily. The usual treatment period should be up to 4 weeks, but it may be extended up to 8 weeks if response to the initial course of the treatment is inadequate.

  For the maintenance therapy to prevent recurrence or relapse of reflux esophagitis, the dosage is 10 mg administered orally once daily. However, when response to the initial dose is inadequate, the dose may be increased to 20 mg once daily.

- Prevention of recurrent gastric or duodenal ulcer assosicated with low-dose aspirin administration:
  The usual adult dosage is 10 mg of vonoprazan administered orally once daily.

- Prevention of recurrent gastric or duodenal ulcer associated with non-steroidal anti-inflammatory drug administration:
  The usual adult dosage is 10 mg of vonoprazan administered orally once daily.

- Adjunct therapy to *Helicobacter pylori* eradication:
  For adults, the following 3-drug regimen should be administered orally at the same time twice daily for 7 days: 20 mg of vonoprazan, 750 mg (potency) of amoxicillin hydrate, and 200 mg (potency) of clarithromycin. The dose of clarithromycin may be increased as clinically warranted, but it should not exceed 400 mg (potency)/dose twice daily.

  In adult patients in whom *Helicobacter pylori* eradication with a 3-drug regimen comprising a proton pump inhibitor, amoxicillin hydrate and clarithromycin was unsuccessful, the following 3 drugs should be administered orally twice daily for 7 days as an alternative treatment: 20 mg of vonoprazan, 750 mg (potency) of amoxicillin hydrate, and 250 mg of metronidazole.

[Conditions for approval]
The applicant is required to develop a risk management plan and implement it appropriately.

Review Report (1)

October 27, 2014

I. Product Submitted for Registration

[Brand name] Takecab Tablets 10 mg, Takecab Tablets 20 mg

[Non-proprietary name] Vonoprazan Fumarate

[Name of applicant] Takeda Pharmaceutical Company Limited

[Date of application] February 28, 2014

[Dosage form/Strength] Each tablet contains Vonoprazan Fumarate equivalent to 10 or 20 mg of vonoprazan.

[Proposed indication]

- Treatment of gastric ulcer, duodenal ulcer, or reflux esophagitis, prevention of recurrent gastric or duodenal ulcer associated with low-dose aspirin administration, and prevention of recurrent gastric or duodenal ulcer associated with non-steroidal anti-inflammatory drug administration

- Adjunct therapy to *Helicobacter pylori* eradication in the following: Gastric or duodenal ulcer, gastric mucosa-associated lymphatic tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, the stomach after endoscopic resection of early stage gastric cancer, or *Helicobacter pylori* gastritis

[Proposed dosage and administration]

- Treatment of gastric ulcer and duodenal ulcer:
  The usual adult dosage is 20 mg of vonoprazan administered orally once daily. The usual treatment period should be up to 8 weeks for gastric ulcer and up to 6 weeks for duodenal ulcer.

- Treatment of reflux esophagitis:
  The usual adult dosage is 20 mg of vonoprazan administered orally once daily. The usual treatment period is up to 4 weeks, but it may be extended up to 8 weeks if the efficacy is inadequate. For the maintenance therapy to prevent recurrence or relapse of reflux esophagitis, the dose for oral use is 10 mg or 20 mg once daily.

- Prevention of recurrent gastric or duodenal ulcer associated with low-dose aspirin administration:
  The usual adult dosage is 10 mg of vonoprazan administered orally once daily.

- Prevention of recurrent gastric or duodenal ulcer associated with non-steroidal anti-inflammatory drug administration:
  The usual adult dosage is 10 mg of vonoprazan administered orally once daily.

- Adjunct therapy to *Helicobacter pylori* eradication:
  For adults, the following 3-drug regimen should be administered orally at the same time twice daily for 7 days: 20 mg of vonoprazan, 750 mg (potency) of amoxicillin hydrate, and 200 mg (potency) of clarithromycin. The dose of clarithromycin may be increased up to 400 mg (potency)/dose twice daily, as clinically warranted. .

  In adults patients in whom *Helicobacter pylori* eradication with a 3-drug regimen comprising vonoprazan or a proton pump inhibitor, amoxicillin hydrate, and clarithromycin was unsuccessful, the following 3 drugs should be administered orally twice daily for 7

days as an alternative treatment: 20 mg of vonoprazan, 750 mg (potency) of amoxicillin hydrate, and 250 mg of metronidazole.

II. Summary of the Submitted Data and the Outline of Review by Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and the outline of review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

Reflux esophagitis is a disease involoving mucosal injury in the lower esophagus due to reflux of gastric acid back into the esophagus and is accompanied by symptoms such as heartburn and acid reflux. Acid reflux symptoms due to reflux esophagitis recur chronically in many patients. For the treatment, it is considered important to alleviate acid reflux symptoms by inhibiting acid secretion.

Peptic ulcer (gastric ulcer, duodenal ulcer) is a mucosal defect caused by autodigestion with gastric acid or pepsin. Presence of gastric acid or hyperacid state is not an underlying cause of peptic ulcer, but healing of peptic ulcer is disturbed in the presence of the acid. Inhibition of the acid secretion would enhance the healing.

In pharmacotherapy for reflux esophagitis and peptic ulcer, proton pump inhibitors (PPIs) are recommended as the first-line drugs.[1,2]

It has been demonstrated that *Helicobacter pylori* (*H. pylori*) infection plays an important role etiologically and pathologically in various upper gastrointestinal diseases such as gastric ulcer, duodenal ulcer, and gastric MALT lymphoma through the underlying chronic inflammation in the gastric mucosa. The major *H. pylori* eradication therapy is a 3-drug combination therapy consisting of a PPI and 2 antimicrobial agents.[3] PPIs are used as an adjunct to the *H. pylori* eradication in order to increase gastric pH to a condition where the antimicrobial agents are effectively antimicrobial.[4]

Low-dose aspirin (LDA) used in antiplatelet therapy and non-steroidal anti-inflammatory drugs (NSAIDs) used in patients with rheumatoid arthritis and osteoarthritis for anti-inflammation and analgesia suppress biosynthesis of endogenous prostaglandin, which protect the gastric mucosa and maintain the gastric mucosal blood flow, and disrupt resistance of gastric mucosa to gastric acid, consequently causing peptic ulcer. In general, the first-line treatment for peptic ulcer associated with the LDA or NSAID administration is to discontinue LDA or NSAID, if possible, and provide regular anti-ulcer therapy. However, it is more clinically important to prevent the development of ulcer associated with the administration of those drugs rather than to provide such treatment after its development because (1) LDA is used to prevent thrombogenesis and embolization in the cerebrovascular and cardiovascular systems, and its discontinuation may induce life-threatening significant cardiovascular events; (2) discontinuation of NSAIDs may lead to development of pain, thereby worsening the quality of life remarkably; and (3) gastrointestinal bleeding associated with the LDA administration may not readily resolve due to the antiplatelet effect of aspirin, resulting in life-threatening events. The combination of LDA or NSAID with acid secretion inhibitors is considered to be effective in preventing development of peptic ulcer associated with LDA or NSAID administration, and the use of PPIs is thus recommended in patients at a high risk of ulcer recurrence due to a history of peptic ulcer.[1]

Vonoprazan fumarate (hereinafter referred to as vonoprazan) is a PPI synthesized and developed by the applicant and expected to inhibit acid secretion by inhibiting H^+,K^+-ATPase in gastric mucosal parietal cells in a reversible and potassium-competitive manner, unlike the existing PPIs. Non-clinical data demonstrated the continuous acid secretion inhibitory effect, and thus clinical development of vonoprazan was initiated.

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1 The Japanese Society of Gastroenterology, eds. *Guideline for peptic ulcer treatment*, Nankodo Co., Ltd., 2009

2 The Japanese Society of Gastroenterology, eds. *Guideline for treatment of gastroesophageal reflux disease*, Nankodo Co., Ltd., 2009

3 *Journal of the Japanese Society for Helicobacter Research.* 2009;10:1-25

4 *Best Pract Res Clin Gastroenterol.* 2001;15:413-431

Vonoprazan has not been approved overseas as of September 2014.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

The drug substance, vonoprazan fumarate, occurs as white crystals or crystalline powder. The determined properties of the drug substance include solubility, hygroscopicity, melting point, thermal analysis, dissociation constant, and partition coefficient.

The chemical structure of the drug substance has been elucidated by elemental analysis, mass spectrometry, ultraviolet-visible spectrophotometry (UV/VIS), infrared spectrophotometry (IR), nuclear magnetic resonance spectrometry (^{1}H-NMR, ^{13}C-NMR), and X ray crystallography.

2.A.(1).2) Manufacturing process

[redacted].

2.A.(1).3) Control of drug substance

[redacted].

2.A.(1).4) Stability of drug substance

The stability studies conducted on the drug substance were as shown in Table 1. Photostability data showed that the drug substance is photolabile.

Table 1. Stability studies on drug substance

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term testing	3 pilot batches	25°C ± 2°C	60%RH ± 5%RH	Polyethylene bag	24 months
Accelerated testing	3 pilot batches	40°C ± 2°C	75%RH ± 5%RH		6 months

Based on the above, a retest period of 3 years has been proposed for the drug substance when placed in a double polyethylene bag and stored in a fiber drum at room temperature, in accordance with the "Guideline on Evaluation of Stability Data" (PMSB/ELD Notification No. 0603004 dated June 3, 2003 [ICH Q1E Guideline]). The long-term stability testing will continue up to 36 months.

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product and formulation development

The drug product is film-coated tablets, containing 13.36 mg (10 mg as vonoprazan) or 26.72 mg (20 mg as vonoprazan) of vonoprazan fumarate per tablet. It contains the following excipients: D-mannitol, microcrystalline cellulose, croscarmellose sodium, hydroxypropylcellulose, fumaric acid, magnesium stearate, hypromellose, macrogol 6000, titanium oxide (in 10 mg and 20 mg tablets); yellow ferric oxide (only in10 mg tablets); and red ferric oxide (only in 20 mg tablets).

2.A.(2).2) Manufacturing process

[redacted].

2.A.(2).3) Control of drug product

The proposed specifications for the drug product include content, description, identification (UV/VIS, HPLC), purity (related substances, HPLC), uniformity of dosage units (content uniformity), dissolution, and assay (HPLC).

2.A.(2).4) Stability of drug product

The stability studies conducted on the drug product were as shown in Table 2, and photostability data showed that the drug product is photostable.

Table 2. Stability studies on drug product

Study	Primary batches[a)]	Temperature	Humidity	Storage form	Storage period
Long-term testing	3 pilot batches	25°C ± 2°C	60%RH ± 5%RH	PTP packaging	24 months
	3 pilot batches			Polyethylene bottle packaging	
Accelerated testing	3 pilot batches	40°C ± 2°C	75%RH ± 5%RH	PTP packaging	6 months
	3 pilot batches			Polyethylene bottle packaging	

a) 3 batches for 10 mg tablets and 20 mg tablets

Based on the above, a shelf life of 3 years has been proposed for the drug product when stored at room temperature in PTP packaging or polyethylene bottle packaging, in accordance with the ICH Q1E Guideline. The long-term stability testing will continue up to 36 months.

2.B Outline of the review by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance and drug product is adequately controlled.

3. Non-clinical data

In the following non-clinical data, the doses and plasma concentrations of vonoprazan fumarate (hereinafter referred to as vonoprazan) are expressed as the amounts of vonoprazan.

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

As primary pharmacodynamic studies, *in vivo* studies on effects on upper gastrointestinal tract injury formation and gastric acid secretion as well as *in vitro* studies on inhibitory effect against H^+,K^+-ATPase and anti-*H. pylori* activity were conducted. As secondary pharmacodynamic studies, studies on inhibition of various enzymes except for H^+,K^+-ATPase were conducted. As safety pharmacology studies, effects on the central nervous, cardiovascular, and respiratory systems were assessed. As pharmacodynamic drug-drug interaction studies, pharmacodynamic interactions with various antimicrobial agents and aspirin were assessed.

Unless otherwise specified, male animals were used in the *in vivo* studies, and the vehicle for vonoprazan was 0.5% methylcellulose solution and the vehicle for lansoprazole (LPZ) was 0.5% methylcellulose/1% sodium hydrogen carbonate solution. The study results are expressed as mean ± standard error (SE).

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) Effects on upper gastrointestinal tract injury formation

(a) Inhibitory effect against reflux esophagitis in rats (4.2.1.1-1, Report TAK-438-10004)

Following single oral administration of vonoprazan (0.5, 1, 2, 4 mg/kg), LPZ (1, 2, 4, 8 mg/kg), or vehicles to fasted rats, the pyloric ring and borderline between the forestomach and gastric corpus were

ligated at 1 hour post-dose, and then 5 hours later the injury index[5] in the esophagus was assessed (Table 3). Compared with the corresponding vehicle group, a statistically significant inhibitory effect against gastrointestinal tract injury formation was observed in the vonoprazan ≥2 mg/kg groups and in the LPZ ≥4 mg/kg groups. The ID_{50} value (95% confidence interval [CI]) was 1.27 [0.90, 1.85] and 3.20 [1.87, 5.43] mg/kg, respectively.

Table 3. Inhibitory effect against gastrointestinal tract injury formation in rats

Vonoprazan group	Esophagus injury index	LPZ group	Esophagus injury index
Vehicle group	3.6 ± 0.2	Vehicle group	3.5 ± 0.3
Vonoprazan 0.5 mg/kg group	3.0 ± 0.4	LPZ 1 mg/kg group	3.5 ± 0.3
Vonoprazan 1 mg/kg group	2.6 ± 0.6	LPZ 2 mg/kg group	1.9 ± 0.7
Vonoprazan 2 mg/kg group	0.6 ± 0.4*	LPZ 4 mg/kg group	1.9 ± 0.4*
Vonoprazan 4 mg/kg group	0.0*	LPZ 8 mg/kg group	0.3 ± 0.3*

n = 7-8, mean ± SE
*, $P \leq 0.025$ (v.s. vehicle group; one-sided *Shirley-Williams* test)

(b) Inhibitory effect against aspirin-induced gastric mucosal injury in rats (4.2.1.1-2, Report TAK-438-10002)

Following single oral administration of vonoprazan (0.5, 1, 2, 4 mg/kg), vonoprazan's vehicle, LPZ (0.5, 1, 2, 4 mg/kg), or LPZ's vehicle to fasted rats, aspirin 200 mg/kg was orally administered at 1 hour. At 3.5 hours after aspirin dosing, 0.5% Evans blue solution was intravenously administered, and 30 minutes later, the gastric mucosal injury index[6] was assessed (Table 4). Compared with the corresponding vehicle group, a statistically significant inhibitory effect against gastric mucosal injury was observed in the vonoprazan ≥0.5 mg/kg groups and in the LPZ ≥2 mg/kg groups, and the ID_{50} value [95% CI] was 0.73 [0.43, 1.01] and 0.77 [0.08, 1.45] mg/kg, respectively.

Table 4. Inhibitory effect against aspirin-induced gastric mucosal injury in rats

Vonoprazan group	Gastric mucosal injury index (mm)	LPZ group	Gastric mucosal injury index (mm)
Vehicle group	32.8 ± 5.2	Vehicle group	35.9 ± 11.6
Vonoprazan 0.5 mg/kg group	19.1 ± 3.5*	LPZ 0.5 mg/kg group	19.0 ± 5.0
Vonoprazan 1 mg/kg group	14.9 ± 3.2*	LPZ 1 mg/kg group	21.6 ± 7.0
Vonoprazan 2 mg/kg group	6.6 ± 2.2*	LPZ 2 mg/kg group	4.8 ± 1.3*
Vonoprazan 4 mg/kg group	2.1 ± 0.9*	LPZ 4 mg/kg group	5.0 ± 1.5*

n = 8, mean ± SE
*, $P \leq 0.025$ (v.s. vehicle group; one-sided *Shirley-Williams* test)

(c) Inhibitory effect against indomethacin-induced gastric mucosal injury in rats (4.2.1.1-3, Report TAK-438-10003)

Following single oral administration of vonoprazan (0.5, 1, 2, 4 mg/kg), LPZ (2, 4, 8, 16 mg/kg), or vehicles to fasted rats, indomethacin 30 mg/kg was orally administered at 1 hour. At 3.5 hours after indomethacin dosing, 0.5% Evans blue solution was intravenously administered, and 30 minutes later, the gastric mucosal injury index6 was assessed (Table 5). Compared with the corresponding vehicle group, a statistically significant inhibitory effect against gastric mucosal injury was observed in the vonoprazan ≥2 mg/kg groups and in the LPZ ≥8 mg/kg groups, and the ID_{50} value [95% CI] was 1.65 [0.00, 2.04] and 4.38 [3.03, 6.32] mg/kg, respectively.

[5] Esophageal injury was grossly observed and rated on a 0 to 4 level according to the affected area (%) as follows: 0, 0%; 1, 1% to 25%; 2, 26% to 50%; 3, 51% to 75%; 4, >75% or perforation.

[6] Total length of each gastric mucosal injury microscopically measured (mm)

Table 5. Inhibitory effect against indomethacin-induced gastric mucosal injury in rats

Vonoprazan group	Gastric mucosal injury index (mm)	LPZ group	Gastric mucosal injury index (mm)
Vehicle group	29.4 ± 4.0	Vehicle group	37.3 ± 6.9
Vonoprazan 0.5 mg/kg group	34.8 ± 4.8	LPZ 2 mg/kg group	30.3 ± 4.8
Vonoprazan 1 mg/kg group	27.0 ± 2.9	LPZ 4 mg/kg group	23.4 ± 5.5
Vonoprazan 2 mg/kg group	7.9 ± 2.3*	LPZ 8 mg/kg group	3.3 ± 0.8*
Vonoprazan 4 mg/kg group	0.6 ± 0.3*	LPZ 16 mg/kg group	4.3 ± 3.0*

n = 7-8, mean ± SE
*, $P \leq 0.025$ (v.s. vehicle group; one-sided *Shirley-Williams* test)

3.(i).A.(1).2) Acid secretion inhibitory effect

(a) Basal acid output in rats (4.2.1.1-4, Report TAK-438/00071)

Following single oral administration of vonoprazan (0.5, 1, 2, 4 mg/kg), LPZ (1, 2, 4, 8 mg/kg), or vehicles to fasted rats, the pyloric ring was ligated at 1 hour post-dose, and then 3 hours later the accumulated gastric fluid was collected to calculate the total acid output[7] (Table 6). Compared with the corresponding vehicle group, a statistically significant inhibitory effect against basal acid output was observed in both vonoprazan and LPZ groups at the doses of ≥2 mg/kg, and the ID_{50} value [95% CI] was 1.26 [0.98, 1.87] and 1.47 [0.92, 2.11] mg/kg, respectively.

Table 6. Inhibitory effect against basal acid output in rats

Vonoprazan group	Total acid output (μEq/3h)	LPZ group	Total acid output (μEq/3h)
Vehicle group	258.3 ± 34.1	Vehicle group	320.8 ± 91.0
Vonoprazan 0.5 mg/kg group	287.1 ± 28.9	LPZ 1 mg/kg group	225.8 ± 56.6
Vonoprazan 1 mg/kg group	176.1 ± 35.6	LPZ 2 mg/kg group	99.1 ± 21.4*
Vonoprazan 2 mg/kg group	44.6 ± 24.8*	LPZ 4 mg/kg group	52.8 ± 21.8*
Vonoprazan 4 mg/kg group	0.0*	LPZ 8 mg/kg group	8.9 ± 3.8*

n = 6-8, mean ± SE
*, $P \leq 0.025$ (v.s. vehicle group; one-sided *Shirley-Williams* test)

(b) Histamine-stimulated acid secretion in rats (4.2.1.1-5, Report TAK-438/00072)

Following single oral administration of vonoprazan (0.5, 1, 2, 4 mg/kg), LPZ (0.5, 1, 2, 4 mg/kg), or vehicles to fasted rats, the pyloric ring was ligated at 1 hour post-dose, and then histamine dihydrochloride (histamine) 30 mg/kg was subcutaneously administered. At 3 hours after histamine dosing, the accumulated gastric fluid was collected to calculate the total acid output7 (Table 7). Compared with the corresponding vehicle group, a statistically significant inhibitory effect against acid secretion was observed in the vonoprazan ≥1 mg/kg groups and in the LPZ ≥2 mg/kg groups, and the ID_{50} value [95% CI] was 0.86 [0.69, 1.05] and 1.14 [0.79, 1.78] mg/kg, respectively.

Table 7. Inhibitory effect against histamine-stimulated acid secretion in rats

Vonoprazan group	Total acid output (μEq/3h)	LPZ group	Total acid output (μEq/3h)
Vehicle group	325.6 ± 45.9	Vehicle group	280.0 ± 45.6
Vonoprazan 0.5 mg/kg group	271.5 ± 42.2	LPZ 0.5 mg/kg group	283.5 ± 37.5
Vonoprazan 1 mg/kg group	129.2 ± 25.7*	LPZ 1 mg/kg group	158.5 ± 47.7
Vonoprazan 2 mg/kg group	8.6 ± 8.3*	LPZ 2 mg/kg group	47.7 ± 20.8*
Vonoprazan 4 mg/kg group	0.0*	LPZ 4 mg/kg group	16.5 ± 3.9*

n = 7-8, mean ± SE
*, $P \leq 0.025$ (v.s. vehicle group; one-sided *Shirley-Williams* test)

(c) 2-deoxy-D-glucose-stimulated acid secretion in rats (4.2.1.1-6, Report TAK-438/00073)

Following single oral administration of vonoprazan (0.5, 1, 2, 4 mg/kg), LPZ (0.5, 1, 2, 4 mg/kg), or vehicles to fasted rats, the pyloric ring was ligated at 1 hour post-dose, and then 2-deoxy-D-glucose (2-DG) 200 mg/kg was subcutaneously administered. At 3 hours after 2-DG dosing, the accumulated gastric fluid was collected to calculate the total acid output7 (Table 8). Compared with the corresponding vehicle group, a statistically significant inhibitory effect against acid secretion was observed in the

[7] Product of gastric juice volume and acidity. The acidity was calculated from the amount of 0.1 mol/L sodium hydroxide solution consumed to achieve neutralization (pH 7.0).

vonoprazan ≥1 mg/kg groups and in the LPZ ≥2 mg/kg groups, and the ID_{50} value [95% CI] was 0.83 [0.70, 0.98] and 1.57 [1.17, 2.12] mg/kg, respectively.

Table 8. Inhibitory effect against 2-DG-stimulated acid secretion in rats

Vonoprazan group	Total acid output (μEq/3h)	LPZ group	Total acid output (μEq/3h)
Vehicle group	256.8 ± 26.3	Vehicle group	235.9 ± 37.9
Vonoprazan 0.5 mg/kg group	191.1 ± 17.7	LPZ 0.5 mg/kg group	191.2 ± 20.3
Vonoprazan 1 mg/kg group	107.9 ± 21.2*	LPZ 1 mg/kg group	178.9 ± 25.0
Vonoprazan 2 mg/kg group	27.2 ± 8.5*	LPZ 2 mg/kg group	83.2 ± 18.4*
Vonoprazan 4 mg/kg group	0.0*	LPZ 4 mg/kg group	43.5 ± 10.4*

n = 7-8, mean ± SE
*, $P \leq 0.025$ (v.s. vehicle group; one-sided *Shirley-Williams* test)

(d) pH of histamine-stimulated gastric perfusate in rats (4.2.1.1-7, Report TAK-438-10863 ver1.0)
In fasted rats receiving intravenous continuous infusion of histamine at 8 mg/kg/h, after the pH of the gastric perfusate[8] was stabilized around 2, a single dose of vonoprazan (2 mg/kg), LPZ (2, 20 mg/kg), or vehicle[9] was intravenously administered, and then the pH was monitored over time up to 5 hours post-dose (Table 9). In the vonoprazan group, the pH increased to 5.8 at 1 hour post-dose and was maintained at this level up to 5 hours post-dose. In the LPZ 2 and 20 mg/kg groups, on the other hand, the pH increased to 3.8 and 5.2 at 1 hour post-dose and then gradually decreased to 2.9 and 3.2, respectively, at 5 hours post-dose. The applicant explained that a long-lasting acid secretion inhibitory effect can be expected for vonoprazan, because it can stay in the acid production site of the gastric parietal cells at a high concentration for a long period of time[10] due to favorable stability to acid and higher basicity (pKa) compared to LPZ.

Table 9. Increasing effect on gastric perfusate pH under histamine stimulation in rats

	Post-dose gastric perfusate pH				
	0 h	0.5 h	1 h	3 h	5 h
Vehicle group	2.1 ± 0.0	2.1 ± 0.1	2.1 ± 0.1	2.3 ± 0.0	2.5 ± 0.0
Vonoprazan 2 mg/kg group	2.2 ± 0.0	4.8 ± 0.2	5.8 ± 0.1	6.0 ± 0.1	5.9 ± 0.1
LPZ 2 mg/kg group	2.1 ± 0.0	3.8 ± 0.1	3.8 ± 0.1	3.2 ± 0.0	2.9 ± 0.1
LPZ 20 mg/kg group	2.1 ± 0.0	5.1 ± 0.2	5.2 ± 0.2	3.7 ± 0.1	3.2 ± 0.1

n = 5, mean ± SE

(e) Histamine-stimulated acid secretion in dogs (4.2.1.1-8, Report TAK-438/00074)
Following single oral administration of vonoprazan (0.1, 0.3, 1 mg/kg), LPZ (0.3, 1, 3 mg/kg), or vehicle to fasted dogs with a Heidenhain pouch and gastric fistula,[11] histamine 30 μg/kg was subcutaneously administered at 1, 3, 6, 24, and 48 hours. At 90 minutes after histamine dosing, the gastric juice was collected to determine the total acid output,[7] and the percentage of the acid output to the baseline[12] was assessed (Table 10). Compared with the corresponding vehicle group, a statistically significant inhibitory effect against acid secretion was observed in the vonoprazan ≥0.1 mg/kg groups and in the LPZ ≥0.3 mg/kg groups, and the ID_{50} value [95% CI] based on AUC of the acid output (percentage of that to the baseline) from 0 hours to 25.5 hours after vonoprazan or LPZ dosing was 0.21 [0.17, 0.24] mg/kg and >3 mg/kg, respectively.

8 A cannula was inserted into the stomach from the duodenum and forestomach followed by ligation of the esophagus. The gastric perfusion was then implemented with physiological saline at 0.5 mL/min.

9 A mixture of *N,N*-dimethyl acetamide and polyethylene glycol 400 at the volume ratio of 1:1

10 *J Pharmacol Exp Ther.* 2011;337:797-804, *Biochem Pharmacol.* 2011;81:1145-1151

11 Administered in a four-treatment, four-period crossover regimen. The washout period was 2 weeks and 1 week in the vonoprazan and LPZ groups, respectively.

12 Histamine-stimulated acid output on the day before the study treatment

Table 10. Inhibitory effect against histamine-stimulated acid secretion in dogs with gastric fistula

		Percentage of acid output to the baseline (%)					
		1-2.5 h	3-4.5 h	6-7.5 h	24-25.5 h	48-49.5 h	$AUC_{0\text{-}25.5h}$
Vonoprazan group	Vehicle group	101.6 ± 2.3	99.8 ± 3.9	97.6 ± 1.5	96.4 ± 1.9	101.3 ± 3.4	2295 ± 28
	Vonoprazan 0.1 mg/kg group	80.4 ± 2.6	60.5 ± 2.2	58.7 ± 3.8	73.5 ± 2.7	77.3 ± 3.6	1579 ± 54*
	Vonoprazan 0.3 mg/kg group	61.5 ± 4.8	22.0 ± 4.0	31.9 ± 4.4	45.0 ± 5.4	56.8 ± 5.3	936 ± 93*
	Vonoprazan 1 mg/kg group	0.0	0.0	0.0	26.2 ± 4.2	47.5 ± 1.2	293 ± 39*
LPZ group	Vehicle group	96.2 ± 5.7	92.9 ± 3.9	95.6 ± 4.8	92.9 ± 3.8	100.3 ± 4.3	2219 ± 86
	LPZ 0.3 mg/kg group	59.7 ± 3.7	70.5 ± 3.2	77.3 ± 2.8	81.0 ± 1.9	97.3 ± 3.5	1818 ± 43*
	LPZ 1 mg/kg group	35.2 ± 9.1	44.6 ± 6.0	57.8 ± 7.1	68.7 ± 7.9	93.1 ± 4.3	1415 ± 164*
	LPZ 3 mg/kg group	3.8 ± 3.0	37.9 ± 3.7	44.9 ± 5.6	66.3 ± 7.7	94.0 ± 4.9	1195 ± 125*

n = 5, mean ± SE
*, $P \leq 0.05$ (v.s. vehicle group; successive approximation from the high dose by closed testing procedure with pairwise comparisons in the analysis of variance)

3.(i).A.(1).3) *In vitro* study on mechanism of action

(a) Inhibitory effect against acid production in the isolated rabbit fundic gland (4.2.1.1-9, 4.2.1.1-10; Reports TAK-438/00067.001R, TAK-438-10130 ver1.0)

Vonoprazan and LPZ inhibited forskolin-induced acid production[13] in the isolated rabbit fundic gland and the IC_{50} value [95% CI] was 0.30 [not calculable] and 0.76 [0.27, 1.54] μmol/L, respectively.

(b) Inhibitory effect against pig gastric mucosal H^+,K^+-ATPase activity (4.2.1.1-11, Report TAK-438-11415 ver3.0)

A study on the inhibitory effect of vonoprazan and LPZ against H^+,K^+-ATPase activity in a pig gastric mucosal microsome fraction at pH 6.5 and 7.5 showed that vonoprazan and LPZ inhibited the activity at either pH. The IC_{50} value [95% CI] of vonoprazan at pH 6.5 and 7.5 was 19.3 [16.5, 22.6] and 28.0 [23.4, 33.4] nmol/L, respectively, while that of LPZ at pH 6.5 and 7.5 was 6.82 [4.64, 10.1] and 65.8 [47.4, 85.5] μmol/L, respectively, indicating that the inhibitory effect of vonoprazan is less susceptible to pH than that of LPZ.

(c) Study on mode of the inhibition against pig gastric mucosal H^+,K^+-ATPase activity (4.2.1.1-13, 4.2.1.1-14; Reports TAK-438/00139, TAK-438/00140.001R)

The effect of approximately 45-time dilution of the reaction solution of pig gastric mucosal microsome fraction and vonoprazan (100 nmol/L) or LPZ (20 μmol/L) on the inhibitory effect against H^+,K^+-ATPase activity was evaluated to investigate reversibility of the inhibitory effect of vonoprazan against H^+,K^+-ATPase activity. The inhibitory rate of vonoprazan was decreased by the dilution, 70.2% ± 1.1% before and 12.3% ± 1.0% after, suggesting that vonoprazan reversibly bound to H^+,K^+-ATPase. On the other hand, the inhibitory rate of LPZ was 85.6% ± 0.9% before and 94.8% ± 3.0% after, and decrease due to the dilution was not observed.

The inhibitory rate of vonoprazan against H^+,K^+-ATPase activity was measured in the presence of KCl (1.56-100 mmol/L) to investigate the mode of the inhibition of vonoprazan against H^+,K^+-ATPase activity, followed by Lineweaver-Burk plot analysis. As a result, the inhibitory rate of vonoprazan decreased depending on the potassium ion concentration, suggesting that vonoprazan inhibited the activity in a potassium-competitive manner.

(d) Pharmacological action of the metabolites (4.2.1.1-10 to 4.2.1.1-12; Reports TAK-438/10130 ver.1.0, TAK-438-11415 ver.3.0, TAK-438/00187)

M-III and M-IV-Sul, metabolites found in human blood,[14] did not inhibit the forskolin-induced acid production in the rabbit isolated fundic gland at the concentrations up to 3 μmol/L.

The inhibitory effect of M-I, M-II, M-III, and M-IV-Sul against H^+,K^+-ATPase activity was investigated in the pig gastric mucosa microsome fraction at pH 6.5 and 7.5. The IC_{50} values of M-I, M-II, and M-III were >10 μmol/L at either pH. On the other hand, M-IV-Sul inhibited the activity in a concentration-

13 Determined based on [^{14}C]-aminopyrine uptake.

14 Following oral administration of vonoprazan in humans, M-I, M-II, M-III, and M-IV-Sul was found in blood and identified as metabolites [see "4.(ii).A.(1).4).(a) Estimated metabolic pathway"].

dependent manner, and the IC_{50} value [95% CI] at pH 6.5 and 7.5 was 4.12 [3.49, 4.91] and 4.61 [3.77, 5.58] μmol/L, respectively. The applicant explained that the inhibitory effect of M-I, M-II, M-III, and M-IV-Sul was ≤1/150 of that of unchanged vonoprazan, and the metabolites were unlikely to contribute to the clinical efficacy.

(e) Studies on anti-*H. pylori* activity (4.2.1.1-15, Report TAK-438-11308)

The anti-*H. pylori* activity of vonoprazan, LPZ, amoxicillin (AMPC), clarithromycin (CAM), and metronidazole (MNZ) was measured by the agar plate dilution method. The minimum inhibitory concentration (MIC) of vonoprazan, LPZ, AMPC, CAM, and MNZ against *H. pylori* (6 strains) was >128 μg/mL, 8 to 32, 0.03 to 0.12, 0.03 to 0.12, and 1 to 128 μg/mL, respectively. Vonoprazan did not show anti-*H. pylori* activity.

(f) Effects of antimicrobial agents on anti-*H. pylori* activity (4.2.1.1-16, Report TAK-438-11307)

The anti-*H. pylori* activity of AMPC, CAM, and MNZ used concomitantly with vonoprazan (0-100 μmol/L) was measured by the agar plate dilution method, but vonoprazan did not affect the anti-*H. pylori* activity of AMPC, CAM, and MNZ.

(g) Study of the effect on *H. pylori* urease activity (4.2.1.1-17, Report TAK-438-11306)

The inhibitory effect of vonoprazan (3-100 μmol/L) and LPZ (1-30 μmol/L) against urease activity was investigated with *H. pylori*-derived urease enzyme solution. The IC_{50} value [95% CI] of vonoprazan and LPZ was >30 μmol/L and 13.6 [8.93, 20.7] μmol/L, respectively. Vonoprazan did not show an inhibitory effect against urease activity.

3.(i).A.(2) Secondary pharmacodynamics

Study on the selectivity (4.2.1.2-1, 4.2.1.1-11; Reports TAK-438/00005 [Reference data], TAK-438-11415 Ver.3.0)

The inhibitory effect of vonoprazan at 10 μmol/L against 133 functional proteins (receptors, ion channels, enzymes, transporters, etc.) was investigated. Vonoprazan inhibited human muscarine M_1, M_2, and M_3 receptors, rat L-type calcium channel, rat sodium channel, rat serotonin 5-HT_2 receptor, as well as guinea-pig sigma receptor by ≥50%. The IC_{50} value for human muscarine M_1 and M_3 receptors, rat L-type calcium channel, as well as serotonin 5-HT_2 receptor, which were inhibited by ≥80% in the above measurement, was 1.49, 0.80, 2.27 and 1.43 μmol/L, respectively.

Vonoprazan at 10 μmol/L and LPZ at 100 μmol/L also inhibited Na^+,K^+-ATPase activity in the pig cerebrocortical microsome fraction by 3.03% ± 0.58% and 25.4% ± 1.21%, respectively.

The applicant explained that vonoprazan is unlikely to affect these receptors because C_{max} of unchanged vonoprazan following its administration at the maximum recommended clinical dose of 40 mg/day to humans was 75.2 ng/mL (0.22 μmol/L).

3.(i).A.(3) Safety pharmacology

3.(i).A.(3).1) Effects on the central nervous system (4.2.1.3-1, Report TAK-438/00080)

A single dose of vonoprazan at 30, 100, or 600 mg/kg or vehicle was orally administered to rats to investigate its effects on general symptoms and behavior using the functional observational battery (FOB method). Mydriasis was observed in ≥100 mg/kg groups. In the 600 mg/kg group, 1 of 6 animals died at 2 to 4 hours post-dose, and the surviving animals (5 animals) exhibited hypotonia, decreased locomotor activity, closed eyes (partial), decreased hopping reaction, decreased fecal volume, and decreased body temperature.

Following an oral dose of 30 mg/kg of vonoprazan, the no-observed effect level (NOEL), to rats, C_{max} of unchanged vonoprazan was 796.5 ng/mL, which was 10.6 times greater than that (75.2 ng/mL) in humans at the dose of 40 mg/day, the maximum recommended clinical dose.

3.(i).A.(3).2) Effects on the cardiovascular system

(a) Inhibitory effect against hERG current (4.2.1.3-2, Report TAK-438/00063)

Vonoprazan at 0.5, 5, and 50 μg/mL or vehicle[15] was added to HEK293 cells stably expressing hERG channel to investigate the effects on the hERG current by the whole-cell patch clamp method. Vonoprazan inhibited the hERG current in a concentration-dependent manner and the IC_{50} value was 4.8 μg/mL.

The plasma unbound concentration at the maximum recommended clinical dose of 40 mg/day in humans was estimated to be approximately 9.0 to 11.1 ng/mL.[16]

(b) Effects on unanesthetized dogs (4.2.1.3-3, Report TAK-438/00081)

A single dose of vonoprazan at 2, 6, or 20 mg/kg or vehicle was orally administered to unanesthetized dogs to investigate the effects on cardiovascular parameters (systolic blood pressure, diastolic blood pressure, mean blood pressure, heart rate, electrocardiogram). Findings included a significant increase in diastolic blood pressure at 8 hours post-dose in the 6 mg/kg group as well as significant increases in systolic blood pressure, diastolic blood pressure, and mean blood pressure at 1 hour post-dose and significant increases in diastolic blood pressure and mean blood pressure at 8 hours post-dose in the 20 mg/kg group. In all groups, an increasing trend in heart rate and a significant decrease in QT interval were observed at 24 hours post-dose, but no significant effect was observed on QTcF interval.[17]

The applicant explained that the increase in diastolic blood pressure at 8 hours post-dose in the 6 mg/kg group as well as the increasing trend in heart rate and a decrease in QT interval at 24 hours post-dose in all groups were considered to be incidental changes unrelated to pharmacokinetics of vonoprazan and its metabolites, because the plasma concentrations of vonoprazan and M-I at 8 and 24 hours post-dose were lower than their C_{max}, and the plasma concentrations of M-II at 6 and 24 hours post-dose were similar, but the blood pressure and electrocardiogram parameters at 8 and 24 hours post-dose did not exhibit any specific trend. The applicant also explained the increases in systolic blood pressure, diastolic blood pressure, and mean blood pressure in the 20 mg/kg group as follows: although the possibility of an association of the increases in those parameters with vonoprazan cannot be ruled out because they were observed at the timepoints where the plasma concentrations were high, they were considered unrelated to vonoprazan, because the changes from the baseline remained unknown.[18]

Following an oral dose of 20 mg/kg of vonoprazan to dogs (NOEL), C_{max} of unchanged vonoprazan was 3426 ng/mL, which was 45.6 times greater than that in humans (75.2 ng/mL) at the dose of 40 mg/day (maximum recommended clinical dose).

3.(i).A.(3).3) Effects on the respiratory system (4.2.1.3-4, Report TAK-438/00082)

A single dose of vonoprazan at 30, 100, or 600 mg/kg or vehicle was orally administered to unanesthetized rats to investigate the effects on respiratory parameters (respiratory rate, tidal volume, minute ventilation, enhanced pause [Penh]) by whole-body plethysmography. A significant decrease in respiratory rate was observed in the 30 mg/kg group at 1 and 8 hours post-dose. In the 600 mg/kg group, decreases in tidal volume and minute ventilation were observed at 4 and 8 hours post-dose, and 4 of 8 animals died at ≥ 2 hours post-dose. Of the dead animals, 1 animal showed a high Penh value, for which the relationship with the death remained unknown. The applicant explained that the decrease in respiratory rate in the 30 mg/kg group occurred at the baseline and was not attributable to vonoprazan.

C_{max} of unchanged vonoprazan following an oral dose of 100 mg/kg of vonoprazan to rats, is 2312 ng/mL (NOEL), which is 30.7 times greater than that in humans (75.2 ng/mL) at the dose of 40 mg/day (maximum recommended clinical dose).

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15 0.1% dimethylsulfoxide solution

16 In a Japanese phase I study (Study CPH-002), vonoprazan was orally administered once daily at a dose of 40 mg for 7 days. C_{max} of plasma vonoprazan on Day 7 was 75.2 ng/mL and human plasma protein binding rate of vonoprazan was 85.2% to 88.0% [see "4.(ii).A.(1).2) *In vitro* plasma protein binding"]. Based on the result, the plasma unbound concentration is estimated to be around 9.0 to 11.1 ng/mL.

17 Calculated using Fridericia correction formula

18 The data were not consistent: the group means of the systolic blood pressure, diastolic blood pressure, and mean blood pressure were 1 to 3 mmHg higher than those at the baseline; and in terms of the individual values, of 4 animals, 2 to 3 animals showed lower values than those at the baseline, and 1 to 2 animals showed higher values than those at the baseline.

3.(i).A.(4) Pharmacodynamic drug interactions

Effects of concomitant use of vonoprazan and aspirin on platelet aggregation in rats (4.2.1.4-1, Report TAK-438-10886 ver.1 [Reference data])

Following oral administration of vonoprazan at 4 mg/kg alone, aspirin at 100 mg/kg alone, vonoprazan at 4 mg/kg concomitantly with aspirin at 100 mg/kg, or vehicle,[19] blood was collected. Platelet-rich plasma prepared from the above blood sample was then exposed to collagen to determine the platelet aggregation rate and thromboxane B_2 (TXB_2) production. The platelet aggregation and TXB_2 production were inhibited in the aspirin alone group, but there were no effects on the platelet aggregation and TXB_2 production in the vonoprazan alone group. Vonoprazan did not affect the inhibitory effects of aspirin against platelet aggregation and TXB_2 production when used concomitantly.

3.(i).B Outline of the review by PMDA

3.(i).B.(1) Pharmacological actions

Based on the submitted study data, PMDA considers that vonoprazan inhibits acid secretion by inhibiting H^+, K^+-ATPase in gastric mucosal parietal cells in a reversible and potassium-competitive manner. Vonoprazan is thus expected to have pharmacological actions against reflux esophagitis and peptic ulcer. Vonoprazan also inhibited aspirin- and indomethacin-induced gastric mucosal injury *in vivo*, and therefore vonoprazan can be expected to have therapeutic actions against gastric mucosal injury attributable to low-dose aspirin and non-steroidal anti-inflammatory drugs.

The submitted study data on *H. pylori* eradication therapy showed that vonoprazan itself has neither an antimicrobial effect against *H. pylori* nor an inhibitory effect against urease activity of *H. pylori.* The *H. pylori* eradication effect observed in a clinical study [see "4.(iii).A.(7) Phase III study for *Helicobacter pylori* eradication"] is considered to be a consequence of increased activities of antimicrobial agents due to gastric pH increased by vonoprazan, but not a direct pharmacological action of vonoprazan.

3.(i).B.(2) Safety pharmacology

In the safety pharmacology study data submitted this time, the vonoprazan group showed statistically significant changes in central nervous, cardiovascular, and respiratory systems in comparison with the vehicle group. PMDA, however, considers that vonoprazan is unlikely to have significant pharmacological actions on the central nervous, cardiovascular, and respiratory systems when used in clinical settings, because these changes were observed at doses higher than the proposed clinical dose, ensuring a sufficient safety margin, and clinical study data did not indicate definite effects [see "4.(iii).B.(2) Safety"].

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

The pharmacokinetics (PK) of vonoprazan and ^{14}C-vonoprazan administered to rats and dogs was investigated, and various *in vitro* studies with biological samples collected from animals were conducted. Plasma concentrations of unchanged vonoprazan and its metabolites, M-I and M-II, were measured by high performance liquid chromatography-tandem mass spectrometry (LC/MS/MS), and the lower limit of quantitation of unchanged vonoprazan, M-I, and M-II was 0.1 ng/mL. To measure radioactivity after dosing ^{14}C-vonoprazan, liquid scintillation counter and liquid chromatography with online flow scintillation analyzer were used.

Unless otherwise mentioned, male animals were used in *in vivo* studies.

[19] Vonoprazan and aspirin were administered 60 and 30 minutes, respectively, before the blood collection.

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) Single-dose studies (4.2.2.2-1 to 4.2.2.2-6, 4.2.2.2-10; Reports TAK-438/00105, TAK-438/00108, TAK-438/00086, TAK-438/00103, TAK-438/00106, TAK-438/00112, TAK-438-11277)

Following a single oral dose (2 mg/kg) or intravenous dose (0.75 mg/kg) of ^{14}C-vonoprazan to rats, the absolute bioavailability (BA)[20] of unchanged vonoprazan (mean, n = 3) was 10.3% and the absorption rate[21] of the radioactivity (mean, n = 3) was 92.2%. Following a single oral dose (0.3 mg/kg) or intravenous dose (0.1 mg/kg) of ^{14}C-vonoprazan to dogs, the absolute BA[20] of unchanged vonoprazan (mean, n = 4) was 52.4% and the absorption rate[21] of the radioactivity (mean, n = 3) was 86.3%. The applicant explained that in either animal species, the absolute BA of unchanged vonoprazan was lower than the absorption rate of the radioactivity, suggesting that vonoprazan was subject to the first-pass effect.

Table 11 shows the PK parameters of unchanged vonoprazan following a single oral dose (2, 6, or 18 mg/kg) or intravenous dose (0.75 or 2.25 mg/kg) of ^{14}C-vonoprazan to rats. Table 12 shows the PK parameters of unchanged vonoprazan, M-I, and M-II following a single oral dose of 0.1, 0.3, or 1 mg/kg of vonoprazan to dogs. In either animal species, $AUC_{0\text{-}24h}$ of unchanged vonoprazan following an oral dose increased more than proportionally to the dose ratio.

Table 11. PK parameters of unchanged vonoprazan following a single oral or intravenous dose to rats

Route of administration	Dose (mg/kg)	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)
Oral	2	17.4 ± 4.3	27.2 ± 5.0	0.3 ± 0.0	1.3 ± 0.1
	6	195.4 ± 78.2	417.2 ± 110.3	0.4 ± 0.1	1.3 ± 0.1
	18	952.7 ± 183.7	2628.7 ± 499.8	0.5 ± 0.0	1.8 ± 0.2
Intravenous	0.75	-	99.2 ± 7.1	-	1.2 ± 0.1
	2.25	-	384.2 ± 44.9	-	1.3 ± 0.0

n = 3; mean ± standard deviation (SD); -, Not calculated

Table 12. PK parameters of unchanged vonoprazan, M-I, and M-II following a single oral dose to dogs

Dose (mg/kg)	Chemical compound	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)
0.1	Unchanged vonoprazan	5.3 ± 2.3	13.9 ± 11.1	0.8 ± 0.8	1.1 ± 0.2
	M-I	40.5 ± 13.7	137.9 ± 40.7	1.0 ± 0.7	2.5 ± 0.7
	M-II	4.0 ± 1.4	60.4 ± 26.6	6.0 ± 2.3	10.4 ± 1.4
0.3	Unchanged vonoprazan	29.9 ± 19.3	80.4 ± 65.7	0.6 ± 0.3	1.3 ± 0.3
	M-I	88.4 ± 30.5	408.8 ± 149.3	1.3 ± 0.5	3.0 ± 0.1
	M-II	10.3 ± 5.1	167.4 ± 84.6	7.0 ± 2.0	11.3 ± 1.5
1	Unchanged vonoprazan	149.2 ± 75.6	600.8 ± 469.0	0.6 ± 0.3	1.9 ± 0.6
	M-I	169.4 ± 63.6	1352.2 ± 598.4	1.5 ± 0.6	3.5 ± 0.6
	M-II	29.2 ± 9.6	517.8 ± 227.6	8.0 ± 0.0	31.5 ± 29.8

n = 4, mean ± SD

3.(ii).A.(1).2) Repeat-dose studies (4.2.3.2-2, 4.2.3.2-4, 4.2.3.2-5, 4.2.3.2-7 to 4.2.3.2-9; Reports TAK-438/00085, TAK-438/00143, TAK-438/00212, TAK-438/00084, TAK-438-10742, TAK-438/00217)

In toxicity studies, vonoprazan was administered to male and female rats for 4, 13, and 26 weeks as well as to male and female dogs for 4, 13, and 39 weeks to investigate the toxicokinetics. Data from rat 26-week and dog 39-week repeat-dose studies are shown below.

Table 13 shows the PK parameters of unchanged vonoprazan, M-I, and M-II following repeated daily oral dose of 1, 5, 10, or 30 mg/kg of vonoprazan to male and female rats for 26 weeks. C_{max} and $AUC_{0\text{-}24h}$ of unchanged vonoprazan increased as the number of repeated doses increased and reached a steady state in Week 13. In addition, C_{max} and $AUC_{0\text{-}24h}$ of unchanged vonoprazan in females were higher than

[20] (Dose-normalized $AUC_{0\text{-}24h}$ of unchanged vonoprazan after oral administration/dose-normalized $AUC_{0\text{-}24h}$ of unchanged vonoprazan after intravenous administration) × 100

[21] (Dose-normalized AUC of the radioactivity after oral administration/dose-normalized AUC of the radioactivity after intravenous administration) × 100. AUC was calculated as $AUC_{0\text{-}96h}$ for rats and $AUC_{0\text{-}168h}$ for dogs.

those in males in the 1 to 10 mg/kg groups, but in the 30 mg group, these parameter values in females were comparable to those in males.

Table 13. PK parameters of unchanged vonoprazan, M-I, and M-II following repeated oral doses to rats

Male or female			Male				Female			
Dose (mg/kg)			1	5	10	30	1	5	10	30
Unchanged vonoprazan	C_{max} (ng/mL)	Day 1	0.7	16.0	89.3	769.5	1.6	93.2	265.1	1017.8
		Week 26	2.0	72.7	281.4	1027.7	8.8	181.5	584.8	1593.2
	$AUC_{0\text{-}24h}$ (ng·h/mL)	Day 1	3	38	239	4031	4	149	532	2633
		Week 26	5	210	1054	8536	20	424	1615	6364
M-I	C_{max} (ng/mL)	Day 1	61.4	511.9	1391.1	2531.4	44.5	210.2	354.3	605.3
		Week 26	130.8	909.4	2035.3	4011.7	69.4	296.7	427.6	1455.7
	$AUC_{0\text{-}24h}$ (ng·h/mL)	Day 1	285	2919	7469	29,878	130	887	1882	5091
		Week 26	415	4921	12,425	46,144	214	1379	2671	9161
M-II	C_{max} (ng/mL)	Day 1	3.0	14.2	42.7	100.0	5.0	15.8	25.8	54.2
		Week 26	6.1	47.8	129.1	387.5	9.4	41.3	61.8	190
	$AUC_{0\text{-}24h}$ (ng·h/mL)	Day 1	35	206	619	1348	43	218	281	726
		Week 26	93	667	1794	5135	135	594	884	2484

Mean, n = 3/timepoint

Table 14 shows the PK parameters of unchanged vonoprazan, M-I, and M-II following repeated daily oral doses of 0.3, 0.6, or 2 mg/kg of vonoprazan to male and female dogs for 39 weeks. $AUC_{0\text{-}24h}$ of unchanged vonoprazan increased as the number of repeated doses increased and reached a steady state in Week 26. No clear differences were observed in C_{max} or $AUC_{0\text{-}24h}$ of unchanged vonoprazan between males and females.

Table 14. PK parameters of unchanged vonoprazan, M-I, and M-II following repeated oral doses to dogs

Male or female			Male			Female		
Dose (mg/kg)			0.3	0.6	2	0.3	0.6	2
Unchanged vonoprazan	C_{max} (ng/mL)	Day 1	40.3 ± 11.7	92.3 ± 34.6	496.6 ± 80.2	29.9 ± 10.9	83.4 ± 16.7	492.9 ± 282.8
		Week 39	45.8 ± 15.9	88.9 ± 35.1	823.1 ± 191.4	39.4 ± 14.0	80.5 ± 2.3	480.5 ± 244.9
	$AUC_{0\text{-}24h}$ (ng·h/mL)	Day 1	97 ± 16	263 ± 62	2762 ± 1873	80 ± 28	275 ± 44	2865 ± 1365
		Week 39	191 ± 37	415 ± 117	4481 ± 1754	134 ± 46	346 ± 63	4026 ± 2310
M-I	C_{max} (ng/mL)	Day 1	46.3 ± 0.9	72.7 ± 1.3	163.3 ± 25.9	73.0 ± 4.1	103.0 ± 29.7	146.4 ± 15.7
		Week 39	38.5 ± 4.8	65.9 ± 11.1	115.0 ± 15.1	64.6 ± 9.3	90.2 ± 16.4	107.8 ± 15.3
	$AUC_{0\text{-}24h}$ (ng·h/mL)	Day 1	214 ± 31	397 ± 64	1596 ± 627	300 ± 23	622 ± 54	1508 ± 97
		Week 39	256 ± 46	517 ± 86	1230 ± 295	328 ± 76	769 ± 155	1161 ± 147
M-II	C_{max} (ng/mL)	Day 1	17.6 ± 9.3	39.7 ± 22.0	70.2 ± 38.5	11.0 ± 5.2	27.6 ± 13.6	59.0 ± 17.0
		Week 39	24.8 ± 9.7	65.9 ± 36.9	92.8 ± 28.7	12.3 ± 6.1	65.2 ± 27.8	119.7 ± 14.1
	$AUC_{0\text{-}24h}$ (ng·h/mL)	Day 1	292 ± 177	669 ± 372	1138 ± 555	187 ± 100	430 ± 236	995 ± 344
		Week 39	402 ± 151	1096 ± 629	1630 ± 521	205 ± 113	1036 ± 491	2021 ± 273

Mean ± SD, n = 3

3.(ii).A.(1).3) Portal absorption (4.2.2.2-7, 4.2.2.2-8; Reports TAK-438-11280, TAK-438-11281)

Following a single oral dose of 2 or 18 mg/kg of ^{14}C-vonoprazan to rats with a jejunal loop, radioactivity (percentage to the dose) recovered in the portal blood by 2 hours post-dose was 41.4% or 39.8%, respectively. The portal blood radioactivity was mainly derived from unchanged vonoprazan in all groups (≥89.1%). The applicant thus explained that vonoprazan is not extensively metabolized in the small intestine.

3.(ii).A.(1).4) Lymph absorption (4.2.2.2-9, Report TAK-438-11257)

Following a single oral dose of 2 mg/kg of ^{14}C-vonoprazan to rats with a thoracic duct fistula, radioactivity (percentage to the dose) recovered in the lymph fluid by 24 hours post-dose was 0.6%. The applicant thus explained that lymph is unlikely to be involved in absorption of vonoprazan.

3.(ii).A.(2) Distribution

3.(ii).A.(2).1) Organ and tissue distribution (4.2.2.3-1, Report TAK-438/00092)

Following a single oral dose of 2 mg/kg of ^{14}C-vonoprazan to rats, the radioactivity concentration in each tissue was determined at 0.25, 1, 2, 24, 48, and 168 hours after administration. The radioactivity concentration reached a maximum at 1 hour post-dose in most of the tissues. At this timepoint, the radioactivity concentration was highest in the liver followed in descending order by the kidneys, intestinal wall, lungs, gastric wall, and plasma. The radioactivity concentration in each tissue decreased over time until 168 hours post-dose, and no residual radioactivity was observed.

3.(ii).A.(2).2) Whole-body autoradiography (4.2.2.3-2, Report TAK-438-11258)

Following a single oral dose of 2 mg/kg of ^{14}C-vonoprazan to rats, radioactivity in each tissue was determined by autoradiography at 0.25, 1, 2, 24, and 168 hours after administration. After dosing, the radioactivity was distributed throughout the body, and high radioactivity concentrations were observed in the liver, stomach, etc. The radioactivity concentration in each tissue decreased over time and disappeared in most of the tissues by 168 hours post-dose.

3.(ii).A.(2).3) Melanin affinity (4.2.2.3-1, Report TAK-438/00092)

Following a single oral dose of 2 mg/kg of ^{14}C-vonoprazan to pigmented and albino rats, the radioactivity concentration in the eye ball was higher in pigmented rats than in albino rats up to 168 hours post-dose. The applicant thus explained that unchanged vonoprazan or its metabolites have melanin affinity.

3.(ii).A.(2).4) Distribution in the gastric wall (4.2.2.3-3, 4.2.2.3-4; Reports TAK-438/00110, TAK-438/00111)

Following a single intravenous dose of 0.75 mg/kg of ^{14}C-vonoprazan to rats, the radioactivity concentrations (unchanged vonoprazan equivalent; mean, n = 3) in the plasma and gastric wall at 5 hours post-dose were 1 ng eq./mL and 1352 ng eq./g, respectively. The applicant thus explained that vonoprazan is distributed in the gastric wall.

3.(ii).A.(2).5) Radioactive components in the tissues (4.2.2.3-5, Report TAK-438/00109)

Following a single oral dose of 2 mg/kg of ^{14}C-vonoprazan to rats, the percentage of $AUC_{0\text{-}24h}$ of unchanged vonoprazan to that of the radioactivity in the plasma, gastric wall, liver, kidneys, and intestinal wall was 0.9%, 64.4%, 4.3%, 5.8%, and 13.1%, respectively. The applicant thus explained that unchanged vonoprazan is distributed in the gastric wall, the target tissue.

3.(ii).A.(2).6) Plasma protein binding

(a) *In vitro* studies (4.2.2.3-6, Report TAK-438/00087)

^{14}C-vonoprazan was added to rat and dog plasmas at 100, 1000, and 10,000 ng/mL and the plasma protein binding rate (mean for each concentration) was measured. The plasma protein binding rates were 67.3% to 69.5% and 71.7% to 83.3%, respectively, and were hardly concentration-dependent in the concentration range investigated.

(b) *In vivo studies* (4.2.2.3-7, Report TAK-438-11249)

Following a single oral dose of 2 mg/kg of ^{14}C-vonoprazan to rats, the plasma protein binding rate of radioactivity at 0.25 to 24 hours post-dose (mean at each timepoint) was 82.8% to 95.1%. Following a single oral dose of 0.3 mg/kg of ^{14}C-vonoprazan to dogs, the plasma protein binding rate of radioactivity at 0.5 to 24 hours post-dose (mean at each timepoint) was 88.5% to 94.0%.

3.(ii).A.(2).7) Distribution in blood cells (4.2.2.3-10, Report TAK-438/00090)

^{14}C-vonoprazan was added to rat and dog plasmas at 10, 100, and 1000 ng/mL and the distribution in blood cells (mean for each concentration) was measured. The distribution in blood cells was 60.3% to 62.9% and 30.0% to 40.6%, respectively, and were hardly concentration-dependent in the concentration range investigated.

3.(ii).A.(2).8) Placental transfer (4.2.2.3-8, 4.2.2.3-9; Reports TAK-438-11240, TAK-438-11247)

Following a single oral dose of 2 mg/kg of ^{14}C-vonoprazan to pregnant rats on Gestation Day 18, the placental transfer was investigated at 0.25, 1, 2, 4, 24, and 48 hours after administration. The radioactivity concentration reached a maximum at 1 hour post-dose in the maternal plasma, placenta, amniotic fluid, and fetal homogenate and at 2 hours post-dose in the fetal plasma and then decreased

over time. The maximum radioactivity concentration (unchanged vonoprazan equivalent; mean, n = 3) in the maternal plasma, placenta, amniotic fluid, fetal plasma, and fetal homogenate was 327, 445, 17, 121, and 145 ng eq./mL, respectively. Unchanged vonoprazan at 0.25 to 48 hours post-dose accounted for 0.0% to 6.8% and 0.0% to 4.5% of the radioactivity in the maternal plasma and fetal plasma, respectively. The applicant thus explained that unchanged vonoprazan and its metabolites crossed the placenta and were transferred to the fetus.

3.(ii).A.(3) Metabolism

3.(ii).A.(3).1) Plasma metabolites (4.2.2.3-5, 4.2.2.4-3 to 4.2.2.4-5; Reports TAK-438/00109, TAK-438/00093, TAK-438-11243, TAK-438-11245)

Following a single oral dose of 2 mg/kg of ^{14}C-vonoprazan to rats, the percentage of $AUC_{0\text{-}24h}$ of each component to that of the radioactivity in the plasma was 0.9% for unchanged vonoprazan, 51.9% for M-I, 11.8% for M-I-G, 7.4% for M-II, 4.5% for M-II-G, and 23.5% for others, indicating that M-I is the major component.

Following a single oral dose of 0.3 mg/kg of ^{14}C-vonoprazan to dogs, the percentage of $AUC_{0\text{-}24h}$ of each component to that of the radioactivity in the plasma was 1.9% for unchanged vonoprazan, 8.8% for M-I, 14.0% for M-I-G, 5.2% for M-II, 39.4% for M-II-G, and 30.7% for others, indicating that M-II-G is the major component.

3.(ii).A.(3).2) Metabolites in urine, feces, and bile (4.2.2.4-2, 4.2.2.4-6 to 4.2.2.4-9; Reports TAK-438-11259, TAK-438/00091, TAK-438/00113, TAK-438-11244, TAK-438-11246)

Table 15 shows the percentage of radioactivity of each component to that in the urine, feces, and bile following a single oral dose of 2 mg/kg of ^{14}C-vonoprazan to rats, a single intraduodenal dose of 2 mg/kg to rats with biliary fistula, and a single oral dose of 0.3 mg/kg to dogs. The major component was M-I-G in the rat bile and M-II-G in the dog urine.

Table 15. Radioactive components in the urine, feces, and bile following a single oral or intraduodenal dose to rats and dogs

Chemical compound	Percentage of radioactivity of each component to the radioactivity in the entire sample (%)				
	Rat[a)]			Dog	
	Urine	Feces	Bile[c)]	Urine[a)]	Feces[b)]
Unchanged vonoprazan	13.3	1.0	0.1	0.9	1.6
M-I	0.6	2.1	1.8	1.0	2.2
M-I-G	8.2	11.1[d)]	34.2	1.4	1.9
M-II	4.4	0.5	0.3	1.7	1.6
M-II-G	8.9	0.8	2.5	72.4	0.3
Others	64.6	84.5	61.1	22.6	92.4

Mean, n = 3

a) Sample collected from 0 to 24 hours post-dose
b) Sample collected from 0 to 48 hours post-dose
c) Intraduodenal administration (rats with biliary fistula), n = 4
d) Including unidentified radioactive components

3.(ii).A.(4) Excretion

3.(ii).A.(4).1) Excretion in urine, feces, expired air, and bile (4.2.2.5-1 to 4.2.2.5-3, 4.2.2.2-6; Reports TAK-438/00075, TAK-438/00076, TAK-438/00088, TAK-438/00112)

Following a single oral dose of 2 mg/kg of ^{14}C-vonoprazan to rats, the percent radioactivity (percentage to the dose, mean ± standard deviation [SD]) excreted in urine and feces by 96 hours post-dose was 16.8% ± 2.1% and 80.0% ± 2.7%, respectively. By 48 hours post-dose, 0.6% ± 0.0% of the administered radioactivity was also excreted in the expired air.

Following a single intraduodenal dose of 2 mg/kg of ^{14}C-vonoprazan to rats with biliary fistula, the percent radioactivity excreted in bile, urine, and feces (including the content in the gastrointestinal tract) by 24 hours post-dose was 88.0% ± 2.3%, 8.7% ± 0.9%, and 2.1% ± 0.4%, respectively. Following an intraduodenal dose of this radioactive bile (10 mL/kg) to the other rats with biliary fistula, the percent radioactivity excreted in bile and urine by 24 hours post-dose was 50.2% and 7.2%, respectively.

The applicant explained that the above findings suggested that, in rats, unchanged vonoprazan and its metabolites are mainly excreted in feces through the bile and those excreted in bile would be partially reabsorbed.

Following a single oral dose of 0.3 mg/kg of ^{14}C-vonoprazan to dogs, the percent radioactivity excreted in the urine and feces by 144 hours post-dose was 64.3% ± 3.4% and 34.2% ± 2.8%, respectively. The applicant explained that unchanged vonoprazan and its metabolites are mainly excreted in urine in dogs.

3.(ii).A.(4).2) Excretion in milk (4.2.2.5-4, 4.2.2.5-5; Reports TAK-438-11241, TAK-438-11248)

Following a single oral dose of 2 mg/kg of ^{14}C-vonoprazan to lactating rats 14 days after delivery, the excretion in milk was investigated at 0.25, 1, 4, 8, and 24 hours after administration. The radioactivity concentration in plasma and milk reached a maximum at 1 and 4 hours, respectively, and then decreased over time. The maximum radioactivity concentration (unchanged vonoprazan equivalent) in plasma and milk was 208 and 131 ng eq./mL, respectively. Unchanged vonoprazan accounted for 0.0% to 7.7% and 0.0% to 22.7% of the radioactivity in plasma and milk, respectively, at 0.25 to 24 hours post-dose. The applicant thus explained that unchanged vonoprazan and its metabolites are excreted in milk.

3.(ii).A.(5) Other pharmacokinetic studies

3.(ii).A.(5).1) Drug interactions of vonoprazan, AMPC, and CAM (4.2.2.7-1, 4.2.2.7-2, 4.2.2.7-4 to 4.2.2.7-6; Reports TAK-438-11288, TAK-438-11297, TAK-438-11287, TAK-438-11298, TAK-438-11299)

Vonoprazan 3 mg/kg alone or 3-drug combination of vonoprazan 3 mg/kg, AMPC 10 mg/kg, and CAM 5 mg/kg[22] was orally administered in a single dose to rats. No remarkable differences in vonoprazan PK parameters were found between the vonoprazan monotherapy and 3-drug combination therapy.

Two drug combination of AMPC 10 mg/kg and CAM 5 mg/kg or 3-drug combination of this 2-drug combination plus vonoprazan 3 mg/kg[22] was orally administered in a single dose. No remarkable differences in the PK parameters of AMPC and CAM were found between the treatments with and without vonoprazan.

3.(ii).A.(5).2) Effects on tissue distributions of AMPC and CAM (4.2.2.7-3, Report TAK-438-11300)

Two drug combination of ^{14}C-AMPC 10 mg/kg and CAM 5 mg/kg or 3-drug combination of this 2-drug combination plus vonoprazan 3 mg/kg[23] was orally administered in a single dose to rats and the tissue radioactivity concentrations at 0.5 hours post-dose (calculated on the basis of AMPC, mean ± SD) were determined. In rats treated with the 2 drug combination and those with 3 drug combination, the concentrations were 6280 ± 636 and 5670 ± 1715 ng eq./g, respectively, in the glandular stomach; and 7362 ± 780 and 3114 ± 1440 ng eq./g, respectively, in the forestomach. Two drug combination of AMPC 10 mg/kg and ^{14}C-CAM 5 mg/kg or 3-drug combination of this 2-drug combination plus vonoprazan 3 mg/kg[23] was orally administered in a single dose to rats and the tissue radioactivity concentrations at 0.5 hours post-dose (CAM equivalent, mean ± SD) were determined. In rats treated with the 2 drug combination and those with 3 drug combination, the concentrations were 8239 ± 2747 and 14,768 ± 2469 ng eq./g, respectively, in the glandular stomach; and 11,238 ± 750 and 17,531 ± 5073 ng eq./g, respectively, in the forestomach. The applicant explained that the above findings suggested that the effect of vonoprazan on distribution of AMPC to the target site was unclear, but vonoprazan enhanced distribution of CAM to the target site.

3.(ii).B Outline of the review by PMDA

Tissue distribution

The study in pigmented and albino rats indicated that unchanged vonoprazan or its metabolites have melanin affinity [see "3.(ii).A.(2).3) Melanin affinity"]. PMDA asked the applicant to explain whether or not there is any safety concern in clinical use due to accumulation of unchanged vonoprazan or its metabolites in the melanin-containing tissues.

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22 AMPC and CAM were administered 1 hour after vonoprazan was.

23 AMPC or ^{14}C-AMPC and CAM or ^{14}C-CAM were administered 1 hour after vonoprazan was.

The applicant responded as follows:
It cannot be ruled out that the concentrations of unchanged vonoprazan or its metabolites increase in the melanin-containing tissues during clinical use because they have melanin affinity. In the repeat-dose toxicity study in dogs, however, no abnormal changes were observed in the melanin-containing tissues such as eyeballs and skin. M-IV-Sul was not detected in the dog plasma and the safety of M-IV-Sul was not evaluated in repeat-dose toxicity studies in dogs. The *in vivo* phototoxicity studies, however, indicated that the phototoxicity of M-IV-Sul was unlikely to develop in clinical use [see "3.(iii).A.(7).2).(d) *In vivo* phototoxicity study in hairless mice"]. In the clinical studies (Study CCT-002, Study CCT-003, Study OCT-001, Study CCT-101, Study CCT-102, Study CCT-401, Study CCT-301, Study CCT-302, Study OCT-301, Study OCT-302, etc.), no clinically significant adverse events occurred in terms of eye disorder as well as skin and subcutaneous tissue disorder. As described above, the safety concerns in clinical use attributable to distribution of unchanged vonoprazan or its metabolites in the melanin-containing tissues are unlikely to be raised.

PMDA has accepted the applicant's response, considering that there are no safety concerns attributable to accumulation of unchanged vonoprazan or its metabolites in the melanin-containing tissues at present.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

As toxicity studies of vonoprazan, single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance, and other toxicity studies (toxicity studies on its metabolites, etc.) were submitted. Some of the studies were non-GLP, and the results were submitted as reference data.

Unless otherwise mentioned, 0.5% methylcellulose solution was used as the vehicle of vonoprazan.

3.(iii).A.(1) Single-dose toxicity

3.(iii).A.(1).1) Oral dose toxicity study in rats (4.2.3.1-2, Report TAK-438/00053)

A single oral dose of vehicle or vonoprazan at 200, 600, or 2000 mg/kg was administered to male and female rats. Death occurred in animals treated at 600 mg/kg (1 of 5 females) and at 2000 mg/kg (5 of 5 in both males and females) by 4 hours post-dose. In these animals, decreased locomotor activity, prone position, bradypnea, hypothermia, tremor, tonic convulsion, mydriasis, and salivation were observed. Findings in survived animals included mydriasis and salivation in ≥200 mg/kg groups; and decreased locomotor activity, prone position, bradypnoea, hypothermia, tremor, lacrimation, stained fur, decreased fecal volume, and reduced body weight gain in the 600 mg/kg groups. All of them resolved by 6 days post-dose. Based on the above, the approximate lethal dose in rats was determined to be 600 to 2000 mg/kg for males and 200 to 600 mg/kg for females.

3.(iii).A.(1).2) Oral dose escalating toxicity study in dogs (4.2.3.1-6, Report No. TAK-438/00066)

The vehicle or vonoprazan at 2, 10, or 60 mg/kg was orally administered to male and female dogs by escalating the dose at an interval of 7 days. Death occurred in animals treated at 60 mg/kg (1 of 2 in both males and females) at approximately 2 hours post-dose. In these animals, vomiting and vocalization were observed within 1 hour of administration, and clonic convulsion, tachypnoea, cyanosis, and mydriasis were observed between 1 hour post-dose and death. Findings in survived animals included vomiting in ≥10 mg/kg groups and salivation and transient hypothermia in the 60 mg/kg groups on the day of dosing as well as increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) in the 60 mg/kg groups on the day after dosing and thereafter. All of these findings resolved on 14 days post-dose. Based on the above, the approximate lethal dose in dogs was determined to be 10 to 60 mg/kg for both males and females.

3.(iii).A.(2) Repeat-dose toxicity

Oral dose toxicity studies in mice (13 weeks), rats (4, 13, and 26 weeks), and dogs (4, 13, and 39 weeks) were conducted. The toxicological target organs were the stomach and liver in mice; the stomach, liver, thyroid, and adrenal gland in rats; and the stomach in dogs. The major findings in the stomach included changes attributable to the pharmacological action (weight increased, thickening of the glandular stomach mucosa, atrophy of the parietal cells, vacuolation of the parietal cells, eosinophilic chief cells and chief cell hyperplasia, hyperplasia of the gastric neck mucous cells) or changes attributable to irritant

properties of vonoprazan (squamous epithelial hyperplasia in the forestomach limiting ridge, globule leukocyte[24] infiltration, eosinophilic infiltration). The applicant, however, explained that, since these findings were mild in severity, did not indicate cytotoxicity, and were reversible, they have low toxicological significance. The applicant also explained that findings observed in mice and rats, increased liver weight and hypertrophy of the centrilobular hepatocytes, were considered to be adaptation changes attributable to liver drug-metabolizing enzyme induction[25] and therefore have low toxicological significance. In the repeat-dose toxicity studies (mice, 13 weeks; rats, 26 weeks; dogs, 39 weeks), the plasma exposure ($AUC_{0\text{-}24h}$) of unchanged vonoprazan at the no observed adverse effect level (NOAEL) for mice (20 mg/kg/day), male rats (5 mg/kg/day), female rats (10 mg/kg/day), and dogs (0.6 mg/kg/day) was approximately 27.8, 1.4, 11, 2.5 times greater, respectively, than the plasma exposure ($AUC_{0\text{-}tau}$)[26] of unchanged vonoprazan at the maximum recommended clinical dose.

3.(iii).A.(2).1) Thirteen-week repeated oral dose toxicity study in mice (4.2.3.4.1-2, Report TAK-438/00144)

Vonoprazan at 6, 20, 60, or 200 mg/kg/day or vehicle was orally administered to male and female mice for 13 weeks. Findings included vacuolation of the parietal cells and eosinophilic chief cells in the stomach in ≥20 mg/kg groups; decreases in serum total protein, albumin, albumin/globulin ratio (A/G ratio), and total cholesterol, an increase in liver weight, thickening of the glandular stomach wall, dilatation of the fundic gland, and hyperplasia of the fundic gland cells, as well as hypertrophy of the centrilobular hepatocytes in ≥60 mg/kg groups; and effects on the erythroid parameters (increased red blood cell count, decreased mean corpuscular volume, etc.), increases in platelet count, white blood cell count, and neutrophil percentage, a decrease in lymphocyte percentage, increases in serum ALT and serum alkaline phosphatase (ALP), a decrease in serum cholesterol, an increase in plasma gastrin concentration, inflammatory cell infiltration in the stomach, intranuclear inclusion in the hepatocytes, and localized hepatocyte necrosis and haemorrhage, as well as decreases in spleen weight and kidney weight in the 200 mg/kg group. Based on the above, the NOAEL was determined to be 20 mg/kg/day for both males and females.

3.(iii).A.(2).2) Four-week repeated oral dose toxicity study with 4-week recovery period in rats (4.2.3.2-2, 4.2.3.2-3; Reports TAK-438/00085, TAK-438/00136)

Vonoprazan at 10, 30, or 100 mg/kg/day or vehicle was orally administered to male and female rats for 4 weeks. The 100 mg/kg group and vehicle group included their recovery sub-group in which reversibility of the toxicity was investigated during 4-week washout period. Findings included an increase in stomach weight, vacuolation of the parietal cells in the stomach, squamous epithelial hyperplasia in the forestomach limiting ridge, hyperplasia of the gastric neck mucous cells, and globule leukocyte and eosinophil infiltration in the stomach in ≥10 mg/kg groups; increases in serum ALT and AST, hypertrophy of the centrilobular hepatocytes, atrophy of the parietal cells and eosinophilic chief cells in the stomach, expanded proliferative zone in the pylorus, and an increase in plasma gastrin concentration in ≥30 mg/kg groups; and effects on the erythroid parameters (decreases in hemoglobin concentration and mean corpuscular hemoglobin, etc.), a decrease in fibrinogen, increases in creatine kinase (CK), ALP, and calcium, a decrease in serum creatinine, an increase in liver weight, a decrease in adrenal gland weight, vacuolation of the midlobular hepatocytes, as well as follicular epithelial hypertrophy in the thyroid in the 100 mg/kg groups. During the recovery period, the effects on the erythroid parameters (a decrease in mean corpuscular hemoglobin, etc.) and an increase in stomach weight continued to be observed in the 100 mg/kg groups. The NOAEL was determined to be 30 mg/kg/day for males and 100 mg/kg/day for females, because the histopathological findings in the stomach were reversible and vacuolation of the midlobular hepatocytes and follicular epithelial hypertrophy in the thyroid were observed only in males of the 100 mg/kg groups.

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[24] Positive in immunostaining with antibody against rat mast cell protease 2, a marker of mucous mast cells.

[25] In the 13-week repeat-dose toxicity study in rats (4.2.3.2-4), *p*-nitrophenol glucuronidation enzyme in ≥10 mg/kg groups and aminopyridine *N*-demethylation enzyme in ≥100 mg/kg groups were induced. In the 13-week repeat-dose toxicity study in mice (4.2.3.4.1-2), aminopyridine *N*-demethylation enzyme, aniline hydroxylase, and ethoxyresorufin *O*-deethylation enzyme were induced in the 6 mg/kg groups.

[26] $AUC_{0\text{-}tau}$ (151.6 ng·h/mL) of unchanged vonoprazan on Day 7 in a Japanese phase I study (Study CPH-002), in which vonoprazan was orally administered once daily for 7 days at a dose of 20 mg (dosage and administration for maintenance therapy of reflux esophagitis).

Vonoprazan at 1 or 3 mg/kg/day or vehicle was orally administered to male and female rats for 4 weeks. Findings included an increase in stomach weight, vacuolation of the parietal cells in the stomach, hyperplasia of the gastric neck mucous cells, and squamous epithelial hyperplasia in the forestomach limiting ridge, as well as globule leukocyte and eosinophil infiltration in the stomach at 3 mg/kg. Based on the above, the NOEL was determined to be 1 mg/kg/day for both males and females.

3.(iii).A.(2).3) Thirteen-week repeated oral dose toxicity study in rats (4.2.3.2-4, Report TAK-438/00143)

Vonoprazan at 1, 10, 100, or 300 mg/kg/day or vehicle was orally administered to male and female rats for 13 weeks. Findings included an increase in stomach weight, atrophy and vacuolation of the parietal cells in the stomach, eosinophilic chief cells in the stomach, squamous epithelial hyperplasia in the forestomach limiting ridge, and globule leukocyte infiltration, as well as an increase in plasma gastrin concentration in ≥10 mg/kg groups; increased urine volume, a decrease in serum glucose, increases in serum triglyceride, serum ALP, and total cholesterol, an increase in liver weight, hyperplasia of the chief cells in the stomach, expanded proliferative zone and inflammatory cell infiltration in the pylorus, hypertrophy of the centrilobular hepatocytes, and vacuolation of the midlobular hepatocytes, as well as hypertrophy of the adrenal gland zona glomerulosa cells in ≥100 mg/kg groups; and a decrease in food consumption (only at the beginning of the treatment period), reduced body weight gain, increased water intake, a decrease in urine osmolality, a decrease in fibrinogen, increases in serum ALT, urea nitrogen, creatinine, and phospholipid, a decrease in serum chloride, thickening of the glandular stomach mucosal wall, swelled and brown liver, and mucous gland metaplasia in the stomach, as well as follicular epithelial hypertrophy in the thyroid in the 300 mg/kg groups. Based on the above, the NOAEL was determined to be 10 mg/kg/day for both males and females.

3.(iii).A.(2).4) Twenty-six-week repeated oral dose toxicity study with 13-week recovery period in rats (4.2.3.2-5, Report TAK-438/00212)

Vonoprazan at 1, 5, 10, or 30 mg/kg/day or vehicle was orally administered to male and female rats for 26 weeks. The vehicle group and 30 mg/kg group included their recovery sub-group in which reversibility of the toxicity was investigated during 13-week washout period. Findings included an increase in stomach weight, eosinophilic chief cells and globule leukocyte infiltration as in the stomach, as well as squamous epithelial hyperplasia in the forestomach limiting ridge in ≥5 mg/kg groups; atrophy and vacuolation of the parietal cells in the stomach, thickening and fibrosis (only males) of the glandular stomach mucosal wall, hypertrophy of centrilobular hepatocytes, as well as an increase in plasma gastrin concentration in ≥10 mg/kg groups; and increased water intake, increased urine volume, a decrease in urine osmolality, an increase in serum CK, increases in liver weight, prostate weight, and vesicular gland weight, red spot on the glandular stomach, inflammatory cell infiltration and vasodilation in the stomach, vacuolation of the hepatocytes, as well as hypertrophy of the adrenal gland zona glomerulosa cells at 30 mg/kg. During the recovery period, an increase in stomach weight, eosinophilic chief cells in the stomach, squamous epithelial hyperplasia in the forestomach limiting ridge, and fibrosis of the glandular stomach mucosa remained. Based on the above, the NOAEL was determined to be 5 mg/kg/day for males and 10 mg/kg/day for females.

3.(iii).A.(2).5) Four-week repeated oral dose toxicity study in dogs (4.2.3.2-7, Report TAK-438/00084)

Vonoprazan at 0.6, 2, 6, or 20 mg/kg/day or vehicle was orally administered to male and female dogs for 4 weeks. Findings included atrophy, vacuolation, single cell necrosis of the parietal cells in the stomach, as well as inflammatory cell infiltration in the fundic gland mucosa in ≥2 mg/kg groups; salivation,[27] vomiting, a decrease in serum chloride, an increase in serum ALP, and an increase in liver weight in ≥6 mg/kg groups; and loose stool in the 20 mg/kg groups. Based on the above, the NOAEL was determined to be 0.6 mg/kg for both males and females.

[27] Salivation mostly occurred just before or after administration, and no clear relationship between the time of occurrence and t_{max} of unchanged vonoprazan was observed. The applicant thus explained that the finding would be a change attributable to the local effect on the oral mucosa. In this study, only salivation observed 1 hour post-dose was assessed as a sign of toxicity.

3.(iii).A.(2).6) Thirteen-week repeated oral dose toxicity study with a 4-week recovery period in dogs (4.2.3.2-8, Report TAK-438-10742)

Vonoprazan at 1, 1.3, 1.6, or 2 mg/kg/day or vehicle was orally administered to male and female dogs for 13 weeks.[28] In addition, the vehicle group and 2 mg/kg group included their recovery sub-group in which reversibility of the toxicity was investigated during the 4-week washout period. Findings included an increase in serum ALT, single cell necrosis of the fundic gland cells in the stomach, inflammatory cell infiltration and hyperplasia in the fundic gland mucosa, as well as degeneration of the tunica muscularis ventriculi in ≥1 mg/kg groups; and vomiting in ≥1.6 mg/kg groups. During the recovery period, the degeneration of the tunica muscularis ventriculi remained. Based on the above, the NOAEL was determined to be <1 mg/kg/day for both males and females. The applicant explained that the degeneration of the tunica muscularis ventriculi may be attributable to enhanced synthesis and secretion of histamine in enterochromaffin-like cells in the gastric mucosa[29] subsequent to increased blood gastrin concentration associated with the gastric acid secretion inhibitory effect of vonoprazan.

3.(iii).A.(2).7) Thirty-nine-week repeated oral dose toxicity study in dogs (4.2.3.2-9, Report TAK-438/00217)

Vonoprazan at 0.3, 0.6, or 2 mg/kg/day or vehicle was orally administered to male and female dogs for 39 weeks. Findings included vacuolation of the parietal cells in the stomach in ≥0.3 mg/kg groups; and an increase in serum ALT, an increase in plasma gastrin concentration, gastric wall thickening, single cell necrosis of the fundic gland cells, inflammatory cell infiltration and hyperplasia in the fundic gland mucosa, as well as degeneration of the tunica muscularis ventriculi in the 2 mg/kg groups. Based on the above, the NOAEL was determined to be 0.6 mg/kg/day for both males and females.

3.(iii).A.(3) Genotoxicity (4.2.3.3.1-1 to 4.2.3.3.1-2, 4.2.3.3.2-1; Reports TAK-438/00052, TAK-438/00051, TAK-438/00083)

A bacterial reverse mutation assay, a chromosomal aberration assay with Chinese hamster lung cells, and a micronucleus assay in rats were conducted, and all the assays showed negative results. Based on the above, vonoprazan was not considered to have genotoxic potential.

3.(iii).A.(4) Carcinogenicity

Two-year repeated oral dose carcinogenicity studies in mice and rats were conducted. Findings included neuroendocrine tumor in the stomach in mice and rats (male mice in ≥6 mg/kg groups, female mice in ≥60 mg/kg groups, male and female rats in ≥5 mg/kg groups) and hepatocyte tumor (male mice in ≥20 mg/kg groups, female mice in ≥60 mg/kg groups, male and female rats in ≥50 mg/kg groups).

The applicant explained about the concerned study data as follows:
Either tumor was based on the nongenetic mechanism, because vonoprazan does not have genotoxic potential. The neuroendocrine tumor in the stomach is little relevant to humans, because the change was also observed in the carcinogenicity studies of the existing proton pump inhibitors (PPIs) and considered attributable to hypergastrinaemia associated with the pharmacological action of vonoprazan. The liver tumor is also little relevant to humans,[30] because liver drug-metabolizing enzyme was induced by vonoprazan in rats and mice[25] and the enzyme was similar to liver drug-metabolizing enzyme[31] induced by phenobarbital.

Except for the neuroendocrine tumor and liver tumor, no neoplastic lesions were observed at up to the highest dose in each carcinogenicity study (200 mg/kg/day for mouse, 150 mg/kg/day for rat), and the plasma exposure ($AUC_{0\text{-}24h}$) of unchanged vonoprazan at the highest dose was approximately 300 times (mice) and approximately 209 times (rats) greater than that ($AUC_{0\text{-}tau}$)[26] at the maximum recommended clinical dose.

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28 Only the stomach was subjected to the necropsy and histopathological examination.

29 *Endocrinology.* 1996;137:4435-4442

30 *Pharmacol Ther.* 1996;71:153-191

31 It has been reported that liver drug-metabolizing enzymes such as CYP2B, 2C, and 3A, as well as UDP-glucuronosyltransferase were induced after phenobarbital administration to mice and rats (*Toxicol Sci.* 2010;116:452-466, *Drug Metab Dispos.* 2010;38:1177-1182, *Biochem.J.* 1992;281:577-592).

3.(iii).A.(4).1) Two-year oral dose carcinogenicity study in mice (4.2.3.4.1-3, Report TAK-438-10883)

Vonoprazan at 6, 20, 60, or 200 mg/kg/day or vehicle was orally administered to male and female B6C3F1 mice for 2 years.[32] Findings included decreased survival, increased food consumption, reduced body weight gain (only males), and pale skin in the 200 mg/kg group. Neoplastic lesions observed included malignant neuroendocrine tumor[33] in the stomach in ≥6 mg/kg groups; benign neuroendocrine tumor[34] in the stomach and hepatocellular adenoma[35] in ≥20 mg/kg groups; and hepatocellular adenocarcinoma[36] in ≥60 mg/kg groups; and adenoma[37] in the stomach in the 200 mg/kg group. Non-neoplastic lesions observed[38] included hyperplastic gastropathy, localized hyperplasia of the gastric neuroendocrine cells, enhanced keratinization in the forestomach, localized hyperplasia of the mucous gland,[39] hypertrophy of centrilobular hepatocytes, foci of acidophilic hepatocyte alterations, midlobular hepatocyte vacuolation, and necrosis and degeneration of the hepatocytes in ≥6 mg/kg groups; squamous epithelial metaplasia in the stomach, localized hyperplasia of the gastric foveolar epithelium, diffuse gastric neuroendocrine cell hyperplasia, and localized hepatocyte necrosis in ≥20 mg/kg groups; localized hyperplasia of the fundic gland mucosa, diffuse hepatocyte vacuolation, dilatation of the urinary bladder and diffuse transitional epithelium hyperplasia, as well as hypertrophy of the thyroid follicular epithelial cells in ≥60 mg/kg groups; and erosion, ulcer, and fibrosis of the glandular stomach mucosa, diffuse hypertrophy of the cortical cells in the adrenal gland, bone atrophy, effects on the hematopoietic and lymphatic tissues (atrophy and granulocytopoiesis increased in the bone marrow in the sternum and femur, extramedullary hematopoiesis and atrophy in the spleen), vacuolation and necrosis of the centrilobular hepatocytes, multinucleated hepatocytes, extramedullary hematopoiesis in the liver, karyomegaly in epithelial cells on the papillary collecting duct in the kidney, atrophy of the female genitalia (ovary, uterus, vagina), as well as ductal dilatation in the mammary gland in the 200 mg/kg. The applicant explained that for the adenoma in the stomach, a neoplastic lesion observed at 200 mg/kg groups, the relationship with vonoprazan cannot be ruled out, but the plasma exposure ($AUC_{0\text{-}24h}$) of unchanged vonoprazan at the NOEL (60 mg/kg/day) for the concerned tumor is approximately 58 (males) and 63 (females) times greater than that ($AUC_{0\text{-}tau}$)[26] of unchanged vonoprazan at the maximum recommended clinical dose, raising no safety concerns in humans.

3.(iii).A.(4).2) Two-year oral dose carcinogenicity study in rats (4.2.3.4.1-4, Report TAK-438-10882)

Vonoprazan at 5, 15, 50, or 150 mg/kg/day or vehicle was orally administered to male and female rats for 2 years. Reduced body weight gain and a decreasing trend in the survival (only females) were observed in the 150 mg/kg groups. Neoplastic lesions observed included benign neuroendocrine cell tumor[40] and malignant neuroendocrine tumor[41] in the stomach in ≥5 mg/kg groups; and hepatocellular

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[32] Males in the 200 mg/kg group discontinued the treatment at Week 88 due to the increased mortality rate attributable to lesions in the urinary tract and stomach and then underwent the necropsy at Week 90.

[33] 0 of 55 males, 2 of 55 males, 7 of 55 males, 4 of 55 males, and 1 of 55 males; and 0 of 55 females, 0 of 55 females, 0 of 55 females, 1 of 55 females, and 7 of 55 females in the vehicle and vonoprazan 6, 20, 60, and 200 mg/kg groups, respectively

[34] 0 of 55 males, 0 of 55 males, 3 of 55 males, 27 of 55 males, and 35 of 55 males; and 0 of 55 females, 0 of 55 females, 0 of 55 females, 4 of 55 females, and 33 of 55 females in the vehicle and vonoprazan 6, 20, 60, and 200 mg/kg groups, respectively

[35] 20 of 55 males, 29 of 55 males, 31 of 55 males, 36, of 55 males and 33 of 55 males; and 16 of 55 females, 15 of 55 females, 18 of 55 females, 40 of 55 females, and 38 of 55 females in the vehicle and vonoprazan 6, 20, 60, and 200 mg/kg groups, respectively

[36] 6 of 55 males, 8 of 55 males, 15 of 55 males, 20 of 55 males, and 13 of 55 males; and 4 of 55 females, 3 of 55 females, 4 of 55 females, 7 of 55 females, and 42 of 55 females in the vehicle and vonoprazan 6, 20, 60, and 200 mg/kg groups, respectively

[37] 0 of 55 males, 0 of 55 males, 0 of 55 males, 0 of 55 males, and 2 of 55 males; and 0 of 55 females, 0 of 55 females, 0 of 55 females, 0 of 55 females, and 1 of 55 females in the vehicle and vonoprazan 6, 20, 60, and 200 mg/kg groups, respectively

[38] Including the findings in which the incidence or severity was increased compared with the vehicle group

[39] Excluding the 200 mg/kg group

[40] 1 of 60 males, 7 of 60 males, 7 of 60 males, 8 of 60 males, and 21 of 60 males; and 0 of 60 females, 18 of 60 females, 31 of 60 females, 33 of 60 females, and 37 of 60 females in the vehicle group and vonoprazan 5, 15, 50, and 150 mg/kg groups, respectively

[41] 0 of 60 males, 1 of 60 males, 0 of 60 males, 0 of 60 males, and 3 of 60 males; and 0 of 60 females, 7 of 60 females, 22 of 60 females, 18 of 60 females, and 11 of 60 females in the vehicle group and vonoprazan 5, 15, 50, and 150 mg/kg groups, respectively

adenoma[42] and hepatoma[43] in ≥50 mg/kg groups. Non-neoplastic lesions[38] included atrophy of the glandular stomach mucosa, fibrosis of the glandular stomach mucosa, diffuse/localized gastric neuroendocrine cell hyperplasia, hyperplastic gastropathy, and hypertrophy of the centrilobular hepatocytes, as well as foci of acidophilic hepatocyte alterations in ≥5 mg/kg groups; localized hyperplasia of the gastric foveolar epithelium, hepatocyte vacuolation in the centrilobular intermediate zone, and diffuse C-cell hyperplasia in the thyroid in ≥15 mg/kg groups; squamous epithelial hyperplasia in the forestomach limiting ridge, intestinal epithelial metaplasia in the pyloric gland in the stomach, hepatic spongiosis, and pigmentation in the tubular epithelial cells in ≥50 mg/kg groups; and multinucleated hepatocytes, tubular dilatation in the outer medullary stratum zonale in the kidney, foam cell infiltration in the lung, alveolar lipoid proteinosis, and diffuse hypertrophy of the follicular epithelial cells in the thyroid in the 150 mg/kg groups.

3.(iii).A.(5) Reproductive and developmental toxicity

A study of fertility and early embryonic development to implantation in rats, embryo-fetal development studies in rats and rabbits, and a study on pre- and postnatal development, including maternal function in rats were conducted. In rats, findings in the parent animals and maternal animals were effects on the clinical conditions associated with reduced body weight gain (decreased locomotor activity) in ≥100 mg/kg groups; findings in embryos and fetuses were external abnormalities (anal stenosis, abnormal tail) and visceral abnormalities (membranous ventricular septal defect, abberant subclavian artery) in the 300 mg/kg group; and findings in offsprings (F_1) were a decrease in body weight (pre-weaning, post-weaning) and effects on the liver (white foci, black or small liver, etc.) in those aged 4 days or weaning (aged 22-23 days) in the 100 mg/kg group. In rabbits, findings in maternal animals were reduced body weight gain associated with decreased food consumption in the ≥10 mg/kg groups, but no abnormalities were observed in embryos or fetuses. The plasma exposure ($AUC_{0\text{-}24h}$) of unchanged vonoprazan in rats and rabbits at the NOAEL observed in the embryo-fetal development studies (100 mg/kg/day for rats, 30 mg/kg/day for rabbits) was approximately 28 and 6.7 times greater, respectively, than that ($AUC_{0\text{-}tau}$)[44] at the maximum recommended clinical dose.

3.(iii).A.(5).1) Study of fertility and early embryonic development to implantation in rats (4.2.3.5.1-2, Report TAK-438/00172)

Vonoprazan at 30, 100, or 300 mg/kg/day or vehicle was orally administered to male rats from 2 weeks prior to mating until the day of necropsy after mating period (approximately 8 weeks) and to female rats from 2 weeks prior to mating up to Gestation Day 6. Death occurred in males in the 300 mg/kg group (4 of 20 animals). Findings included mydriasis in ≥100 mg/kg groups; and reduced body weight gain, decreased food consumption, tremor, stained perineal fur, decreased locomotor activity, red rhinorrhea, prone position, reddish tear, and red foci in the stomach in the 300 mg/kg group. There were no effects on reproductive functions or early embryonic development. Based on the above, the NOAEL was determined to be 30 mg/kg/day for general toxicity in male and female parent animals, and ≥300 mg/kg/day for reproductive performance and early embryonic development.

3.(iii).A.(5).2) Rat embryo-fetal development study (4.2.3.5.2-2, Report TAK-438/00135)

Vonoprazan at 30, 100, or 300 mg/kg/day or vehicle was orally administered to pregnant rats from Gestation Day 6 to Gestation Day 17. Death occurred in maternal animals in the 300 mg/kg group (1 of 20 animals). Findings included reduced body weight gain/decreased body weight and decreased food consumption in ≥100 mg/kg groups; and mydriasis, tremor, prone position, decreased fecal volume, and a decrease in placenta weight in the 300 mg/kg group. Findings in embryos and fetuses included a decrease in body weight, external abnormalities (anal stenosis, abnormal tail) and visceral abnormalities (membranous ventricular septal defect, abberant subclavian artery) in the 300 mg/kg group. Based on

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[42] 3 of 60 males, 3 of 60 males, 7 of 60 males, 15 of 60 males, and 31 of 60 males; and 2 of 60 females, 2 of 60 females, 5 of 60 females, 14 of 60 females, and 20 of 60 females in the vehicle group and vonoprazan 5, 15, 50, and 150 mg/kg groups, respectively

[43] 0 of 60 males, 0 of 60 males, 0 of 60 males, 1 of 60 males, and 7 of 60 males; and 0 of 60 females, 0 of 60 females, 0 of 60 females, 0 of 60 females, and 1 of 60 females in the vehicle group and vonoprazan 5, 15, 50, and 150 mg/kg groups, respectively. Although there was no statistically significant difference from the vehicle group, hepatocyte or cholangiocyte adenoma (1 of 60 males in the 50 mg/kg groups) and hepatocyte or cholangiocyte adenocarcinoma (3 of 60 males in the 150 mg/kg groups) were observed. The applicant explained that they could develop in association with hepatocyte tumor.

[44] $AUC_{0\text{-}tau}$ (458.5 ng·h/mL) of unchanged vonoprazan on Day 7 in a Japanese phase I study (Study CPH-002) in which vonoprazan was orally administered once daily for 7 days at a dose of 40 mg/kg (in the dosage and administration for adjunct to *H. pylori* eradication, vonoprazan is administered twice daily at a dose of 20 mg).

the above, the NOAEL was determined to be 30 mg/kg/day for maternal animals and 100 mg/kg/day for embryos and fetuses.

3.(iii).A.(5).3) Rabbit embryo-fetal development study (4.2.3.5.2-4, Report TAK-438/00137)

Vonoprazan at 3, 10, or 30 mg/kg/day or vehicle was orally administered to pregnant rabbits from Gestation Day 6 to Gestation Day 18. Abortion occurred in maternal animals in the 30 mg/kg group (2 of 20 animals). Findings included decreased food consumption, reduced body weight gain, and decreased fecal volume in ≥10 mg/kg groups; and vaginal haemorrhage [45] and intrauterine haemorrhage[46] in the 30 mg/kg group. There were no effects on the embryos or fetuses. Based on the above, the NOAEL was determined to be 3 mg/kg/day for maternal animals and ≥30 mg/kg/day for embryos and fetuses.

3.(iii).A.(5).4) Study on pre- and postnatal development, including maternal function in rats (4.2.3.5.3-3, Report TAK-438-11215)

Vonoprazan at 1, 3, 10, or 100 mg/kg/day or vehicle was orally administered to pregnant rats from Gestation Day 6 to Lactation Day 21. Findings in maternal animals included decreased food consumption and reduced body weight gain during the lactation period in the 100 mg/kg group. Findings in offspring (F_1) were a decrease in body weight (pre-weaning, post-weaning) and effects on the liver (white foci, black or small liver, etc.) in those aged 4 days or weaning (aged 22-23 days) in the 100 mg/kg group. The effects on the liver in suckling offspring were also observed in the dose-finding study (4.2.3.5.3-1) and supplemental study (4.2.3.5.3-2), which were conducted prior to this study. Based on the above, the NOAEL was determined to be 10 mg/kg/day for maternal animals and 10 mg/kg/day for offspring.

3.(iii).A.(6) Local tolerance

Rabbit venous tolerance study and perivenous tolerance study (4.2.3.6-2, 4.2.3.6-3; Reports TAK-438-11232, TAK-438-11233)

To male rabbits, 1 mg/mL vonoprazan solution[47] was administered into the auricular vein for 7 days or around the auricular vein subcutaneously as a single dose. Following the intravenous administration, visual observation of the auricle and auricular vein, necropsy, and histopathological examination were performed, but no abnormalities were observed. Following subcutaneous administration, the severity of subcutaneous haemorrhage increased up to 2 days after administration, but the reversibility was observed. Based on the above, 1 mg/mL vonoprazan solution was determined to cause mild local irritation in the perivenous tissue.

3.(iii).A.(7) Other toxicity study

3.(iii).A.(7).1) Study on sensitivity to rat offspring hepatic changes (4.2.3.7.3-1, Report TAK-438-10873 [Reference data])

Concerning discolored foci in the liver observed in the offspring, to identify the sensitive period in which vonoprazan affected the liver development, vonoprazan at 100 mg/kg/day or vehicle[48] was orally administered from Gestation Day 6 to Lactation Day 13, from Gestation Day 6 to Gestation Day 21, or from Lactation Day 0 to Lactation Day 13 to pregnant SD rats. From Gestation Day 6 to Lactation Day 13, from Gestation Days 6 to 21, and from Lactation Days 0 to 13, an increase in stomach weight or its trend[49] in the offspring aged 4 days and 14 days and increased incidence of the diffuse hepatocyte vacuolation in the offspring aged 4 days were observed. From Gestation Day 6 to Lactation Day 13 and from Lactation Days 0 to 13, a decrease in offspring body weight as well as white foci, black, and small caudate lobe in the liver, diffuse hepatocyte vacuolation, and hepatic infarction[50] in breast-fed offspring were observed. The applicant explained that the diffuse hepatocyte vacuolation and hepatic infarction were considered to be ischemic changes due to compression against the vessel at the hepatic caudate

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45 Of animals with vaginal haemorrhage, 1 animal had an abortion.

46 In animals with intrauterine haemorrhage, all fetuses died.

47 Vonoprazan was dissolved in a solution containing citric acid hydrate (1.31 mg/mL), sodium citrate hydrate (1.10 mg/mL), and sodium chloride (9.00 mg/mL).

48 In the vehicle group, 0.5w/v% methylcellulose solution was administered from Gestation Day 6 to Lactation Day 13.

49 Excluding offspring aged 14 days in the group receiving vonoprazan from Gestation Days 6 to 21

50 In the group that received from Gestation Day 6 to Lactation Day 13, hepatic infarction was also observed in offspring aged 4 days (1 of 31 neonates).

lobe papillary stem caused by stomach distension associated with increased gastric milk volume, because these changes were localized in the caudate lobe.

3.(iii).A.(7).2) Toxicity study on the metabolite (M-IV-Sul)

Of the human major metabolites (M-I, M-II, M-III, M-IV-sul), M-IV-sul was subjected to the repeat-dose toxicity studies, genotoxicity studies, embryo-fetal toxicity studies, and phototoxicity studies, because it was determined that the exposure of M-IV-sul was not sufficient in the toxicity studies of vonoprazan. No genotoxicity studies of M-I, M-II, or M-III have been conducted. The applicant, however, explained that clinical use of vonoprazan was unlikely to raise any concern of genotoxicity of its metabolites, because the concentrations of the metabolites in reaction solutions in the *in vitro* genotoxicity tests of vonoprazan, and estimated concentrations of the metabolites at the highest dose (250 mg/kg/day) in the micronucleus test of vonoprazan, which showed negative results, and the plasma exposure ($AUC_{0\text{-}24h}$) of each metabolite in the carcinogenicity study of vonoprazan was equivalent to or higher than the plasma exposure ($AUC_{0\text{-}tau}$)[51] of each metabolite at the maximum recommended clinical dose.

(a) Repeated subcutaneous dose toxicity study in rats (4.2.3.7.5-3, 4.2.3.7.5-4; Reports TAK-438-00213, TAK-438-10049)

M-IV-Sul at 6 or 20 mg/kg/day or vehicle[52] was subcutaneously administered to male and female rats for 2 weeks and 13 weeks. No effects of M-IV-Sul were observed, and the NOAEL was thus determined to be 20 mg/kg/day for both males and females.

(b) Genotoxicity study (4.2.3.7.5-9 to 4.2.3.7.5-11; Reports TAK-438/00203, TAK-438/00211, TAK-438/00202)

A bacterial reverse mutation assay, a chromosomal aberration assay with Chinese hamster lung cells, and a micronucleus assay in rats were conducted for M-IV-Sul, and all the assays showed negative results. Based on the above, M-IV-Sul was not considered to have genotoxic potential.

(c) Subcutaneous dose embryo-fetal toxicity study in rats (4.2.3.7.5-15, Report TAK-438-10069)

M-IV-Sul at 6, 20, or 60 mg/kg/day or vehicle was subcutaneously administered to pregnant rats from Gestation Day 6 to Gestation Day 17. There were no effects on the dams or embryos or fetuses and the NOAEL was determined to be 60 mg/kg/day for both dams and embryo-fetal development.

(d) *In vivo* phototoxicity study in hairless mice (4.2.3.7.5-18, Report TAK-438-10089)

SKH-1 hairless mice subcutaneously received a single dose of M-IV-Sul at 40, 200, or 1000 mg/kg or vehicle and then were exposed to the simulated sunlight at a half of the minimal erythema dose for 4 hours[53] starting at 18 minutes post-dose. In the dose groups of 1000 mg/kg, of 10 animals each exposed to either light or simulated sunlight, 2 animals died or were sacrificed moribund, and some presented discoloration at the injection site, crust formation/ulcer, and hypothermia. Animals exposed to light at the dose of 1000 mg/kg presented skin reactions (erythema, edema), suggesting phototoxicity. The applicant, however, explained that such findings were observed at the dose equivalent to the lethal dose and the clinical use was unlikely to lead to development of the phototoxicity of M-IV-Sul.

3.(iii).A.(7).3) Toxicity studies of the impurities

No toxicity studies of the impurities were conducted. For 5 related substances, however, the specifications were set exceeding the qualification threshold, which is defined in the revised versions of "Impurities in New Drug Substances" (PMSB/ELD Notification No. 1216001 dated December 16, 2002, ICH Q3A guideline) and "Impurities in New Drug Products" (PMSB/ELD Notification No. 0624001 dated June 24, 2003, ICH Q3B guideline). The safety of these substances was evaluated based on their contents in lots of the test article used in the toxicity studies and the NOAEL in each toxicity study. As a result, it was determined that the clinical use of vonoprazan did not raise safety issues.

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51 $AUC_{0\text{-}tau}$ of each metabolite (478.5 ng·h/mL for M-I, 88.4 ng·h/mL for M-II, 161.9 ng·h/mL for M-III) on Day 7 in a Japanese phase I study (Study CPH-002), in which vonoprazan was orally administered once daily for 7 days at a dose of 20 mg (dosage and administration of the maintenance therapy for reflux esophagitis).

52 Physiological saline containing sodium hydroxide

53 In the 1000 mg/kg group, the simulated irradiation group was also included.

3.(iii).A.(7).4) *In vivo* phototoxicity study in hairless mice (4.2.3.7.7-1, Report TAK-438/00197)

SKH-1 hairless mice orally received a single dose of vonoprazan at 20, 60, or 200 mg/kg or vehicle and then were exposed to simulated sunlight at a half of the minimum erythema dose for 4 hours, starting at 30 minutes post-dose. In animals treated with vonoprazan, no findings suggesting phototoxicity were observed. It was thus considered that vonoprazan did not induce a phototoxic skin reaction.

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Neuroendocrine tumor in the stomach

Regarding neuroendocrine tumor in the stomach observed in the carcinogenicity studies of vonoprazan in mice and rats, PMDA asked the applicant to explain whether or not there is any relevant safety concern in humans in consideration of the mechanism of the development and the incidence related to the existing PPIs.

The applicant responded as follows:

In the carcinogenicity study of vonoprazan in mice, hyperplasia and tumor of the neuroendocrine cells were observed in males at ≥6 mg/kg and females at ≥60 mg/kg, and an increase in plasma gastrin concentration was observed in ≥6 mg/kg groups. In the carcinogenicity study of vonoprazan in rats, hyperplasia and tumor of the neuroendocrine cells in the stomach were also observed in males and females in ≥5 mg/kg groups, and an increase in plasma gastrin concentration was observed in ≥5 mg/kg groups.

Neuroendocrine tumor was also observed in the carcinogenicity studies of the existing PPIs (omeprazole, LPZ, sodium rabeprazole) in mice and rats, but the malignant tumor rate with respect to all the rats with neuroendocrine tumor in the vonoprazan group was comparable to or tended to be lower than that in the LPZ group.[54]

The mechanism of the development of neuroendocrine tumor in animals treated with the existing PPIs is considered to be caused by enhanced gastrin production with gastric acid secretion inhibition and persistent gastrin stimulation to neuroendocrine cells.[55] From a molecular biological viewpoint, gastrin inhibits the apoptosis and enhances the proliferation of neuroendocrine cells, potentially contributing to development of malignant neuroendocrine tumor, because it has been reported that after omeprazole is administered to rats, the expression of anti-apoptosis pathway-related genes associated with hypergastrinaemia increases.[56] The neuroendocrine tumor observed in animals treated with vonoprazan is thus considered to develop through the same mechanism above as with the existing PPIs.

Regarding the relevance of the neuroendocrine tumor risk to humans, it has been reported that neuroendocrine tumor develops in the Norwegian Lundehund (a dog breed), which, though a non-rodent species, presents pathological condition of hypergastrinaemia,[57] and therefore the concerned tumor may develop in dogs, but in the 39-week repeat-dose toxicity study of vonoprazan in dogs, no changes such as hyperplasia were observed in the neuroendocrine cells. Because it has been reported that the density of neuroendocrine cells correlates to the gastrin sensitivity,[58] neuroendocrine tumor was considered not to develop in dogs,[59] whose cell density is lower than that in rodent species. In humans, the density of neuroendocrine cells is lower than that in rodent species as with dogs.[59] Therefore, it is considered that the development of neuroendocrine tumor, which was observed in the carcinogenicity studies of vonoprazan in mice and rats, is little relevant to humans.

Based on the above, it is considered unlikely that the clinical use of vonoprazan will raise significant safety issues related to neuroendocrine cell tumor, which was observed in the carcinogenicity studies of vonoprazan in rats and mice.

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54 The malignant tumor rate in carcinogenicity studies of LPZ in rats is 33% to 50% in males and 47% to 52% in females (applicant internal data), while the rate in carcinogenicity studies of vonoprazan in rats was 13% to 14% in males and 33% to 70% in females.

55 Summary of application data for the initial new drug application of "Takepron Capsules 15 and 30," *Digestion.* 1990;45:189-195, *Toxicol Pathol.* 1988;16:267-272

56 *Regul.Pept.* 2007;140:153-161, *J clin Gastroenterol.* 1998;27:S116-124, *Physiol Genomics.* 2004;20:131-142

57 *J Comp Pathol.* 2008;139:194-201

58 *Physiol Genomics.* 2004;20:131-142

59 *Histochemistry.* 1986;86:5-17

PMDA considers that the applicant's response on the mechanism of development of the neuroendocrine tumor observed in the carcinogenicity studies of vonoprazan in mice and rats and their relevance to humans is acceptable from a toxicological viewpoint. The concerns of development of the neuroendocrine tumor following administration of vonoprazan will be, however, additionally reviewed in the clinical sections [see "4.(iii).B.(2).2) Serum gastrin levels"].

3.(iii).B.(2) Effects on the liver and stomach observed in offspring

Regarding the effects on the stomach and liver observed in the reproductive and developmental toxicity study in rats and study on sensitivity to rat offspring hepatic changes, PMDA asked the applicant to explain whether or not there are any safety concerns relevant to humans.

The applicant responded as follows:

In the study on sensitivity to rat offspring hepatic changes, an increase in stomach weight or its trend was observed in all the offspring aged 4 days from Gestation Day 6 to Lactation Day 13 group, from Gestation Days 6 to 21 group, and from Lactation Days 0 to 13 group. These changes are potentially attributable to pharmacological action with exposure to vonoprazan through milk or increased gastric milk volume associated with the decreased gastric emptying rate.[60] In addition, since vonoprazan is transferred to fetuses in rats by passing through the placenta [see "3.(ii).A.(2).8) Placental transfer"], it cannot be ruled out that fetal exposure to vonoprazan during the gestation period would lead to the increase in stomach weight. From Gestation Days 6 to 21, however, the increase in stomach weight resolved on Lactation Day 14, and thus the effect on the stomach is unlikely to become a safety concern in humans. The package insert will still include cautions that vonoprazan should not be administered to nursing women and, if the administration is unavoidable, nursing women should discontinue breast-feeding. The rat embryo-fetal development study showed a decrease in body weight, external abnormalities, and visceral abnormalities in the embryos and fetuses. A caution will therefore be provided, stating that vonoprazan should be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment.

In the study on the sensitivity of rat offspring hepatic changes to vonoprazan, the increased incidence of diffuse hepatocyte vacuolation (9 of 31 animals in the vehicle group, 22 of 31 animals in Gestation Day 6 to Lactation Day 13 group, 25 of 32 animals in Gestation Days 6 to 21 group, 21 of 30 animals in Lactation Days 0 to 13 group) was observed in offspring aged 4 days. In consideration of localization of the concerned finding in the caudate lobe as well as anatomical structure[61] of the liver and stomach in rats, this change is possibly attributable to ischemic conditions as a consequence of the compression against the blood vessel toward the hepatic caudate lobe by the distended stomach. As observed in the vehicle group, the diffuse hepatocyte vacuolation is a finding that can develop in response to physiological stomach distension. The increased incidence in the vonoprazan group is considered as a secondary effect of the increase in the stomach weight associated with the stomach distension. In consideration of anatomical structure of the liver and stomach in humans, the effect on the liver caused by the concerned mechanism is unlikely to become a concern in humans.

PMDA considers as follows:

In terms of the effects on the stomach, an increase in stomach weight was observed in the Gestation Day 6 to Lactation Day 13 group and in the Gestation Days 6 to 21 group in the offspring in the study on the sensitivity of rat offspring hepatic changes to vonoprazan. A relationship of the concerned finding with the fetal exposure to vonoprazan during the gestation period cannot be ruled out. The applicant, however, claimed that the effect on the stomach observed in rat offspring was unlikely to become a safety concern in humans, because the increase in stomach weight was found to be reversible; the plasma exposure of unchanged vonoprazan in maternal animals following administration of vonoprazan to pregnant rats at a dose of 100 mg/kg, expressed as C_{max} of 1.4 μg/mL and $AUC_{0\text{-}24h}$ of 12.9 μg·h/mL, was approximately

60 It has been reported that in rats aged 1 to 3 weeks treated with pantoprazole, a PPI, the gastric content (milk) weight increased due to a decreased gastric emptying rate (*Am J Physiol Gastrointest Liver Physiol.* 2014;307:G390-396.).

61 The caudate lobe is placed on the lesser curvature of the stomach covering the ventral and dorsal regions of the stomach, and the blood vessel running from the head to the tail of the caudate lobe diverges from the portal system after the hepatic portal region (*Kanzo.* 1986;27:113-118, *J Hepatobiliary Pancreat Surg.* 1999;6:171-175.).

18 and 28 times[62] greater, respectively, than the exposure at the maximum recommended clinical dose; and no abnormalities were observed in the gastrointestinal tract including the stomach in the rat embryo-fetal toxicity study. PMDA has concluded that the above applicant's response is acceptable. It is appropriate for the applicant to include cautions against the use during pregnancy or lactation in the package insert.

In addition, PMDA has concluded that the applicant's response on the effect on the liver is acceptable.

4. Clinical data

In the following clinical data, the doses and plasma concentrations of vonoprazan fumarate (hereinafter referred to as vonoprazan) are expressed as the amounts of vonoprazan.

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A Summary of the submitted data

In clinical studies included in the evaluation data submitted in the application, the formulations as shown in Table 16 were used.

Table 16. Formulations used in clinical studies (evaluation data)

Formulation	Dosage form	Strength	Clinical studies
Formulation A	Film-coated tablets	1 mg 10 mg 40 mg	Japanese phase I study (CPH-001)
Formulation B	Film-coated tablets	5 mg 10 mg 20 mg	Japanese phase I study (CPH-002) Japanese phase II study (CCT-001, CPH-003)
Formulation C	Film-coated tablets	10 mg 20 mg 40 mg	Japanese phase III study (OCT-301, CCT-301, CCT-302, OCT-001, CCT-003, OCT-302, CCT-101, CCT-102, CCT-002, OCT-303, OCT-304, CPH-401, CCT-401) Foreign phase I study (111, 112, 113)
Proposed formulation	Film-coated tablets	10 mg 20 mg	Japanese phase III study (CPH-007)

Vonoprazan concentrations were measured by liquid chromatography in the dissolution test.

The following analytical techniques were used on the biological samples in the clinical studies.

Plasma and urine concentrations of unchanged vonoprazan and its metabolites (M-I, M-II, M-III, M-IV-Sul) were measured by high performance liquid chromatography tandem-mass spectrometry (LC/MS/MS). The lower limits of quantification for unchanged vonoprazan, M-I, M-II, M-III, and M-IV-Sul were 0.1, 1, 1, 0.1, and 1 ng/mL, respectively, for plasma concentrations and 1, 10, 10, 10, and 10 ng/mL, respectively, for urine concentrations.

Plasma concentrations of aspirin and its metabolites (salicylic acid), loxoprofen sodium hydrate (loxoprofen) and its active metabolite (*trans*-OH form), and diclofenac sodium as well as meloxicam were measured by LC-MS/MS. The lower limits of quantification for aspirin, salicylic acid, loxoprofen, loxoprofen *trans*-OH form, diclofenac, and meloxicam were 2, 100, 10, 2, 1, and 3 ng/mL, respectively.[63]

Plasma concentrations of amoxicillin hydrate (AMPC), and clarithromycin (CAM) and its metabolites (14–hydroxyclarithromycin) as well as metronidazole (MNZ) and its metabolites (hydroxymetronidazole) were measured by LC-MS/MS. The lower limits of quantification for AMPC,

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62 Plasma exposure of unchanged vonoprazan (C_{max}, 75.2 ng/mL; $AUC_{0\text{-}tau}$, 458.5 ng·h/mL) on Day 7 in a Japanese phase I study (Study CPH-002) in which vonoprazan was orally administered once daily for 7 days at a dose of 40 mg/kg (in the dosage and administration for adjunct to *H. pylori* eradication, vonoprazan is administered twice daily at a dose of 20 mg).

63 Concentration as the anhydrous compound of loxoprofen sodium hydrate

CAM, 14-hydroxyclarithromycin, MNZ, and hydroxymetronidazole were 50, 10, 10, 50, and 50 ng/mL, respectively.

4.(i).A.(1) Dissolution test (5.3.1.2-1)

In accordance with the "Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms" (PMSB/ELD Notification No. 67 dated February 14, 2000, partially revised by PFSB/ELD Notification No. 0229-10 dated February 29, 2012), the change from Formulation B (10 mg tablets, 20 mg tablets) to Formulation C (10 mg tablets, 20 mg tablets) corresponds to level [redacted]. The dissolution test required in the level was performed. The results showed that the dissolution profile of Formulation B was comparable to that of Formulation C at either strength.

In accordance with the above guideline, the change from Formulation C (10 mg tablets, 20 mg tablets) to the proposed formulation (10 mg tablets, 20 mg tablets) corresponds to level [redacted] for the 10 mg tablets and level [redacted] for the 20 mg tablets. The dissolution tests required in the levels were performed. The results showed that the dissolution profile of Formulation C was comparable to that of the proposed formulation at either strength.

In accordance with the "Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms" (PMSB/ELD Notification No. 64 dated February 14, 2000, partially revised by PFSB/ELD Notification No. 0229-10 dated February 29, 2012), the formulation change to the proposed 10 mg tablets corresponds to level [redacted] if the proposed 20 mg tablets is chosen as the standard formulation. The dissolution test required for the concerned level was performed. The results showed that the dissolution profile was comparable between the 2 formulations.

4.(i).A.(2) Japanese phase III study (food effect) (5.3.1.1-1, Study TAK-438/CPH-007 [[redacted] 20[redacted]])

A randomized, open-label, two-treatment, two-period crossover study was conducted at a single center in Japan to evaluate the effects of food on the pharmacokinetics (PK) following a single oral dose of vonoprazan in healthy adult male subjects aged 20 to 35 years (target sample size: 12 subjects in total, 6 subjects/group).

A single oral dose of 1 proposed 20 mg tablet was to be administered without breakfast or after breakfast[64] followed by ≥7 days of the washout period to the next dosing period.

All of the 12 treated subjects were included in the safety and PK analysis sets.

Regarding safety, no adverse events were reported.

In terms of the PK, the adjusted geometric mean ratios of C_{max} and $AUC_{0\text{-}48h}$ of vonoprazan administered in the fed state to those in the fasted state (postprandial/fasted) [two-sided 90% CI] were 1.09 [0.94, 1.26] and 1.08 [1.01, 1.14], respectively. The upper limit of the two-sided 90% CI for C_{max} exceeded the range of 0.80 to 1.25, the acceptance criterion for bioequivalence, but the extent was minor. The applicant therefore explained that food has no considerable effect on the PK of vonoprazan.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

4.(ii).A.(1) *In vitro* studies using human biological samples

4.(ii).A.(1).1) Membrane permeability in Caco-2 cells (4.2.2.2-11, Study TAK-438-10811)

Caco-2 cells cultured on a transwell plate were incubated with ^{14}C-vonoprazan (3 μmol/L) to investigate the membrane permeability. Apparent permeability coefficients from the apicolateral surface to the basolateral surface and from the basolateral surface to the apicolateral surface ($Papp_{A\rightarrow B}$, $Papp_{B\rightarrow A}$) (mean) were 17.8×10^{-6} and 21.3×10^{-6} cm/sec, respectively. The applicant explained that the apparent elimination ratio ($Papp_{B\rightarrow A}/Papp_{A\rightarrow B}$) was 1.2, close to 1, suggesting that vonoprazan did not serve as a substrate of P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP). Also, the $Papp_{A\rightarrow B}$ was comparable to those of metoprolol, propranolol, theophylline, and verapamil ($Papp_{A\rightarrow B}$, 16.1-19.2 $\times 10^{-6}$

64 For administration without breakfast, subjects were to be fasted at least 10 hours before administration of vonoprazan, and for administration after breakfast, they were to have a meal 30 minutes before taking the drug. For both administration regimens, subjects were to be fasted until 4 hours after administration of vonoprazan.

cm/sec), which are highly permeable compounds. The applicant therefore explained that the membrane permeability of vonoprazan was high.

4.(ii).A.(1).2) *In vitro* plasma protein binding (4.2.2.3-6, Study TAK-438/00087)

^{14}C-vonoprazan was added to human plasma at 100, 1000, and 10,000 ng/mL, and the plasma protein binding (mean for each concentration) was measured. The plasma protein binding was 85.2% to 88.0%, indicating little dependency on the concentration in the investigated range.

^{14}C-vonoprazan was added to 4% human serum albumin (HSA) solution, 0.05% α_1-acid glycoprotein (AGP) solution, and 4% HSA/0.05% AGP mixture solution at 100, 1000, and 10,000 ng/mL and the plasma protein binding (mean) was measured. The plasma protein binding was 43.0% to 44.6%, 21.4% to 45.7%, and 51.1% to 60.1%, respectively. Vonoprazan bound to both HSA and AGP. The binding in human plasma, on the other hand, was higher than that in 4% HSA/0.05% AGP mixture solution. Based on the above, the applicant explained that it has been suggested that vonoprazan binds to plasma protein other than HSA and AGP.

4.(ii).A.(1).3) Distribution in blood cells (4.2.2.3-10, Study TAK-438/00090)

^{14}C-vonoprazan was added to human plasma at 10, 100, and 1000 ng/mL and the distribution in blood cells (mean for each concentration) was measured. The distribution in blood cells was 43.7% to 46.0%, indicating little dependency on the concentration in the investigated range.

4.(ii).A.(1).4) Metabolism

(a) Possible metabolic pathway (4.2.2.4-1, 4.2.2.4-2, 4.2.2.4-10 to 4.2.2.4-12, 4.2.2.4-15, 4.2.2.4-17; Studies TAK-438/00102, TAK-438-11259, TAK-438/00131, TAK-438-10735, TAK-438/00095, TAK-438-11250, TAK-438-11251)

The metabolites of vonoprazan identified in humans included the followings: M-I (5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrole-3-carboxylic acid), M-II (5-(2-Fluorophenyl)-1*H*-pyrrole-3-carboxylic acid), M-III (*N*-{(*Z*)-[5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]methylidene}-*N*-methyl amine oxide), M-I-G (glucuronate conjugate of M-I), M-II-G (glucuronate conjugate of M-II), and M-IV-Sul (sulfate conjugate of M-IV). It was presumed that unchanged vonoprazan was metabolized into M-I through oxidative deamination, and M-I was metabolized into M-II through cleavage of the sulfonamide. Furthermore, M-I and M-II were presumed to be metabolized into M-I-G and M-II-G, respectively, through glucuronidation. Unchanged vonoprazan was presumed to be metabolized into M-III through nitrone oxidation of amine moiety, a side chain of unchanged vonoprazan, as well as into M-IV-Sul through sulfate conjugation of amine moiety, a side chain of unchanged vonoprazan, followed by hydroxylation of the phenyl group.

(b) CYP isoforms involved in the metabolism (4.2.2.4-13, 4.2.2.4-14; Studies TAK-438/00096, TAK-438/00097)

^{14}C-vonoprazan (10 μmol/L) was incubated with human liver microsome and correlation of the metabolic rate of ^{14}C-vonoprazan to activity of each CYP isoform (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5, 4A11)[65] was investigated. As a result, the elimination rate of unchanged vonoprazan and the production rate of M-I, M-III, and *N*-desmethyl form of unchanged vonoprazan all showed strong correlation with the activity of CYP3A4/5.

Following incubation of ^{14}C-vonoprazan (10 μmol/L) with human CYP isoform-expressed microsomes (CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4), unchanged vonoprazan was metabolized mainly in CYP2D6-, 2C19-, and 3A4-expressed microsomes. In the CYP2D6- and 2C19-expressed microsomes, *N*-desmethyl form of unchanged vonoprazan was mainly produced, and in the CYP3A4-expressed microsome, M-I, M-III, and *N*-desmethyl forms of unchanged vonoprazan were mainly produced. Unchanged vonoprazan was also metabolized in the CYP2B6-expressed microsome, producing M-I, M-III, and *N*-desmethyl forms of unchanged vonoprazan.

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[65] The following activities were used as the indicators: CYP1A2, phenacetin *O*-deethylation; 2A6, coumarin 7-hydroxylation; 2B6, bupropion hydroxylation; 2C8, paclitaxel 6α-hydroxylation; 2C9, diclofenac 4'-hydroxylation, 2C19, *S*-mephenytoin 4'-hydroxylation; 2D6, dextromethorphan *O*-demethylation; 2E1, chlorzoxazone 6-hydroxylation; 3A4/5, midazolam 1'-hydroxylation; 4A11, lauric acid 12-hydroxylation

Based on the above, the applicant explained that unchanged vonoprazan is metabolized mainly by CYP3A4 and partially by CYP2B6, 2C19, and 2D6.

(c) Sulfotransferase involved in sulfate conjugation (4.2.2.4-16, Study TAK-438-11263)
Following incubation of ^{14}C-vonoprazan (10 μmol/L) with human sulfotransferase (SULT)-expressed cytosol (SULT1A1, 1A3, 1B1, 1E1, 2A1) in the presence of PAPS, *N*-sulfate conjugate of unchanged vonoprazan was produced in the SULT2A1-expressed cytosol.

(d) CYP isoforms involved in metabolism from *N*-sulfate conjugate of unchanged vonoprazan into M-IV-Sul (4.2.2.4-17, Study TAK-438-11251)
Following incubation of ^{14}C-*N*-sulfate conjugate of unchanged vonoprazan (10 μmol/L) with human CYP isoform-expressed microsome (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4), *N*-sulfate conjugate of unchanged vonoprazan was metabolized mainly in the CYP2C9- and 3A4-expressed microsomes. In the CYP2C9- and CYP3A4-expressed microsomes, M-IV-Sul and an unidentified metabolite, respectively, were produced. Based on the above, the applicant explained that *N*-sulfate conjugate of unchanged vonoprazan is metabolized into M-IV-Sul by CYP2C9.

(e) CYP inhibition (4.2.2.4-18, 4.2.2.4-19; Studies TAK-438-11256, TAK-438-11315)
Vonoprazan (1-30 μmol/L) was incubated with human liver microsome and the direct inhibitory effect of vonoprazan against the activity of each CYP isoforms (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4/5)[66] was investigated. As a result, vonoprazan inhibited CYP2B6 and 3A4/5 (midazolam 1'-hydroxylation) activities. The residual activities at a vonoprazan concentration of 30 μmol/L were 37.9% and 49.9%, respectively, and the IC_{50} values were 16 and 29 μmol/L, respectively. For the other CYP isoforms, the IC_{50} value was >30 μmol/L.

Vonoprazan (1-30 μmol/L) was preincubated with human liver microsome for 30 minutes and the time-dependent inhibitory effect of vonoprazan against activities of the above CYP isoforms was investigated. As a result, vonoprazan inhibited CYP2B6, 2C19, and 3A4/5 (midazolam 1'-hydroxylation, testosterone 6β-hydroxylation). The residual activities at a vonoprazan concentration of 30 μmol/L were 16.8%, 34.0%, 32.6%, and 32.4%, respectively, and the IC_{50} values were 2.6, 13, 10, and 9.8 μmol/L, respectively. Compared with the direct inhibitory effect, all of the IC_{50} values decreased. The applicant therefore explained that vonoprazan inhibited CYP2B6, 2C19, and 3A4/5 in a time dependent manner.

Following incubation of vonoprazan (2-50 μmol/L) with human liver microsome, k_{inact} of the time dependent inhibitory effect of vonoprazan against CYP2B6 (bupropion hydroxylation) and 3A4/5 (midazolam 1'-hydroxylation) was 0.0115 and 0.0161 min^{-1}, respectively, and K_I was 3.50 and 1.22 μmol/L, respectively.

(f) CYP induction (4.2.2.4-20 to 4.2.2.4-22; Studies TAK-438-10443, TAK-438-11235, TAK-438/00216)
Vonoprazan (1-30 μmol/L) was incubated with human hepatocytes for 1 to 4 days[67] and the induction effect of vonoprazan based on the activity of each CYP isoforms (CYP1A2, 2B6, 3A4/5)[68] was investigated. As a result, the induction rate[69] of CYP1A2 increased in a concentration dependent manner, but even at a vonoprazan concentration of 30 μmol/L, the induction rate was as small as 7.3% to 9.3%. The applicant explained that the induction rate of CYP2B6 and 3A4/5 remained almost unchanged.

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66 The following activities were used as the indicators: CYP1A2, phenacetin *O*-deethylation; 2B6, bupropion hydroxylation; 2C8, paclitaxel 6α-hydroxylation; 2C9, diclofenac 4'-hydroxylation; 2C19, *S*-mephenytoin 4'-hydroxylation; 2D6, bufuralol 1'-hydroxylation; 3A4/5, midazolam 1'-hydroxylation, and testosterone 6β-hydroxylation

67 CYP1A2, 1 to 2 days; 2B6, 2 to 3 days; 3A4/5, 3 to 4 days

68 The following activities were used as the indicators: CYP1A2, phenacetin *O*-deethylation; 2B6, bupropion hydroxylation; 3A4/5, testosterone 6β-hydroxylation

69 Activity (%) relative to the activity (100%) of the sample spiked with the positive control for the CYP isoform (CYP1A2, omeprazole at 50 μmol/L; 2B6, phenobarbital at 1 mmol/L; 3A4/5, rifampicin at 10 μmol/L)

4.(ii).A.(1).5) Pharmacokinetic drug-interactions

(a) Interaction through plasma protein binding (4.2.2.6-1 to 4.2.2.6-7; Studies TAK-438-11302, TAK-438-11301, TAK-438-11317, TAK-438-11285, TAK-438-11284, TAK-438-11283, TAK-438-11286)

The following drugs, potentially used concomitantly with vonoprazan in routine clinical practice, were investigated *in vitro* for their effects on human plasma protein binding of ^{14}C-vonoprazan (100 ng/mL): warfarin, ibuprofen, diazepam, phenytoin, propranolol hydrochloride, diclofenac sodium, loxoprofen sodium, meloxicam, celecoxib, and SR26334 hydrochloride (metabolite of clopidogrel).[70]. As a result, the concentration of unbound ^{14}C- vonoprazan in the presence of concomitant drugs was 92.5% to 111.1% of that in their absence. The applicant therefore explained that these drugs hardly affect the human plasma protein binding of vonoprazan.

The effects of vonoprazan (100 ng/mL) on human plasma protein binding of the above drugs and digoxin[71] were also investigated *in vitro*. As a result, the concentration of the unbound form of each of these concomitant drugs in the presence of vonoprazan was 92.6% to 104.5% of that in its presence. The applicant therefore explained that vonoprazan hardly affects the human plasma protein binding of these drugs.

(b) OATP1B1 and 1B3 (4.2.2.6-8, Study TAK-438-11344)

Following incubation of ^{14}C-vonoprazan (0.3 μmol/L) with human organic anion transport polypeptide (OATP) 1B1 and 1B3-expressed cells, the radioactivity uptake in the expressed cells was comparable to that in non-OATP1B1- and non-1B3-expressed cells. The applicant explained the result has suggested that vonoprazan is not a substrate of OATP1B1 or 1B3.

(c) Inhibition against P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2 (4.2.2.6-9 to 4.2.2.6-11; Studies TAK-438-10807, TAK-438-11346, TAK-438-11345)

Caco-2 cells cultured on a transwell plate were incubated with vonoprazan (1-100 μmol/L) and ^{3}H-digoxin (3 μmol/L), a P-gp substrate, and the inhibitory effect of vonoprazan against P-gp was investigated. Human BCRP-expressed cells cultured on a transwell plate were also incubated with vonoprazan (1-100 μmol/L) and ^{3}H-prazosin (0.01 μmol/L), a BCRP substrate, and the inhibitory effect of vonoprazan against BCRP was investigated. Furthermore, vonoprazan (0.3-30 μmol/L) was incubated with ^{3}H-estradiol-17β-D-glucuronide (0.05 μmol/L), a substrate of OATP1B1 and 1B3; ^{3}H-*p*-aminohippurate (1 μmol/L), a substrate of organic anion transporter (OAT) 1; ^{3}H-estrone-3-sulfate (0.05 μmol/L), a substrate of OAT3; and ^{14}C-metformin hydrochloride (10 μmol/L), a substrate of organic cation transporter (OCT) 2; on human OATP1B1 and 1B3, OAT1, OAT3 as well as OCT2-expressed cells, respectively, and the inhibitory effect of vonoprazan against various transporters was investigated. As a result, vonoprazan inhibited P-gp. The residual activity at a vonoprazan concentration of 100 μmol/L was 39.7%, and the IC_{50} value was 50.3 μmol/L. For the other transporters, the IC_{50} value was ≥30 or >100 μmol/L.

4.(ii).A.(2) Japanese phase I single dose study (5.3.3.1-1, Study TAK-438/CPH-001 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted at a single center in Japan to investigate the safety and PK following a single oral dose of vonoprazan in healthy adult male subjects aged 20 to 45 years (target sample size: 84 subjects in total; 9 subjects in the vonoprazan group and 3 subjects in the placebo group for each dose). Although the food effect on PK of vonoprazan was also investigated in this study, the relevant study data are omitted, because Formulation A, prepared only for clinical studies, was used instead of the proposed formulation.

Placebo or vonoprazan at 1 mg, 5 mg, 10 mg, 20 mg, 40 mg, 80 mg, or 120 mg was to be administered orally in a single dose without breakfast.

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[70] Warfarin, 1 μg/mL; ibuprofen, 20 μg/mL; diazepam, 0.3 μg/mL; phenytoin, 2 μg/mL; propranolol hydrochloride, 0.1 μg/mL (as propranolol); diclofenac sodium, 1 μg/mL (as diclofenac); loxoprofen sodium, 5.5 μg/mL (as loxoprofen); meloxicam, 1 μg/m; celecoxib, 1.5 μg/mL; SR26334 hydrochloride, 2.5 μg/mL

[71] ^{3}H-warfarin, 1 μg/mL; ^{3}H-ibuprofen, 20 μg/mL; ^{3}H-diazepam, 0.3 μg/mL; ^{14}C-phenytoin, 2 μg/mL; ^{3}H-propranolol hydrochloride, 0.1 μg/mL (as propranolol); ^{14}C-diclofenac sodium, 1 μg/mL (as diclofenac); loxoprofen sodium, 5.5 μg/mL (as loxoprofen); meloxicam, 1 μg/mL; celecoxib, 1.5 μg/mL; SR26334 hydrochloride, 2.5 μg/mL; ^{3}H-digoxin, 0.01 μg/mL

All of the 84 treated subjects (63 subjects in the vonoprazan group, 21 subjects in the placebo group) were included in the safety and PK [72] analysis sets, and 82 subjects were included in the pharmacodynamic (PD) analysis set.[73]

Regarding safety, no adverse events were reported.

Regarding PK, plasma PK parameters and urinary excretion rate of unchanged vonoprazan and its metabolites are as shown in Table 17 and Table 18.

The relationships between the dose of vonoprazan and the C_{max} and $AUC_{0\text{-}inf}$ of unchanged vonoprazan were investigated using an exponential regression model ($y = A \cdot Dose^B$). As a result, the point estimate [95% CI] of the regression coefficient (B) was 1.29 [1.22, 1.35] for C_{max} and 1.29 [1.23, 1.34] for $AUC_{0\text{-}inf}$ C_{max} and $AUC_{0\text{-}inf}$ increased slightly more than dose-proportionally with an increasing dose. The relationships between CYP2C19 genotype[74] and the dose-adjusted C_{max} and $AUC_{0\text{-}inf}$ of unchanged vonoprazan were also investigated, but no clear relationship between the genotype and the C_{max} or $AUC_{0\text{-}inf}$ was observed.

The urinary excretion rate of unchanged vonoprazan increased almost with the increasing dose.

Table 17. Plasma PK parameters of unchanged vonoprazan and its metabolites following a single oral dose of vonoprazan

Dose		1 mg	5 mg	10 mg	20 mg	40 mg	80 mg	120 mg
n		5	9	8	7	9	7	8
Unchanged vonoprazan	C_{max} (ng/mL)	0.7 ± 0.3	4.2 ± 1.4	9.7 ± 2.1	25.0 ± 5.6	71.9 ± 23.3	129.8 ± 40.6	303.8 ± 64.3
	$AUC_{0\text{-}24h}$ (ng·h/mL)	3.7 ± 1.6	28.5 ± 9.4	56.5 ± 8.4	148.9 ± 35.1	433.3 ± 125.8	797.3 ± 213.3	1828 ± 344.5
	$AUC_{0\text{-}inf}$ (ng·h/mL)	4.3 ± 1.6	31.6 ± 10.4	60.8 ± 8.9	161.6 ± 39.3	474.6 ± 141.0	911.3 ± 243.1	1985 ± 403.2
	t_{max} [a)] (h)	1.50 [1.50, 2.00]	1.50 [1.00, 3.00]	1.75 [1.00, 2.00]	1.50 [0.75, 2.00]	1.50 [1.00, 3.00]	1.50 [1.00, 3.00]	1.00 [0.75, 2.00]
	$t_{1/2}$ (h)	5.11 ± 1.08	7.62 ± 1.14	6.95 ± 1.03	6.85 ± 0.80	7.09 ± 0.55	8.66 ± 1.01	6.58 ± 0.75
M-I	C_{max} (ng/mL)	3.7 ± 1.1	14.8 ± 2.0	36.2 ± 6.0	70.8 ± 12.6	101.1 ± 20.6	175.4 ± 56.2	314.1 ± 49.7
	$AUC_{0\text{-}24h}$ (ng·h/mL)	11.6 ± 3.4	91.8 ± 15.4	219.3 ± 23.7	415.6 ± 77.7	612.1 ± 98.8	1107 ± 245.6	1953 ± 379.6
	$AUC_{0\text{-}inf}$ (ng·h/mL)	15.6 ± 4.1	102.9 ± 20.3	244.1 ± 20.3	481.4 ± 95.0	730.3 ± 120.7	1374 ± 308.3	2394 ± 463.6
	t_{max} [a)] (h)	0.75 [0.50, 1.50]	1.50 [0.75, 3.00]	1.50 [0.75, 3.00]	1.00 [0.75, 1.50]	1.00 [0.75, 2.00]	1.00 [0.75, 3.00]	1.00 [0.75, 1.50]
	$t_{1/2}$ (h)	2.51 ± 0.59	7.05 ± 3.72	8.22 ± 1.83	10.58 ± 3.03	11.46 ± 1.81	11.12 ± 1.00	11.63 ± 2.62
M-II	C_{max} (ng/mL)	0.0 ± 0.0	0.6 ± 0.8	2.4 ± 0.4	4.8 ± 1.3	6.3 ± 1.9	11.2 ± 3.1	17.5 ± 4.5
	$AUC_{0\text{-}24h}$ (ng·h/mL)	0.0 ± 0.0	3.8 ± 5.3	22.1 ± 8.8	65.8 ± 23.1	94.5 ± 39.5	187.0 ± 44.3	288.4 ± 86.0
	$AUC_{0\text{-}inf}$ (ng·h/mL)	nc	nc	37.3 ± 12.9	85.4 ± 36.9	130.8 ± 56.1	276.0 ± 56.7	408.3 ± 125.9
	t_{max} [a)] (h)	nc	3.00 [3.00, 4.00] [b)]	4.00 [3.00, 6.00]	4.00 [4.00, 10.00]	4.00 [4.00, 8.00]	4.00 [4.00, 10.00]	4.00 [2.00, 10.00]
	$t_{1/2}$ (h)	nc	nc	9.02 ± 4.25	9.19 ± 3.47	10.90 ± 4.08	11.48 ± 1.51	9.99 ± 2.72

Mean ± SD; nc, Not calculated
a) Median [minimum, maximum], b) n = 4

[72] Specimens from 70 subjects, excluding those from 14 subjects with hemolysis, were used for evaluation of the plasma concentrations, and all the 84 specimens for evaluation of urine concentrations.

[73] Two subjects were excluded due to inappropriate 24-hour gastric pH monitoring.

[74] **1/*1*, **1/*2*, **1/*3*, **2/*2*, **2/*3*, and **3/*3*

Table 18. Urinary excretion rate of unchanged vonoprazan and its metabolites following a single oral dose of vonoprazan

Dose		1 mg	5 mg	10 mg	20 mg	40 mg	80 mg	120 mg
n		9	9	9	9	9	9	9
Fe_{0-48h}[a] (%)	Unchanged vonoprazan	1.9 ± 0.8	3.5 ± 10.0	2.4 ± 0.7	4.1 ± 1.4	7.1 ± 2.5	7.6 ± 1.5	8.4 ± 1.8
	M-I	1.7 ± 1.1	2.4 ± 0.7	2.4 ± 0.5	2.3 ± 0.6	1.5 ± 0.3	1.6 ± 0.4	1.7 ± 0.5
	M-II	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

Mean ± SD
a) Urinary excretion rate up to 48 hours post-dose (percentage of the dose)

Regarding PD, the 24-hour intragastric pH Holding Time Ratio (HTR)[75] was as shown in Table 19. The 24-hour pH 3 HTR, pH 4 HTR, and pH 5 HTR increased with the increasing dose and at the doses of vonoprazan ≥40 mg reached >90% and then a plateau. The relationships between the C_{max} and AUC_{0-24h} of unchanged vonoprazan and the 24-hour pH4 HTR on Day 1 were also investigated. As a result, the Spearman's rank correlation coefficient for C_{max} and AUC_{0-24h} was 0.9339 and 0.9324, respectively, indicating favorable correlations.

Table 19. 24-hour intragastric pH HTR following a single oral dose of vonoprazan

Dose		Placebo	1 mg	5 mg	10 mg	20 mg	40 mg	80 mg	120 mg
n		21	9	9	9	9	8	8	9
24-hour pH 3 HTR (%)	Baseline	17.0 ± 8.8	15.9 ± 7.1	9.1 ± 7.1	18.0 ± 9.8	15.9 ± 8.4	14.0 ± 5.2	10.2 ± 6.9	20.2 ± 13.7
	Day 1	14.3 ± 8.6	17.3 ± 7.3	28.1 ± 12.6	45.2 ± 13.6	85.9 ± 9.9	92.9 ± 3.5	94.9 ± 1.4	95.1 ± 1.6
24-hour pH 4 HTR (%)	Baseline	10.1 ± 6.5	7.5 ± 3.2	5.8 ± 5.4	12.7 ± 7.2	9.7 ± 6.5	8.7 ± 4.3	6.1 ± 4.5	13.1 ± 12.3
	Day 1	7.9 ± 5.9	8.8 ± 5.2	16.9 ± 7.9	31.1 ± 12.8	81.6 ± 11.1	92.1 ± 2.8	94.4 ± 1.4	94.6 ± 1.8
24-hour pH 5 HTR (%)	Baseline	5.9 ± 4.2	4.0 ± 2.1	3.3 ± 3.1	7.8 ± 4.9	5.1 ± 4.4	5.6 ± 3.3	3.4 ± 2.6	6.7 ± 5.5
	Day 1	4.2 ± 3.5	4.7 ± 3.5	9.6 ± 4.8	17.6 ± 8.4	74.1 ± 14.1	90.6 ± 2.9	93.7 ± 1.9	93.0 ± 2.8

Mean ± SD

4.(ii).A.(3) Japanese phase I multiple-dose study (5.3.3.1-3, Study TAK-438/CPH-002 [20 to 20])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted at a single center in Japan to investigate the safety and PK following multiple oral doses of vonoprazan in healthy adult male subjects aged 20 to 45 years (target sample size: 60 subjects in total; 9 subjects in the vonoprazan group and 3 subjects in the placebo group for each dose).

Placebo or vonoprazan at 10 mg, 15 mg, 20 mg, 30 mg, or 40 mg was to be orally administered once daily in the fasted state in the morning for 7 days.

All of the 60 treated subjects (45 subjects in the vonoprazan group, 15 subjects in the placebo group) were included in the safety, PK, and PD analysis sets.

Adverse events occurred in 13.3% (2 of 15 subjects) of the placebo group; 0.0% (0 of 9 subjects) of the vonoprazan 10 mg group; 33.3% (3 of 9 subjects) of the 15 mg group; 11.1% (1 of 9 subjects) of the 20 mg group; 22.2% (2 of 9 subjects) of the 30 mg group; and 11.1% (1 of 9 subjects) of the 40 mg group. Adverse events of which a causal relationship to the study drug could not be denied (adverse drug reactions) occurred in 6.7% (1 of 15 subjects) of the placebo group and 11.1% (1 of 9 subjects) of the vonoprazan 30 mg group. There were no adverse events or adverse drug reactions reported by ≥2 subjects. There were no deaths, serious adverse events, or adverse events leading to study drug discontinuation.

Plasma PK parameters and urinary excretion rate of unchanged vonoprazan and its metabolites were as shown in Table 20 and Table 21. The trough plasma concentration of unchanged vonoprazan remained constant from Day 3 to Day 7. The applicant therefore explained that the PK of unchanged vonoprazan reached the steady state by Day 3.

75 For example, pH 4 HTR indicates the ratio of time during which the gastric pH was maintained at ≥pH4.

The relationships between the dose of vonoprazan and the C_{max} and AUC of unchanged vonoprazan were investigated using an exponential regression model ($y = A \cdot Dose^B$). As a result, the point estimate [95% CI] of the regression coefficient (B) was 1.26 [1.05, 1.47] for C_{max} and 1.28 [1.07, 1.49] for $AUC_{0\text{-}inf}$ on Day 1 as well as 1.31 [1.12, 1.51] for C_{max} and 1.26 [1.08, 1.45] for $AUC_{0\text{-}tau}$ on Day 7. C_{max} and AUC on Day 1 and Day 7 increased slightly more than dose-proportionally. The cumulative factor[76] (mean) for C_{max} and $AUC_{0\text{-}tau}$ of unchanged vonoprazan fell within a range from 1.142 to 1.318 for each dose level. The plasma concentration of unchanged vonoprazan increased with the increasing number of doses. The accumulation index[77] (mean) was investigated based on AUC and $t_{1/2}$ of unchanged vonoprazan. The index ranged from 0.935 to 1.193, close to 1, for each dose level. The PK of unchanged vonoprazan during the multiple-dose regimen was time-independent. The relationships between CYP2C19 genotype[78] and the dose-adjusted C_{max} (Day 1, Day 7), $AUC_{0\text{-}inf}$ (Day 1), and $AUC_{0\text{-}tau}$ (Day 7) of unchanged vonoprazan were also investigated, but no clear relationship between the genotype and the C_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}tau}$ was observed.

The urinary excretion rate of unchanged vonoprazan increased with the increasing dose on both Day 1 and Day 7.

[76] C_{max}, C_{max} on Day 7/C_{max} on Day 1; $AUC_{0\text{-}tau}$, $AUC_{0\text{-}tau}$ on Day 7/$AUC_{0\text{-}tau}$ on Day 1

[77] AUC, $AUC_{0\text{-}tau}$ on Day 7/$AUC_{0\text{-}inf}$ on Day 1; $t_{1/2}$, $t_{1/2}$ on Day 7/ $t_{1/2}$ on Day 1

[78] **1/*1*, **1/*2*, **1/*3*, and **2/*2*

Table 20. Plasma PK parameters of unchanged vonoprazan and its metabolites following multiple oral doses of vonoprazan

Dose			10 mg	15 mg	20 mg	30 mg	40 mg
n			9	9	9	9	9
Unchanged vonoprazan	C_{max} (ng/mL)	Day 1	10.1 ± 2.0	16.0 ± 4.8	19.5 ± 6.1	38.8 ± 16.7	62.0 ± 24.9
		Day 7	12.0 ± 1.8	18.1 ± 5.8	23.3 ± 6.6	48.6 ± 17.4	75.2 ± 25.3
	$AUC_{0\text{-}tau}$ (ng·h/mL)	Day 1	61.6 ± 13.6	97.5 ± 33.5	121.6 ± 32.8	231.3 ± 72.6	391.6 ± 176.1
		Day 7	79.5 ± 16.1	112.4 ± 35.6	151.6 ± 40.3	291.2 ± 101.2	458.5 ± 151.7
	$AUC_{0\text{-}inf}$ (ng·h/mL)	Day 1	67.4 ± 14.7	103.3 ± 36.3	129.3 ± 34.9	247.4 ± 79.1	429.8 ± 205.3
		Day 7	-	-	-	-	-
	t_{max} [a)] (h)	Day 1	1.50 [0.75, 3.00]	2.00 [1.00, 3.00]	1.50 [1.50, 3.00]	1.50 [1.00, 3.00]	1.50 [0.75, 2.00]
		Day 7	1.50 [0.75, 3.00]	1.50 [0.75, 2.00]	1.50 [0.75, 3.00]	1.50 [1.00, 2.00]	1.50 [0.75, 3.00]
	$t_{1/2}$ (h)	Day 1	7.00 ± 1.89	5.76 ± 0.71	5.79 ± 0.98	5.71 ± 0.74	6.73 ± 1.84
		Day 7	6.97 ± 1.56	6.03 ± 0.90	6.14 ± 1.19	5.85 ± 0.65	6.15 ± 1.13
M-I	C_{max} (ng/mL)	Day 1	34.8 ± 7.4	50.6 ± 11.4	74.8 ± 19.5	94.2 ± 13.2	126.0 ± 41.8
		Day 7	39.7 ± 10.0	54.7 ± 12.7	73.9 ± 16.3	88.2 ± 15.5	132.1 ± 30.6
	$AUC_{0\text{-}tau}$ (ng·h/mL)	Day 1	202.6 ± 37.3	320.1 ± 59.0	448.7 ± 110.0	542.1 ± 91.0	742.4 ± 190.3
		Day 7	241.6 ± 59.7	334.4 ± 54.8	478.5 ± 93.9	641.7 ± 95.0	837.5 ± 194.9
	$AUC_{0\text{-}inf}$ (ng·h/mL)	Day 1	256.8 ± 94.6	368.2 ± 69.8	520.8 ± 144.4	637.2 ± 157.2	923.2 ± 185.2
		Day 7	-	-	-	-	-
	t_{max} [a)] (h)	Day 1	1.00 [0.50, 2.00]	1.50 [0.75, 2.00]	1.00 [0.75, 2.00]	1.00 [0.75, 3.00]	1.00 [0.75, 2.00]
		Day 7	1.50 [0.50, 3.00]	1.00 [0.75, 3.00]	1.50 [0.75, 1.50]	1.50 [0.75, 2.00]	1.50 [0.75, 3.00]
	$t_{1/2}$ (h)	Day 1	12.40 ± 8.49	8.57 ± 2.07	9.57 ± 1.78	9.12 ± 3.62	12.11 ± 5.17
		Day 7	10.86 ± 2.70	10.23 ± 3.74	9.48 ± 2.17	10.00 ± 2.30	12.55 ± 2.34
M-II	C_{max} (ng/mL)	Day 1	2.7 ± 0.8	3.8 ± 0.9	5.9 ± 1.5	7.2 ± 2.5	8.0 ± 1.8
		Day 7	3.6 ± 1.5	4.9 ± 1.3	6.7 ± 1.0	10.4 ± 3.7	10.8 ± 2.6
	$AUC_{0\text{-}tau}$ (ng·h/mL)	Day 1	21.1 ± 11.0	41.6 ± 14.1	69.0 ± 17.1	98.7 ± 44.0	108.1 ± 34.5
		Day 7	40.2 ± 24.2	60.2 ± 20.6	88.4 ± 17.3	144.2 ± 64.8	157.3 ± 40.0
	$AUC_{0\text{-}inf}$ (ng·h/mL)	Day 1	34.7 ± 10.4	60.9 ± 14.9	83.4 ± 20.8	132.3 ± 51.9	161.0 ± 81.4
		Day 7	-	-	-	-	-
	t_{max} [a)] (h)	Day 1	3.00 [2.00, 10.00]	4.00 [3.00, 6.00]	4.00 [3.00, 4.00]	4.00 [3.00, 10.00]	4.00 [2.00, 10.00]
		Day 7	4.00 [3.00, 12.00]	4.00 [2.00, 10.00]	4.00 [4.00, 6.00]	4.00 [3.00, 8.00]	4.00 [4.00, 4.00]
	$t_{1/2}$ (h)	Day 1	9.22 ± 5.33	10.80 ± 4.34	8.24 ± 2.24	11.85 ± 2.39	12.61 ± 4.84
		Day 7	10.89 ± 5.95	7.88 ± 2.07	8.65 ± 2.59	10.43 ± 2.19	12.83 ± 3.79
M-III	C_{max} (ng/mL)	Day 1	14.4 ± 4.7	19.9 ± 3.3	24.7 ± 3.3	40.8 ± 5.5	48.9 ± 9.9
		Day 7	15.8 ± 4.0	20.4 ± 3.4	28.5 ± 3.3	44.7 ± 8.7	56.6 ± 10.0
	$AUC_{0\text{-}tau}$ (ng·h/mL)	Day 1	70.6 ± 23.4	100.8 ± 15.2	130.1 ± 28.1	244.7 ± 53.8	316.6 ± 143.9
		Day 7	85.8 ± 25.9	111.0 ± 19.9	161.9 ± 31.0	284.0 ± 59.7	390.2 ± 129.2
	$AUC_{0\text{-}inf}$ (ng·h/mL)	Day 1	73.0 ± 24.6	103.7 ± 16.5	133.6 ± 30.0	253.3 ± 57.1	335.9 ± 165.5
		Day 7	-	-	-	-	-
	t_{max} [a)] (h)	Day 1	1.50 [0.75, 3.00]	2.00 [1.50, 3.00]	1.50 [1.00, 3.00]	2.00 [1.50, 4.00]	2.00 [1.50, 2.00]
		Day 7	2.00 [0.75, 3.00]	2.00 [0.75, 3.00]	2.00 [1.50, 3.00]	2.00 [1.50, 3.00]	1.50 [1.50, 3.00]
	$t_{1/2}$ (h)	Day 1	5.62 ± 1.30	5.16 ± 0.54	5.23 ± 0.72	5.17 ± 0.73	5.66 ± 1.42
		Day 7	4.90 ± 0.93	5.24 ± 0.79	5.05 ± 0.38	4.97 ± 0.79	5.05 ± 0.87
M-IV-Sul	C_{max} (ng/mL)	Day 1	24.2 ± 6.0	40.1 ± 10.1	47.8 ± 8.5	79.8 ± 13.2	103.5 ± 28.5
		Day 7	23.3 ± 6.2	36.9 ± 9.8	46.1 ± 4.8	66.4 ± 14.9	87.7 ± 25.1
	$AUC_{0\text{-}tau}$ (ng·h/mL)	Day 1	92.7 ± 27.5	150.2 ± 42.1	184.4 ± 32.1	329.7 ± 61.4	453.1 ± 167.1
		Day 7	96.8 ± 31.6	152.5 ± 54.5	192.1 ± 31.9	305.8 ± 63.6	434.1 ± 154.4
	$AUC_{0\text{-}inf}$ (ng·h/mL)	Day 1	95.8 ± 27.5	154.0 ± 42.4	187.4 ± 29.7	339.7 ± 64.5	472.0 ± 184.3
		Day 7	-	-	-	-	-
	t_{max} [a)] (h)	Day 1	1.50 [1.00, 3.00]	2.00 [1.50, 2.00]	1.50 [1.50, 2.00]	1.50 [1.50, 3.00]	1.50 [1.50, 3.00]
		Day 7	1.50 [1.00, 3.00]	1.50 [1.00, 3.00]	2.00 [1.50, 2.00]	2.00 [1.50, 3.00]	2.00 [1.50, 3.00]
	$t_{1/2}$ (h)	Day 1	3.07 ± 1.11	3.75 ± 1.55	3.77 ± 1.23	5.57 ± 1.22	5.38 ± 1.69
		Day 7	4.10 ± 1.84	4.68 ± 1.88	4.89 ± 1.08	6.63 ± 2.04	6.77 ± 1.45

Mean ± SD; -, Not applicable
a) Median [minimum, maximum]

Table 21. Urinary excretion rate of unchanged vonoprazan and its metabolites following multiple oral doses of vonoprazan

Dose			10 mg	15 mg	20 mg	30 mg	40 mg
n			9	9	9	9	9
$Fe_{0\text{-}24h}$[a] (%)	Unchanged vonoprazan	Day 1	3.9 ± 1.1	3.8 ± 1.1	3.5 ± 1.0	4.9 ± 1.1	5.8 ± 2.6
		Day 7	4.5 ± 1.0	4.3 ± 1.2	4.0 ± 0.9	5.2 ± 1.2	6.3 ± 2.3
	M-I	Day 1	1.6 ± 0.6	1.5 ± 0.7	2.1 ± 0.6	1.6 ± 0.4	1.3 ± 0.5
		Day 7	2.7 ± 0.9	2.9 ± 0.9	2.8 ± 0.4	2.6 ± 0.5	2.6 ± 0.7
	M-II	Day 1	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
		Day 7	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	M-III	Day 1	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
		Day 7	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	M-IV-Sul	Day 1	1.9 ± 0.4	1.7 ± 0.6	2.2 ± 0.5	2.0 ± 0.6	2.2 ± 0.6
		Day 7	1.8 ± 0.4	1.6 ± 0.7	1.9 ± 0.5	1.8 ± 0.5	2.1 ± 0.6

Mean ± SD
a) Urinary excretion rate up to 24 hours post-dose (percentage of the dose)

Regarding PD, the 24-hour intragastric pH HTR was as shown in Table 22. The 24-hour pH 3 HTR, pH 4 HTR, and pH 5 HTR increased with the increasing dose on both Day 1 and Day 7. The relationships between the C_{max} and $AUC_{0\text{-}tau}$ of unchanged vonoprazan and the 24-hour pH 4 HTR on Day 1 and Day 7 were also investigated. As a result, the Spearman's rank correlation coefficient for C_{max} and $AUC_{0\text{-}tau}$ was 0.8709 and 0.8996, respectively, on Day 1 and 0.8970 and 0.9225, respectively, on Day 7, indicating favorable correlations.

Table 22. 24-hour intragastric pH HTR following multiple oral doses of vonoprazan

Dose		Placebo	10 mg	15 mg	20 mg	30 mg	40 mg
n		15	9	9	9	9	9
24-hour pH 3 HTR (%)	Baseline	13.9 ± 9.0	12.4 ± 9.6	16.4 ± 7.3	13.9 ± 9.4	20.3 ± 12.0	17.2 ± 9.6
	Day 1	12.9 ± 6.4	50.1 ± 24.1	65.6 ± 12.7	69.9 ± 16.6	85.6 ± 12.3	89.3 ± 4.8
	Day 7	10.7 ± 6.0	73.0 ± 7.9	76.0 ± 13.8	87.2 ± 13.0	96.3 ± 8.8	100.0 ± 0.0
24-hour pH 4 HTR (%)	Baseline	7.9 ± 5.7	7.5 ± 6.4	9.2 ± 5.2	8.1 ± 6.3	12.0 ± 8.5	10.0 ± 7.0
	Day 1	8.3 ± 4.0	38.4 ± 22.3	55.4 ± 13.2	63.3 ± 17.9	80.8 ± 14.0	85.3 ± 8.3
	Day 7	5.6 ± 3.5	63.3 ± 8.7	68.5 ± 16.1	83.4 ± 16.7	95.2 ± 10.1	100.0 ± 0.0
24-hour pH 5 HTR (%)	Baseline	2.5 ± 2.2	4.3 ± 4.6	4.4 ± 2.7	3.9 ± 3.7	5.4 ± 6.1	3.2 ± 2.7
	Day 1	3.7 ± 2.5	25.1 ± 19.0	40.3 ± 16.8	53.5 ± 21.5	73.1 ± 16.1	78.3 ± 10.6
	Day 7	1.4 ± 1.5	52.6 ± 10.7	60.2 ± 16.8	73.2 ± 18.9	92.0 ± 12.5	98.6 ± 2.0

Mean ± SD

4.(ii).A.(4) Foreign phase I study (mass balance study) (5.3.3.1-5 [Reference], Study TAK-438_103 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted at a single center overseas to investigate the mass balance following a single oral dose of ^{14}C-vonoprazan in healthy adult male subjects aged 30 to 55 years (target sample size: 6 subjects).

^{14}C-vonoprazan at 15 mg was to be administered orally in a single dose under fasted conditions.

All of the 6 treated subjects were included in the safety, PK, and radioactivity analysis sets.

The incidence of adverse events was 50.0% (3 of 6 subjects), and that of adverse drug reactions was 16.7% (1 of 6 subjects). There were no adverse events or adverse drug reactions reported by ≥2 subjects. There were no deaths, serious adverse events, or adverse events leading to study discontinuation.

Regarding mass balance, 67.4% and 31.1% of the administered radioactivity were excreted in urine and feces, respectively, by 168 hours post-dose, indicating that the primary excretion route after oral dosing is via the urine.

Regarding plasma metabolic profile, the percentage of unchanged vonoprazan, M-I, M-II, M-III, M-IV-Sul, and M-I-G of the plasma radioactivity up to 24 hours post-dose was 13.9%, 8.2%, 6.8%, 4.3%, 16.9%, and 19.2%, respectively.

Regarding metabolic profiles in urine and feces, the percentage of unchanged vonoprazan, M-I, M-II, M-III, M-IV-Sul, and M-I-G of the urine radioactivity up to 168 hours post-dose was 12.0%, 2.8%, 0.1%, 1.1%, 11.4%, and 20.6%, respectively, and that of the fecal radioactivity from 0 to 168 hours post-dose was 4.4%, 1.0%, 0.2%, 2.4%, 15.9%, and not detected, respectively. The components other than the above (unidentified components) accounted for 52.0% and 76.1%, respectively, of the urinary and fecal radioactivity.

4.(ii).A.(5) Foreign phase I study (QT/QTc evaluation study) (5.3.3.1-6, Study TAK-438_111 [20 to 20])

A randomized, double-blind,[79] placebo- and active-drug-controlled, four-treatment, four-period crossover study was conducted at a single center overseas to evaluate the effect of a single oral dose of vonoprazan on the QT/QTc interval in healthy adult subjects aged 18 to 55 years (target sample size: 64 subjects in total; 8 subjects/group).

Placebo, vonoprazan 40 mg or 120 mg, or moxifloxacin 400 mg, the positive control, was to be administered orally in a single dose under fasted conditions followed by ≥4 days washout period prior to the next dosing period.

All of the 64 subjects treated were included in the safety, PK, and PD analysis sets.

Adverse events occurred in 6.3% (4 of 63 subjects) of the placebo group; 17.5% (11 of 63 subjects) of the vonoprazan 40 mg group; 18.8% (12 of 64 subjects) of the 120 mg group; and 18.8% (12 of 64 subjects) of the moxifloxacin group. Adverse drug reactions occurred in 3.2% (2 of 63 subjects) of the placebo group; 14.3% (9 of 63 subjects) of the vonoprazan 40 mg group; 15.6% (10 of 64 subjects) of the 120 mg group; and 17.2% (11 of 64 subjects) of the moxifloxacin group. Adverse events or adverse drug reactions reported by ≥2 subjects in any group were as shown in Table 23 and Table 24. No deaths or serious adverse events were reported. Adverse events leading to study drug discontinuation occurred in 1.6% (1 of 64 subjects) of the 120 mg group.

Table 23. Adverse events reported by ≥2 subjects in any group

	Placebo group (N = 63)		40 mg group (N = 63)		120 mg group (N = 64)		Moxifloxacin group (N = 64)	
	Incidence	N	Incidence	N	Incidence	N	Incidence	N
Overall	6.3%	4	17.5%	11	18.8%	12	18.8%	12
Nausea	0.0%	0	1.6%	1	7.8%	5	3.1%	2
Abdominal pain	1.6%	1	1.6%	1	1.6%	1	3.1%	2
Diarrhoea	3.2%	2	1.6%	1	1.6%	1	0.0%	0
Headache	1.6%	1	9.5%	6	7.8%	5	4.7%	3
Hot flush	0.0%	0	0.0%	0	1.6%	1	3.1%	2

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Table 24. Adverse drug reactions reported by ≥2 subjects in any group

	Placebo group (N = 63)		40 mg group (N = 63)		120 mg group (N = 64)		Moxifloxacin group (N = 64)	
	Incidence	N	Incidence	N	Incidence	N	Incidence	N
Overall	3.2%	2	14.3%	9	15.6%	10	17.2%	11
Nausea	0.0%	0	1.6%	1	7.8%	5	3.1%	2
Abdominal pain	1.6%	1	1.6%	1	1.6%	1	3.1%	2
Diarrhoea	3.2%	2	1.6%	1	1.6%	1	0.0%	0
Headache	0.0%	0	7.9%	5	7.8%	5	4.7%	3
Hot flush	0.0%	0	0.0%	0	1.6%	1	3.1%	2

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[79] The active control drug (moxifloxacin) was unblinded.

In terms of the difference in the time-matched mean change in QTcF interval from baseline compared with placebo (ddQTcF), the upper limit of one-sided 95% confidence interval (two-sided 90%) of the ddQTcF was up to 4.9 msec in both vonoprazan 40 mg group and 120 mg group, which was below 10 msec. Vonoprazan was thus assessed as negative. The lower limit of one-sided 95% confidence interval (two-sided 90%) of the ddQTcF was 9.9 msec in the moxifloxacin group, which was above 5 msec. The analytical sensitivity was thus qualified.

Plasma PK parameters of unchanged vonoprazan and its metabolites are as shown in Table 25.

Table 25. Plasma PK parameters of unchanged vonoprazan and its metabolites following a single oral dose of vonoprazan

Dose		40 mg	120 mg
n		63	64
Unchanged vonoprazan	C_{max} (ng/mL)	47.1 ± 15.8	225.7 ± 76.5
	$AUC_{0\text{-}inf}$ (ng·h/mL)	498.3 ± 187.4	2466 ± 745.2
M-I	C_{max} (ng/mL)	94.6 ± 28.5	241.0 ± 73.7
	$AUC_{0\text{-}inf}$ (ng·h/mL)	935.8 ± 213.9[a)]	2652 ± 632.4
M-II	C_{max} (ng/mL)	7.3 ± 3.0	18.9 ± 8.1
	$AUC_{0\text{-}inf}$ (ng·h/mL)	147.7 ± 58.3[b)]	532.6 ± 196.8[c)]
M-III	C_{max} (ng/mL)	39.7 ± 9.1	113.8 ± 27.3
	$AUC_{0\text{-}inf}$ (ng·h/mL)	306.6 ± 108.8	1241 ± 323.0
M-IV-Sul	C_{max} (ng/mL)	82.5 ± 23.3	261.2 ± 65.1
	$AUC_{0\text{-}inf}$ (ng·h/mL)	454.9 ± 180.3[a)]	1840 ± 645.8

Mean ± SD
a) n = 62, b) n = 26, c) n = 52

4.(ii).A.(6) Foreign phase I study (gender and food effect) (5.3.3.3-1 [Reference], Study TAK-438_109 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A gender-stratified, randomized, open-label, two-treatment, two-period crossover study was conducted at a single center overseas to evaluate the effects of gender and food on the PK following a single oral dose of vonoprazan in healthy adult subjects aged 18 to 45 years (target sample size: 24 subjects in total; 12 male subjects and 12 female subjects). The study data on the effect of food on the PK of vonoprazan are omitted, because the formulation proposed in Japan was not used.

Vonoprazan 20 mg was to be administered orally in a single dose under fasted conditions or after meals followed by 5-day washout period prior to the next dosing period.

All of the 24 treated subjects were included in the safety and PK analysis sets.

Regarding safety, adverse events occurred in 16.7% (2 of 12 subjects) each in male and female subjects and no adverse drug reactions occurred in either males or females. There were no adverse events reported by ≥2 subjects. There were no deaths, serious adverse events, or adverse events leading to study discontinuation. Abortion spontaneous (during the first trimester) was reported by 1 female subject after the end of the study (approximately 1 month after the vonoprazan administration), but a causal relationship to the study drug was ruled out.

The adjusted geometric mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of unchanged vonoprazan and its metabolites in female subjects to those in male subjects (females/males ratio) were as shown in Table 26. C_{max} and $AUC_{0\text{-}inf}$ of unchanged vonoprazan in female subjects were lower than those in male subjects, but its reason remains unknown. The applicant explained that no clear gender differences were observed in the efficacy and safety of vonoprazan in the phase III studies (Studies CCT-002, CCT-003, CCT-101, CCT-102, CCT-401, CCT-301, CCT-302).

Table 26. Effects of gender on PK of unchanged vonoprazan and its metabolites

		Adjusted geometric mean ratio (females/males ratio) [95% CI][a)]
Unchanged vonoprazan	C_{max}	0.78 [0.52, 1.17]
	$AUC_{0\text{-}inf}$	0.84 [0.54, 1.31]
M-I	C_{max}	- [b)]
	$AUC_{0\text{-}inf}$	1.11 [0.88, 1.40]
M-II	C_{max}	- [b)]
	$AUC_{0\text{-}inf}$	Not estimated
M-III	C_{max}	0.58 [0.41, 0.83]
	$AUC_{0\text{-}inf}$	0.54 [0.31, 0.94]
M-IV-Sul	C_{max}	0.98 [0.66, 1.47]
	$AUC_{0\text{-}inf}$	1.11 [0.65, 1.89]

n = 12 each of male and female subjects

a) Pooled data including results from fasted administration and fed administration

b) The pooled data including results from fasted administration and fed administration are not shown, because a statistically significant interaction (significance level of 10%) was observed between genders and between having and not having food.

4.(ii).A.(7) Foreign phase I study (effect of hepatic impairment) (5.3.3.3-2, Study TAK-438_112 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label parallel-group study was conducted at 2 centers overseas to investigate the effect of hepatic impairment on the PK following a single oral dose of vonoprazan in subjects with normal hepatic function as well as subjects with mild (Child-Pugh score A), moderate (Child-Pugh score B), and severe (Child-Pugh score C) hepatic impairment, aged 18 to 75 years (target sample size: 32 subjects in total; 8 subjects/group[80,81]).

Vonoprazan 20 mg was to be administered orally in a single dose under fasted conditions.

All of the 34 treated subjects were included in the safety and PK analysis sets.

Adverse events occurred in 33.3% (4 of 12 subjects) of the normal hepatic function group; 12.5% (1 of 8 subjects) of the mild hepatic impairment group; 25.0% (2 of 8 subjects) of the moderate hepatic impairment group; and 33.3% (2 of 6 subjects) of the severe hepatic impairment group. Adverse drug reactions occurred in 8.3% (1 of 12 subjects) of the normal hepatic function group; 12.5% (1 of 8 subjects) of the mild hepatic impairment group; 12.5% (1 of 8 subjects) of the moderate hepatic impairment group; and 16.7% (1 of 6 subjects) of the severe hepatic impairment group. There were no adverse events or adverse drug reactions reported by ≥2 subjects. Ankle fracture was reported by 1 subject as a serious adverse event of the moderate hepatic impairment group, but a causal relationship to the study drug was ruled out. There were neither deaths nor adverse events leading to study discontinuation.

The adjusted geometric mean ratios of C_{max} and $AUC_{0\text{-}inf}$ (for M-II, $AUC_{0\text{-}tlqc}$[82]) of unchanged vonoprazan and its metabolites in the subjects with hepatic impairment to those in the subjects with normal hepatic function (subjects with hepatic impairment/subjects with normal hepatic function ratio) were as shown in Table 27. The subject exposure to unchanged vonoprazan increased with the decreasing hepatic function. The percent plasma protein unbound form (mean) of unchanged vonoprazan was 21.4% in the normal hepatic function group, 18.6% in the mild hepatic impairment group, 23.5% in the moderate hepatic impairment group, and 23.3% in the severe hepatic impairment group, all of which were almost the same.

80 Based on the prior review of PK draft data, 6 subjects in the severe hepatic impairment group were considered allowable.

81 The profile of the subjects with normal hepatic function matched that of the subjects with hepatic impairment in terms of the age (± 10 years), gender, race, body weight (± 20%), and smoking status (smoker/non-smoker).

82 $AUC_{0\text{-}tlqc}$, AUC from time 0 to time of the last quantifiable concentration.

Table 27. Effect of hepatic impairment on PK of unchanged vonoprazan and its metabolites

		Adjusted geometric mean ratios (subjects with hepatic impairment/subjects with normal hepatic function) [90% CI]		
		Mild hepartic impairment group	Moderate hepatic impairment group	Severe hepatic impairment group
Unchanged vonoprazan	C_{max}	1.24 [0.91, 1.68]	1.75 [1.29, 2.37]	1.76 [1.26, 2.46]
	$AUC_{0\text{-}inf}$	1.20 [0.87, 1.67]	2.38 [1.72, 3.31]	2.61 [1.82, 3.73]
M-I	C_{max}	0.92 [0.73, 1.16]	0.72 [0.58, 0.91]	0.58 [0.45, 0.75]
	$AUC_{0\text{-}inf}$	0.78 [0.62, 0.98]	0.94 [0.74, 1.18]	0.63 [0.46, 0.88]
M-II	C_{max}	0.91 [0.65, 1.27]	0.73 [0.52, 1.02]	0.47 [0.32, 0.67]
	$AUC_{0\text{-}tlqc}$	0.79 [0.40, 1.59]	1.10 [0.55, 2.21]	0.25 [0.12, 0.54]
M-III	C_{max}	0.99 [0.79, 1.24]	0.60 [0.48, 0.75]	0.53 [0.41, 0.68]
	$AUC_{0\text{-}inf}$	1.20 [0.93, 1.54]	1.22 [0.94, 1.58]	1.20 [0.92, 1.58]
M-IV-Sul	C_{max}	1.65 [1.14, 2.38]	0.99 [0.69, 1.44]	0.89 [0.60, 1.34]
	$AUC_{0\text{-}inf}$	1.85 [1.19, 2.88]	2.01 [1.29, 3.14]	2.24 [1.38, 3.64]

Normal hepatic function group, n = 12; mild hepatic impairment group, n = 8; moderate hepatic impairment group, n = 8; severe hepatic impairment group, n = 6

4.(ii).A.(8) Foreign phase I study (effect of renal impairment) (5.3.3.3-3, Study TAK-438_113 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label parallel-group study was conducted at a single center overseas to investigate the effect of renal impairment on the PK following a single oral dose of vonoprazan in subjects with normal renal function (eGFR, ≥90 mL/min/1.73 m^2) and subjects with mild (60-89 mL/min/1.73 m^2), moderate (30-59 mL/min/1.73 m^2), and severe (15-29 mL/min/1.73 m^2) renal impairment and in patients with end stage renal failure (<15 mL/min/1.73 m^2), aged 18 to 75 years (target sample size: 32 subjects; 8 subjects/group[83]).

In the normal renal function group, mild renal impairment group, moderate renal impairment group, and severe renal impairment group, a single dose of vonoprazan at 20 mg was to be orally administered under fasted conditions. In the end stage renal failure group, vonoprazan at 20 mg was to be orally administered under fasted conditions on Day 1 and Day 6.[84] In the end stage renal failure group, hemodialysis was not performed until 24 hours post-dose on Day 1 and was performed at 2 hours post-dose on Day 6.

All of the 45 subjects treated were included in the safety and PK analysis sets.

Regarding safety, adverse events occurred in 15.4% (2 of 13 subjects) of the normal renal function group; 50.0% (4 of 8 subjects) of the mild renal impairment group; 25.0% (2 of 8 subjects) of the moderate renal impairment group; 12.5% (1 of 8 subjects) of the severe renal group; and 50.0% (4 of 8 subjects) of the end stage renal failure group. Adverse drug reactions occurred in 15.4% (2 of 13 subjects) of the normal renal function group; 50.0% (4 of 8 subjects) of the mild renal impairment group; 12.5% (1 of 8 subjects) of the moderate renal group; 0.0% (0 of 8 subjects) of the severe renal impairment group; and 37.5% (3 of 8 subjects) of the end stage renal failure group. Adverse events reported by ≥2 subjects in any group were fatigue (0.0% [0 of 13 subjects] in the normal renal function group; 12.5% [1 of 8 subjects] in the mild renal impairment group; 25.0% [2 of 8 subjects] in the moderate renal impairment group; 0.0% [0 of 8 subjects] in the severe renal impairment group; 0.0% [0 of 8 subjects] in the end stage renal failure group) and headache (0.0% [0 of 13 subjects], 0.0% [0 of 8 subjects], 0.0% [0 of 8 subjects], 0.0% [0 of 8 subjects], 25.0% [2 of 8 subjects], respectively). There were no adverse drug reactions reported by ≥2 subjects. There were no deaths, serious adverse events, or adverse events leading to study discontinuation.

The adjusted geometric mean ratios of C_{max} and $AUC_{0\text{-}inf}$ (for M-II, $AUC_{0\text{-}tlqc}$82) of unchanged vonoprazan and its metabolites in the subjects with renal impairment to those in the subjects with normal renal function (subjects with renal impairment/subjects with normal renal function ratio) were as shown

[83] The profile of the subjects with normal renal function matched that of the subjects with renal impairment in terms of the age (± 10 years), gender, race, body weight (± 20%), and smoking status (smoker/non-smoker).

[84] The treatment scheduled to be on Day 6 was allowed to be given on Day 7 or 8 instead, according to the dialysis schedule of the subject.

in Table 28. The exposure of unchanged vonoprazan increased with the decreasing renal function. The percent plasma protein unbound form (mean) of unchanged vonoprazan was 20.9% in the normal renal function group, 21.1% in the mild renal impairment group, 20.9% in the moderate renal impairment group, 22.7% in the severe renal impairment group, and 19.6% in the end stage renal failure group, all of which were almost at the same level.

The renal clearance (mean) of unchanged vonoprazan decreased with the decreasing renal function: compared with 6.4 L/h in the normal renal function group, it was 1.8 L/h in the severe renal impairment group and 0.5 L/h in the end stage renal failure group. The dialysate excretion rate of unchanged vonoprazan (percentage of the dose) was 0.94%.

Table 28. Effect of renal impairment on PK of unchanged vonoprazan and its metabolites

		Adjusted geometric mean ratios (subjects with renal impairment/subjects with normal renal function) [90% CI]			
		Mild renal impairment group	Moderate renal impairment group	Severe renal impairment group	End stage renal failure group[a)]
Unchanged vonoprazan	C_{max}	1.33 [0.96, 1.84]	1.22 [0.88, 1.69]	1.80 [1.30, 2.50]	1.21 [0.87, 1.68]
	$AUC_{0\text{-inf}}$	1.67 [1.15, 2.45]	1.30 [0.89, 1.89]	2.39 [1.63, 3.49]	1.26 [0.86, 1.84]
M-I	C_{max}	1.06 [0.82, 1.37]	1.14 [0.88, 1.47]	0.80 [0.62, 1.03]	0.98 [0.76, 1.27]
	$AUC_{0\text{-inf}}$	1.20 [1.00, 1.46]	1.30 [1.07, 1.58]	1.57 [1.30, 1.90]	1.60 [1.32, 1.93]
M-II	C_{max}	1.05 [0.74, 1.49]	0.93 [0.65, 1.32]	0.60 [0.43, 0.86]	0.63 [0.44, 0.89]
	$AUC_{0\text{-tlqc}}$	1.55 [0.90, 2.67]	1.10 [0.64, 1.90]	0.87 [0.50, 1.49]	1.17 [0.67, 2.07]
M-III	C_{max}	1.24 [1.02, 1.50]	0.88 [0.72, 1.06]	0.73 [0.60, 0.88]	0.70 [0.58, 0.85]
	$AUC_{0\text{-inf}}$	1.58 [1.14, 2.19]	0.96 [0.69, 1.33]	1.24 [0.89, 1.71]	0.76 [0.55, 1.05]
M-IV-Sul	C_{max}	1.42 [1.05, 1.91]	1.29 [0.96, 1.74]	1.17 [0.87, 1.57]	1.13 [0.84, 1.52]
	$AUC_{0\text{-inf}}$	1.67 [1.08, 2.58]	1.53 [0.99, 2.37]	2.00 [1.30, 3.09]	1.43 [0.92, 2.21]

Normal renal function group, n = 13; mild renal impairment group, n = 8; moderate renal impairment group, n = 8; severe renal impairment group, n = 8; end stage renal failure group, n = 8
a) Calculated from the PK parameters on Day 1

4.(ii).A.(9) Japanese phase II study (study of drug interactions of vonoprazan with low-dose aspirin and non-steroidal anti-inflammatory drugs) (5.3.3.4-1, Study TAK-438/ CPH-003 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted at a single center in Japan to investigate drug interactions of vonoprazan with aspirin, loxoprofen, diclofenac, and meloxicam in healthy adult male subjects aged 20 to 45 years (target sample size: 64 subjects in total; 8 subjects/cohort).

The dosing regimens for the drugs in each cohort were as shown in Table 29. Drug A was to be orally administered in a single dose followed by a washout period, and then Drug B was to be orally administered for 6 days. On Day 5 of the Drug B treatment period, Drug A was to be concomitantly administered as a single dose.

Table 29. Dosing regimens of drugs

Cohort	Drug A	Drug B	Washout period
1	Vonoprazan 40 mg, once daily after breakfast	Aspirin 100 mg, once daily after breakfast	2 days
2	Vonoprazan 40 mg, once daily after breakfast	Loxoprofen 60 mg,[a)] three times daily after meals	2 days
3	Vonoprazan 40 mg, once daily after breakfast	Diclofenac 25 mg,[b)] three times daily after meals	2 days
4	Vonoprazan 40 mg, once daily after breakfast	Meloxicam 10 mg, once daily after breakfast	2 days
5	Aspirin 100 mg, once daily after breakfast	Vonoprazan 40 mg, once daily after breakfast	13 days
6	Loxoprofen 60 mg,[a)] once daily after breakfast	Vonoprazan 40 mg, once daily after breakfast	2 days
7	Diclofenac 25 mg, once daily after breakfast	Vonoprazan 40 mg, once daily after breakfast	2 days
8	Meloxicam 10 mg, once daily after breakfast	Vonoprazan 40 mg, once daily after breakfast	4 days

a) 60 mg as the anhydrous compound of loxoprofen sodium hydrate
b) 25 mg as diclofenac sodium

All of the 64 subjects treated were included in the safety analysis set, and 61 subjects were included in the PK analysis set.[85]

[85] Three subjects in whom PK examination or observation was found flawed were excluded.

Regarding safety, adverse events occurred in 0.0% (0 of 8 subjects) of Cohort 1, 12.5% (1 of 8 subjects) of Cohort 2, 0.0% (0 of 8 subjects) of Cohort 3, 0.0% (0 of 8 subjects) of Cohort 4, 12.5% (1 of 8 subjects) Cohort 5, 25.0% (2 of 8 subjects) of Cohort 6, 25.0% (2 of 8 subjects) of Cohort 7, and 0.0% (0 of 8 subjects) of Cohort 8. Adverse events reported by ≥2 subjects in any cohort were blood creatine phosphokinase increased (25.0% [2 of 8 subjects] of Cohort 6, 0.0% [0 of 8 subjects] of all the other cohorts). No adverse drug reactions were reported. No deaths or serious adverse events were reported. Adverse events leading to study drug discontinuation occurred only in 12.5% (1 of 8 subjects) of Cohort 5.

The adjusted geometric mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of unchanged vonoprazan and its metabolites following concomitant use of vonoprazan with aspirin, loxoprofen, diclofenac, or meloxicam to those following administration of vonoprazan alone (concomitant use/vonoprazan monotherapy ratio) were as shown in Table 30. The applicant explained that concomitant use with aspirin, loxoprofen, diclofenac, or meloxicam did not remarkably affect the PK of unchanged vonoprazan.

Table 30. Effects of concomitant use with aspirin, loxoprofen, diclofenac, or meloxicam on the PK of unchanged vonoprazan and its metabolites

		Adjusted geometric mean ratios (concomitant use/vonoprazan monotherapy ratio) [90% CI]			
		Concomitant use with aspirin	Concomitant use with loxoprofen	Concomitant use with diclofenac	Concomitant use with meloxicam
n		7	8	8	7
Unchanged vonoprazan	C_{max}	1.06 [0.90, 1.26]	0.83 [0.70, 1.00]	1.00 [0.95, 1.07]	0.97 [0.82, 1.16]
	$AUC_{0\text{-}inf}$	1.01 [0.94, 1.09]	0.98 [0.89, 1.07]	0.98 [0.93, 1.02]	0.99 [0.95, 1.03]
M-I	C_{max}	0.99 [0.86, 1.14]	0.90 [0.79, 1.03]	0.87 [0.76, 0.99]	1.00 [0.86, 1.16]
	$AUC_{0\text{-}inf}$	1.11 [1.04, 1.19]	1.03 [0.96, 1.11]	0.90 [0.84, 0.96]	1.17 [1.11, 1.23]
M-II	C_{max}	1.22 [1.05, 1.42]	1.05 [0.93, 1.18]	0.90 [0.80, 1.00]	1.09 [1.00, 1.18]
	$AUC_{0\text{-}inf}$	1.13 [0.97, 1.32]	1.12 [1.00, 1.26]	0.88 [0.68, 1.14]	1.12 [0.99, 1.26]
M-III	C_{max}	1.04 [0.96, 1.14]	0.96 [0.90, 1.02]	0.92 [0.88, 0.96]	0.95 [0.87, 1.04]
	$AUC_{0\text{-}inf}$	1.03 [0.99, 1.07]	0.99 [0.96, 1.03]	0.94 [0.89, 1.00]	0.98 [0.95, 1.01]
M-IV-Sul	C_{max}	0.96 [0.85, 1.08]	0.85 [0.77, 0.94]	0.86 [0.80, 0.92]	0.92 [0.83, 1.02]
	$AUC_{0\text{-}inf}$	0.97 [0.90, 1.04]	0.92 [0.87, 0.97]	0.91 [0.85, 0.98]	1.00 [0.95, 1.05]

The adjusted geometric mean ratios of C_{max} and $AUC_{0\text{-}inf}$ ($AUC_{0\text{-}tlqc}$ for unchanged aspirin) of aspirin, loxoprofen, diclofenac, meloxicam, and their metabolites following concomitant use of vonoprazan with any one of these drugs to those following administration of aspirin, loxoprofen, diclofenac, or meloxicam alone (concomitant use/single-agent use ratio) were as shown in Table 31. The adjusted geometric means of C_{max} and $AUC_{0\text{-}tlqc}$ of unchanged aspirin following concomitant use of aspirin with vonoprazan were higher than those following administration of aspirin alone, but the inter-individual variability was high. The effect of vonoprazan on the PK of unchanged aspirin therefore remained unclear. The applicant explained that no remarkable effects on the PK of salicylic acid (aspirin metabolite), unchanged loxoprofen, *trans*-OH loxoprofen, diclofenac, and meloxicam were observed following concomitant use of vonoprazan.

Table 31. Effects of concomitant use of vonoprazan on the PK of aspirin, loxoprofen, diclofenac, meloxicam, and their metabolites

			Adjusted geometric mean ratios (concomitant use/monotherapy ratio) [90% CI]
Aspirin (n = 8)	Unchanged aspirin	C_{max}	1.83 [0.80, 4.21]
		$AUC_{0\text{-}tlqc}$	1.39 [0.74, 2.61]
	Salicylic acid	C_{max}	1.07 [0.80, 1.43]
		$AUC_{0\text{-}inf}$	0.85 [0.78, 0.92][a)]
Loxoprofen (n = 8)	Unchanged loxoprofen	C_{max}	0.98 [0.89, 1.06]
		$AUC_{0\text{-}inf}$	1.07 [0.99, 1.15]
	trans-OH loxoprofen	C_{max}	1.00 [0.98, 1.03]
		$AUC_{0\text{-}inf}$	1.07 [0.99, 1.16]
Diclofenac (n = 7)	Unchanged diclofenac	C_{max}	1.27 [0.92, 1.76]
		$AUC_{0\text{-}inf}$	1.04 [0.92, 1.17]
Meloxicam (n = 8)	Unchanged meloxicam	C_{max}	1.05 [0.97, 1.12]
		$AUC_{0\text{-}inf}$	1.18 [1.11, 1.26]

a) n = 7

In Cohort 5, the effect of vonoprazan on aspirin's platelet aggregation inhibition was investigated. The collagen-induced platelet aggregation following concomitant use of aspirin with vonoprazan slightly increased compared with that following administration of aspirin alone, but the arachidonic acid-induced platelet aggregation was not affected by concomitant use of vonoprazan.

4.(ii).A.(10) Japanese phase III study (study of drug interactions of vonoprazan with antimicrobial drugs) (5.3.3.4-2, Study TAK-438/CPH-401 [[redacted]])

A randomized, open-label, four-treatment four-period crossover study was conducted at a single center in Japan to investigate drug interactions of vonoprazan with AMPC and CAM as well as with AMPC and MNZ in *Helicobacter-pylori* (*H. pylori)*-negative healthy adult male subjects aged 20 to 35 years (target sample size: 24 subjects; 3 subjects in Cohort 1, 3 subjects in Cohort 2).

In Cohort 1, subjects were allocated to different sequences of treatments in which they were to receive vonoprazan, AMPC, or CAM alone or vonoprazan in combination with AMPC and CAM in each period.Treatment periods were separated by a washout period of ≥7 days. Vonoprazan 20 mg, AMPC 750 mg, or CAM 400 mg was orally administered twice daily after meals in the morning and evening[86] for 7 days. In Cohort 2, subjects were allocated to different sequences of treatments in which they were to receive vonoprazan, AMPC, or MNZ alone or vonoprazan in combination with AMPC and MNZ in each period. Treatment periods were separated by a washout period of ≥14 days. Vonoprazan and AMPC were to be administered as done in Cohort 1, and MNZ 250 mg was to be orally administered twice daily86 after meals in the morning and evening for 7 days.

All of the 24 treated subjects were included in the safety analysis set, and 22 subjects were included in the PK analysis set.[87]

In Cohort 1, adverse events occurred in 0.0% (0 of 11 subjects) of the vonoprazan alone group; 0.0% (0 of 11 subjects) of the AMPC alone group; 0.0% (0 of 11 subjects) of the CAM alone group; and 8.3% (1 of 12 subjects) of the 3-drug combination group. In Cohort 2, such events occurred in 8.3% (1 of 12 subjects) of the vonoprazan alone group; 8.3% (1 of 12 subjects) of the AMPC alone group; 18.2% (2 of 11 subjects) of the MNZ alone group; and 8.3% (1 of 12 subjects) of the 3-drug combination group. In Cohort 1, adverse drug reactions occurred in 0.0% (0 of 11 subjects) of the vonoprazan alone group; 0.0% (0 of 11 subjects) of the AMPC alone group; 0.0% (0 of 11 subjects) of the CAM alone group; and 8.3% (1 of 12 subjects) of the 3-drug combination group. In Cohort 2, such reactions occurred in 8.3% (1 of 12 subjects) of the vonoprazan alone group; 0.0% (0 of 12 subjects) of the AMPC alone group; 18.2% (2 of 11 subjects) of the MNZ alone group; and 8.3% (1 of 12 subjects) of the 3-drug combination group. There were no adverse events or adverse drug reactions reported by ≥2 subjects. No deaths or serious adverse events were reported. Adverse events leading to study drug discontinuation occurred

86 On Day 7 of each period, the drug was administered once daily only after breakfast.

87 Two subjects in whom PK examination or evaluation was incomplete were excluded.

only in 8.3% (1 of 12 subjects) each in the 3-drug combination groups in both Cohort 1 and 2.

The adjusted geometric mean ratios of C_{max} and $AUC_{0\text{-}12h}$ of unchanged vonoprazan and the antimicrobial drugs following the 3-drug combination administration to those following single-agent administration of each drug (3-drug combination /single-agent ratio) in Cohort 1 and 2 were as shown in Table 32.

The applicant explained the study results as follows:
In Cohort 1, the exposure to unchanged vonoprazan and CAM was increased by 3-drug combination of vonoprazan, AMPC, and CAM. The increase in exposure to unchanged vonoprazan is considered attributable to CAM's inhibition against CYP3A4, a major metabolizing enzyme of unchanged vonoprazan. Regarding the increased exposure to CAM, it has been reported that the exposure to CAM increases when omeprazole is concomitantly administered,[88] as a possible consequence of increased bioavailability of CAM by increased gastric pH. Vonoprazan is therefore considered to have affected the PK of CAM by the same mechanism.

In Cohort 2, on the other hand, 3-drug combination of vonoprazan, AMPC, and MNZ did not remarkably affect the PK of each of these drugs.

Table 32. Effects of 3-drug concomitant use on PK of unchanged vonoprazan and the concomitant antimicrobial drugs

			Adjusted geometric mean ratios (3-drug combination therapy/monotherapy ratio) [90% CI]
Cohort 1	Unchanged vonoprazan	C_{max}	1.87 [1.69, 2.07]
		$AUC_{0\text{-}12h}$	1.85 [1.63, 2.09]
	AMPC	C_{max}	0.99 [0.91, 1.08]
		$AUC_{0\text{-}12h}$	0.97 [0.93, 1.01]
	CAM	C_{max}	1.63 [1.35, 1.97]
		$AUC_{0\text{-}12h}$	1.45 [1.28, 1.64]
Cohort 2	Unchanged vonoprazan	C_{max}	0.91 [0.78, 1.05]
		$AUC_{0\text{-}12h}$	0.97 [0.89, 1.05]
	AMPC	C_{max}	0.83 [0.70, 0.98]
		$AUC_{0\text{-}12h}$	1.01 [0.91, 1.12]
	MNZ	C_{max}	0.99 [0.95, 1.03]
		$AUC_{0\text{-}12h}$	1.00 [0.97, 1.02]

n = 11 in each cohort

4.(ii).A.(11) Foreign phase I study (study on drug interaction with CAM) (5.3.3.4-3 [Reference], Study TAK-438_110 [[redacted] to [redacted]])

An open-label study was conducted at a single center overseas to investigate drug interaction of vonoprazan with CAM in healthy adult male subjects aged 18 to 45 years (target sample size of 16).

Following a single oral dose of vonoprazan 40 mg on Day 1, CAM was to be orally administered twice daily at a dose of 500 mg for 7 days from Day 3 to Day 9, and vonoprazan was to be concomitantly administered at a dose of 40 mg on Day 8.

All of the 16 treated subjects were included in the safety and PK analysis sets.

Adverse events occurred in 12.5% (2 of 16 subjects) of the subjects during the vonoprazan alone period, 18.8% (3 of 16 subjects) of subjects during the CAM multiple-dose period, and 18.8% (3 of 16 subjects) of subjects during the coadministration period. Adverse drug reactions occurred in 6.3% (1 of 16 subjects) of the subjects during the vonoprazan alone period, 12.5% (2 of 16 subjects) of subjects during the CAM multiple-dose period, and 6.3% (1 of 16 subjects) of subjects during the coadministration period. Adverse events reported by ≥2 subjects during any period were hypertension (0.0% [0 of 16 subjects] during the vonoprazan alone period, 0.0% [0 of 16 subjects] during the CAM multiple-dose period, 12.5% [2 of 16 subjects] during the coadministration period). There were no deaths, serious

[88] *Antimicrob Agents Chemother*. 1995;39:2078-2083

adverse events, or adverse events leading to study drug discontinuation.

In terms of the PK of unchanged vonoprazan, the adjusted geometric mean ratios of C_{max} and $AUC_{0\text{-}inf}$ following concomitant use of vonoprazan with CAM to those following administration of vonoprazan alone (concomitant use/single-agent use ratio) [two-sided 90% CI] were 1.35 [1.20, 1.52] and 1.58 [1.47, 1.69], respectively. The exposure to unchanged vonoprazan was increased by concomitant use with CAM.

4.(ii).A.(12) Japanese phase II study (5.3.5.1-1, Study TAK-438/CCT-001 [[redacted] 20[redacted] to [redacted] 20[redacted]])
For the summary of the study, see "4.(iii).A.(1) Phase II dose finding study for treatment of reflux esophagitis."

Based on the plasma trough concentrations of unchanged vonoprazan (592 subjects, 1751 timepoints) in this study, population pharmacokinetic analysis using a nonlinear mixed-effects model was performed to investigate the effects of patient historical backgrounds (dose, gender, age, body weight, body mass index, CYP2C19 genotype, total protein, albumin, total bilirubin, direct bilirubin, urea nitrogen, creatinine, creatinine clearance,[89] uric acid, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], lactate dehydrogenase [LDH], γ-glutamyl transpeptidase [γ-GTP], creatinine kinase [CK]) on clearance of unchanged vonoprazan. As a result, dose, gender, age, and CYP2C19 genotype were identified as covariates that affected the clearance. The data were stratified according to the dose (vonoprazan: 5 mg, 10 mg, 20 mg, and 40 mg) and each factor of the above covariates. The following results on the medians of the clearance values (Bayes estimate in each subject) at each level were observed: (a) the medians in female subjects were approximately 5% to 24% higher than that in male subjects; (b) the medians in the subjects aged ≥65 years and <75 years and subjects aged ≥75 years were approximately 18% to 25% and 19% to 35% lower, respectively, than the median in subjects aged <65 years; and (c) the median in the subjects classified as Poor Metabolizers (PM) based on the CYP2C19 genotype was approximately 15% to 29% lower than the medium in subjects classified as Extensive Metabolizers (EM). However, the extent of the effect of each covariate was not considerable, and distributions of the individual values for the clearance in each of the strata overlapped. The applicant therefore explained that dose adjustment according to gender, age, and CYP2C19 genotype is unnecessary.

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Pharmacokinetic drug-interactions

4.(ii).B.(1).1) Effects on other drugs from the inhibitory action of vonoprazan against drug-metabolizing enzymes

Vonoprazan has been shown to have a direct or time-dependent inhibitory effect against CYP2B6, 2C19, and 3A4/5 and to inhibit P-gp [see "4.(ii).A.(1).4).(e) CYP inhibition" and "4.(ii).A.(1).5).(c) Inhibition against P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2"]. PMDA asked the applicant to explain their view on the possibility that vonoprazan interacts with the other drugs in rutine clinical use through the above inhibitory effect against CYP isoforms or P-gp.

The applicant responded as follows:
Regarding inhibition against CYP isoforms, the IC_{50} value of the direct inhibitory effect against CYP2B6 and 3A4/5 (midazolam 1'-hydroxylation) was 16 and 29 μmol/L, respectively. The IC_{50} value of the time-dependent inhibitory effect against CYP2B6, 2C19, and 3A4/5 (midazolam 1'-hydroxylation, testosterone 6β-hydroxylation) was 2.6, 13, 10, and 9.8 μmol/L, respectively. The highest plasma C_{max} of unchanged vonoprazan at the clinical dose was 203 nmol/L,[90] which was ≥12.8 times smaller than the IC_{50} value of each CYP isoform. Vonoprazan is a substrate of CYP3A4, and in a clinical study, the exposure of unchanged vonoprazan increased when vonoprazan was administered concomitantly with CAM, a CYP3A4 inhibitor [see "4.(ii).A.(11) Foreign phase I study"]. Furthermore, the *in vitro* study data showed that vonoprazan is metabolized by not only CYP3A4 but also CYP2B6, 2C19, and 2D6. After multiple dose of vonoprazan alone, however, the exposure of unchanged vonoprazan hardly

89 Calculated using Cockcroft-Gault formula

90 C_{max} of unchanged vonoprazan on Day 7 in a Japanese phase III study (Study CPH-401) where vonoprazan 20 mg, AMPC 750 mg, and CAM 400 mg were orally administered twice daily for 7 days (on Day 7, once daily only after breakfast)

increased [see "4.(ii).A.(3) Japanese phase I multiple-dose study"], and the effect of autoinhibition (metabolic inhibition of unchanged vonoprazan through inhibition against CYP2B6, 2C19, and 3A4/5) was found to be small. Based on the above, drug interaction attributable to the inhibitory effect of vonoprazan against CYP2B6, 2C19, and CYP3A4/5 is considered unlikely to occur in clinical use.

The IC_{50} value of the inhibition against P-gp was 50.3 μmol/L. The highest plasma C_{max} of unchanged vonoprazan at the clinical dose was 203 nmol/L,90 which was 250 times smaller than the IC_{50} value. Also, the draft guidance of the US Food and Drug Administration (FDA)[91] and guideline of the European Medicines Agency (EMA)[92] require conduct of clinical studies to investigate the drug interaction through P-gp if the gastrointestinal concentration ≥10 times the IC_{50} value. The expected highest concentration of unchanged vonoprazan in the gastrointestinal tract in clinical use was 232 μmol/L,[93] which was 4.6 times the IC_{50} value, i.e. < 10 times. Based on the above, drug interaction attributable to the inhibitory effect of vonoprazan against P-gp is considered unlikely to occur in clinical use.

PMDA largely accepted the applicant's response. The time-dependent inhibitory effect of vonoprazan against CYP2B6, 2C19, and 3A4/5 was not properly assessed based on the data from Study CPH-002, because it was not designed to investigate the drug interactions; and the effect of metabolizing enzyme inhibition did not appear clearly due to complicated metabolism of vonoprazan involving multiple enzymes such as CYP2B6, 2C19, and CYP3A4 as well as CYP2D6. PMDA therefore considers that it is necessary to collect information further on including published literature on the effect of the time-dependent inhibitory effect of vonoprazan against CYP2B6, 2C19, and 3A4/5 on other drugs, and appropriately provide the information to healthcare providers in clinical settings when new findings become available.

4.(ii).B.(1).2) Effects on vonoprazan from the inhibitory action of other drugs against drug-metabolizing enzymes

In a Japanese phase III study (Study CPH-401), C_{max} and $AUC_{0\text{-}12h}$ of unchanged vonoprazan following 3-drug combination therapy including CAM, a CYP3A4 inhibitor, were 1.87 and 1.85 times higher, respectively, than those following monotherapy. In a foreign phase I study (Study 110), C_{max} and $AUC_{0\text{-}inf}$ of unchanged vonoprazan following concomitant use with CAM were 1.35 and 1.58 times higher, respectively, than those following monotherapy. PMDA asked the applicant to explain the necessity of providing cautions against concomitant use with CYP3A4 inhibitors.

The applicant responded as follows:
The recommended clinical dose of vonoprazan used for treatment other than an adjunct to *H. pylori* eradication is up to 20 mg daily. In a Japanese phase II dose-finding study (Study CCT-001) in patients with reflux esophagitis (RE), the incidence of adverse events in the group of vonoprazan 40 mg, twice the recommended dose, was comparable to that in the group of lansoprazole (LPZ) 30 mg. In addition, during the primary eradication period in a Japanese phase III study in patients with *H. pylori* positive gastric ulcer scar or duodenal ulcer scar (Study CCT-401), the incidence of adverse events in the vonoprazan group, in which vonoprazan 20 mg, AMPC 750 mg, and CAM 200 mg or 400 mg were administered twice daily, was comparable to that in the LPZ group. Based on the above, concomitant use of vonoprazan with a CYP3A4 inhibitor may increase the exposure to unchanged vonoprazan, but the clinical use does not raise safety concerns. The applicant therefore considers it unnecessary to identify CYP3A4 inhibitors as concomitant drugs requiring cautions for use.

Study CCT-401 did not show clinically significant safety concerns and PMDA considers that there is no particular problem with concomitant use of vonoprazan, CAM, and AMPC in adjunct to *H. pylori* eradication at present. Although there are CYP3A4 inhibitors having a more potent inhibitory effect than CAM (voriconazole, itraconazole, etc.), the extent of the increase in exposure to unchanged

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91 Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry. Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. Draft guidance. 2012.

92 European Medicines Agency, Committee for Human Medicinal Products. Guideline on the Investigation of Drug Interactions. Publication No. CPMP/EWP/560/95/Rev.1. 2012.

93 Calculated from the clinical maximum dose/250 mL. Clinical maximum dose of vonoprazan (dose per administration) is 20 mg (57.9 μmoL)

vonoprazan and the safety in the concomitant use with such drugs remain unclear at present. In the medical practice, multiple drugs with a CYP3A4 inhibitory effect may be concomitantly used. Therefore, CYP3A4 inhibitors should be identified as concomitant drugs requiring cautions for use in the package insert. PMDA also considers that it is necessary to collect information on the effect of concomitant drugs on vonoprazan further on including post-marketing surveillance and published literature, and appropriately provide the information to healthcare providers in clinical settings when new beneficial findings become available.

4.(ii).B.(2) Use of vonoprazan in patients with hepatic impairment and renal impairment

The applicant explained about the use of vonoprazan in patients with hepatic impairment and renal impairment as follows:

The exposure to unchanged vonoprazan following a single dose of vonoprazan at 20 mg was higher in subjects with mild to severe hepatic impairment than in subjects with normal hepatic function in a foreign phase I study (Study 112). Although the number of subjects with hepatic impairment for each severity was limited, there was no problem with the tolerability of vonoprazan in all of the subjects with mild to severe hepatic impairment. Data from phase III studies (Studies CCT-002, CCT-003, CCT-101, CCT-102, CCT-401, CCT-301, and CCT-302) were stratified according to the ALT baseline value (≤45 IU/L, normal; >45 IU/L, abnormal) and the AST baseline value (≤40 IU/L, normal; >40 IU/L, abnormal) to investigate the safety by severity of hepatic impairment. Although the number of subjects with abnormal ALT or AST was limited in these clinical studies due to the criteria to exclude abnormal liver function test values, the incidence of adverse events did not tend to increase with decreasing hepatic function.

For the effect of renal impairment, the exposure to unchanged vonoprazan following a single dose of vonoprazan at 20 mg was higher in subjects with mild to severe renal impairment and patients with end stage renal failure than in subjects with normal renal function in a foreign phase I study (Study 113). Although the number of subjects with renal impairment for each severity was limited, there was no problem with the tolerability of vonoprazan in all of the subjects with mild to severe hepatic impairment and patients with end stage renal failure. Data from phase III clinical studies (Studies CCT-002, CCT-003, CCT-101, CCT-102, CCT-401, CCT-301, and CCT-302) were stratified according to the eGFR baseline value (<30 mL/min/1.73 m^2, severe; 30-60 mL/min/1.73 m^2, moderate; 60-90 mL/min/1.73 m^2, mild; ≥90 mL/min/1.73 m^2, normal) to investigate the safety by severity of renal impairment. Although the number of subjects with severe and moderate renal impairment was limited in these clinical studies due to the criteria to exclude abnormal renal function test values, the incidence of adverse events did not tend to increase with decreasing renal function.

Based on the above, a clear effect on the safety of vonoprazan in patients with hepatic or renal impairment has not been observed. The applicant therefore considered it unnecessary to adjust the dose according to severity of hepatic or renal impairment. A caution recommending careful administration of vonoprazan to patients with hepatic or renal impairment will be provided in the package insert, because the exposure to unchanged vonoprazan increased in the subjects with hepatic or renal impairment; and as described above, the safety evaluation of vonoprazan in the subjects with hepatic or renal impairment has limitations.

No significant safety concerns have been observed in the subjects with hepatic or renal impairment at present, PMDA considers that there is no particular problem with the applicant's explanation. As explained by the applicant, the safety evaluation in patients with hepatic or renal impairment based on the currently available study data has limitations. PMDA therefore considers that it is necessary to continue to collect information on the safety of vonoprazan in patients with hepatic or renal impairment via post-marketing surveillance.

4.(ii).B.(3) Use of foreign clinical pharmacology data

The applicant explained use of foreign clinical pharmacology data in this application as follows:

Table 33 and Table 34 show PK parameters of unchanged vonoprazan following single administration (Study CPH-001) and multiple administrations (Study CPH-002), respectively, of vonoprazan to Japanese healthy adult male subjects as well as single administration (Study 101) and multiple administrations (Study 107), respectively, of vonoprazan to foreign healthy adult male subjects.

Compared to foreign subjects, Japanese subjects presented slightly shorter $t_{1/2}$ following single and multiple administrations, slightly higher C_{max} following single administration, and slightly lower $AUC_{0\text{-}tau}$ following multiple administrations. However, taking into account the distribution of individual values for each parameter, these differences were considered attributable to inter-individual variability. Based on the above, no clear differences were observed in PK of vonoprazan between Japanese and foreign subjects. The applicant therefore considers it appropriate to use clinical pharmacology data of vonoprazan obtained from foreign subjects (Studies 111, 112, and 113) in this application.

Table 33. Plasma PK parameters of unchanged vonoprazan in Japanese and foreign subjects following single oral administration of vonoprazan (Studies CPH-001 and 101)

Dose		1 mg	5 mg	10 mg	20 mg	40 mg
n	Japanese subjects	5	9	8	7	9
	Foreign subjects	6	6	6	6	6
C_{max} (ng/mL)	Japanese subjects	0.7 ± 0.3	4.2 ± 1.4	9.7 ± 2.1	25.0 ± 5.6	71.9 ± 23.3
	Foreign subjects	0.4 ± 0.1	3.9 ± 1.9	7.9 ± 3.89	23.0 ± 6.4	51.8 ± 17.0
$AUC_{0\text{-}24h}$ (ng·h/mL)	Japanese subjects	3.7 ± 1.6	28.5 ± 9.4	56.5 ± 8.4	148.9 ± 35.1	433.3 ± 125.8
	Foreign subjects	3.3 ± 1.5	29.0 ± 13.5	52.8 ± 19.2	152.9 ± 39.2	418.7 ± 157.9
$AUC_{0\text{-}inf}$ (ng·h/mL)	Japanese subjects	4.3 ± 1.6	31.6 ± 10.4	60.8 ± 8.9	161.6 ± 39.3	474.6 ± 141.0
	Foreign subjects	4.6 ± 2.1	33.4 ± 15.9	59.2 ± 21.8	169.9 ± 49.5	475.2 ± 190.7
t_{max}[a)] (h)	Japanese subjects	1.50 [1.50, 2.00]	1.50 [1.00, 3.00]	1.75 [1.00, 2.00]	1.50 [0.75, 2.00]	1.50 [1.00, 3.00]
	Foreign subjects	1.50 [1.50, 3.03]	2.00 [1.50, 2.00]	1.50 [0.75, 4.00]	1.50 [1.00, 3.00]	1.75 [0.75, 3.00]
$t_{1/2}$ (h)	Japanese subjects	5.1 ± 1.1	7.6 ± 1.1	6.9 ± 1.0	6.9 ± 0.8	7.1 ± 0.5
	Foreign subjects	7.8 ± 3.0	9.0 ± 5.9	8.1 ± 1.5	7.8 ± 1.1	8.4 ± 0.9

Mean ± SD
a) Median [minimum, maximum]

Table 34. Plasma PK parameters of unchanged vonoprazan in Japanese and foreign subjects following 7-day multiple oral administration of vonoprazan (Studies CPH-002 and 107)

Dose		10 mg	20 mg	30 mg	40 mg
n	Japanese subjects	9	9	9	9
	Foreign subjects	9	9	9	9
C_{max} (ng/mL)	Japanese subjects	12.0 ± 1.8	23.3 ± 6.6	48.6 ± 17.4	75.2 ± 25.3
	Foreign subjects	12.3 ± 4.0	26.2 ± 10.7	41.6 ± 11.0	59.9 ± 15.4
$AUC_{0\text{-}tau}$ (ng·h/mL)	Japanese subjects	79.5 ± 16.1	151.6 ± 40.3	291.2 ± 101.2	458.5 ± 151.7
	Foreign subjects	104.9 ± 41.5	195.7 ± 66.0	338.5 ± 83.8	488.4 ± 130.9
t_{max}[a)] (h)	Japanese subjects	1.50 [0.75, 3.00]	1.50 [0.75, 3.00]	1.50 [1.00, 2.00]	1.50 [0.750, 3.00]
	Foreign subjects	1.50 [1.00, 2.00]	1.07 [0.75, 2.00]	1.50 [1.10, 4.00]	1.50 [0.750, 4.00]
$t_{1/2}$ (h)	Japanese subjects	7.0 ± 1.6	6.1 ± 1.2	5.8 ± 0.6	6.1 ± 1.1
	Foreign subjects	8.8 ± 3.0	8.6 ± 1.9	8.8 ± 1.2	8.2 ± 0.8

Mean ± SD
a) Median [minimum, maximum]

PMDA considers that there is no particular problem with the use of foreign clinical pharmacology data in this application.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

As for the efficacy and safety evaluation data, the results from a total of 21 Japanese and foreign clinical studies were submitted. Of these, 13 Japanese clinical studies excluding 8 clinical pharmacology studies are as shown in Table 35. For a summary and the safety results of the clinical pharmacology studies, see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies."

Table 35. Summary of Japanese clinical studies for the efficacy and safety

Study Number	Study design	Study population	Group, No. of subjects	Treatment period	Major results
CCT-001	Phase II Dose-finding study Active drug controlled Double blind Parallel group	RE	LPZ 30 mg/day, n = 140 Vonoprazan 5 mg/day, n = 148 Vonoprazan 10 mg/day, n = 145 Vonoprazan 20 mg/day, n = 154 Vonoprazan 40 mg/day, n = 146	8 weeks	Cure rate (%) at Week 4 LPZ 30 mg group, 93.2 Vonoprazan 5 mg group, 92.3 Vonoprazan 10 mg group, 92.5 Vonoprazan 20 mg group, 94.4 Vonoprazan 40 mg group, 97.0
CCT-002	Phase III Comparative study Active drug controlled Double blind Parallel group	RE	LPZ 30 mg/day, n = 202 Vonoprazan 20 mg/day, n = 207	Up to 8 weeks	Cure rate (%) at Week 8 LPZ 30 mg group, 95.5 Vonoprazan 20 mg group, 99.0
CCT-003	Phase III Comparative study Active drug controlled Double blind Parallel group	RE	[Treatment period] Vonoprazan 20 mg/day, n = 627 [Maintenance period] LPZ 15 mg/day, n = 201 Vonoprazan 10 mg/day, n = 202 Vonoprazan 20 mg/day, n = 204	Treatment period Up to 8 weeks Maintenance period 24 weeks	Recurrence rate (%) in Week 24 of the maintenance period LPZ 15 mg group, 16.8 Vonoprazan 10 mg group, 5.1 Vonoprazan 20 mg group, 2.0
OCT-001	Phase III Comparative study Single blind Randomized Parallel group	RE	Vonoprazan 10 mg/day, n = 154 Vonoprazan 20 mg/day, n = 151	52 weeks	Safety evaluation
CCT-101	Phase III Comparative study Active drug controlled Double blind Parallel group	Gastric ulcer	LPZ 30 mg/day, n = 238 Vonoprazan 20 mg/day, n = 244	Up to 8 weeks	Cure rate (%) at Week 8 LPZ 30 mg group, 93.8 Vonoprazan 20 mg group, 93.5
CCT-102	Phase III Comparative study Active drug controlled Double blind Parallel group	Duodenal ulcer	LPZ 30 mg/day, n = 188 Vonoprazan 20 mg/day, n = 184	Up to 6 weeks	Cure rate (%) at Week 6 LPZ 30 mg group, 98.3 Vonoprazan 20 mg group, 95.5
CCT-401	Phase III Comparative study Active drug controlled Double blind Parallel group	*H. pylori* positive gastric ulcer scar or duodenal ulcer scar	[Primary eradication] AMPC 750 mg CAM 200 mg or 400 mg LPZ 30 mg/dose, twice daily, n = 321 AMPC 750 mg CAM 200 mg or 400 mg Vonoprazan 20 mg/dose, twice daily, n = 329 [Secondary eradication] AMPC 750 mg MNZ 250 mg Vonoprazan 20 mg/dose, twice daily, n = 50	Primary eradication 7 days Secondary eradication 7 days	*H. pylori* eradication rate (%) at 4 weeks after the end of the primary eradication treatment LPZ 30 mg group, 75.9 Vonoprazan 20 mg group, 92.6 *H. pylori* eradication rate (%) at 4 weeks after the end of the secondary eradication treatment Vonoprazan 20 mg group, 98.0
CCT-302	Phase III Comparative study Active drug controlled Double blind Parallel group	LDA ulcer	LPZ 15 mg/day, n = 217 Vonoprazan 10 mg/day, n = 202 Vonoprazan 20 mg/day, n = 202	24 weeks	Recurrence rate (%) of gastric or duodenal ulcer in Week 24 LPZ 15 mg group, 2.8 Vonoprazan 10 mg group, 0.5 Vonoprazan 20 mg group, 1.5
OCT-302	Phase III Long-term treatment Comparative study Active drug controlled Single blind Parallel group	LDA ulcer	LPZ 15 mg/day, n = 152 Vonoprazan 10 mg/day, n = 152 Vonoprazan 20 mg/day, n = 135	28 weeks to 80 weeks	Safety evaluation
OCT-304	Phase III Long-term treatment study Open-label uncontrolled	LDA ulcer	Vonoprazan 20 mg/day, n = 27	24 weeks	Safety evaluation

CCT-301	Phase III Comparative study Active drug controlled Double blind Parallel group	NSAID ulcer	LPZ 15 mg/day, n = 210 Vonoprazan 10 mg/day, n = 218 Vonoprazan 20 mg/day, n = 212	24 weeks	Recurrence rate (%) of gastric or duodenal ulcer in Week 24 LPZ 15 mg group, 5.5 Vonoprazan 10 mg group, 3.3 Vonoprazan 20 mg group, 3.4
OCT-301	Phase III Long-term treatment Comparative study Active drug controlled Single blind Parallel group	NSAID ulcer	LPZ 15 mg/day, n = 121 Vonoprazan 10 mg/day, n = 148 Vonoprazan 20 mg/day, n = 137	28 weeks to 80 weeks	Safety evaluation
OCT-303	Phase III Long-term treatment study Open-label uncontrolled	NSAID ulcer	Vonoprazan 20 mg/day, n = 30	24 weeks	Safety evaluation

RE, Reflux esophagitis; *H. pylori*, *Helicobacter pylori*; LDA, Low-dose aspirin; NSAID, Non-steroidal anti-inflammatory drug

4.(iii).A.(1) Phase II dose finding study of the treatment for RE (5.3.5.1-1, Study TAK-438/CCT-001 [[redacted] to [redacted]])

A multi-center, randomized, active-controlled, double-blind, parallel-group study was conducted at 66 centers in Japan to investigate the dose-response relationship of vonoprazan in terms of the efficacy and safety in RE patients aged ≥20 years[94] (target sample size: 725 subjects in total; 145 subjects/group).

Vonoprazan 5 mg, 10 mg, 20 mg, or 40 mg or LPZ 30 mg was to be orally administered once daily after breakfast for 8 weeks.

Of all the 732 subjects treated, 731 subjects (148 subjects in the vonoprazan 5 mg group, 145 subjects in the vonoprazan 10 mg group, 154 subjects in the vonoprazan 20 mg group, 145 subjects in the vonoprazan 40 mg group, 139 subjects in the LPZ group) were included in the full analysis set (FAS) and safety analysis set, excluding 1 subject (critical protocol deviation) in the vonoprazan 40 mg group. The FAS was used for the primary efficacy analysis.

The RE cure rate[95] at Week 4, the primary endpoint, was as shown in Table 36. For any vonoprazan groups, non-inferiority to the LPZ 30 mg group was verified ($P < 0.025$ for any comparison, non-inferiority Cochran-Mantel-Haenszel test, one-sided significance level of 2.5%, adjusted the multiplicity of the test in accordance with the closed testing procedure).

Table 36. RE cure rate at Week 4 (FAS)[a)]

Treatment group	No. of subjects with cured RE	Cure rate (%) [95% CI]	Difference from the LPZ 30 mg group (%) [95% CI]	*P* value[b)]
LPZ 30 mg group (N = 132)	123	93.2 [87.5, 96.8]	-	-
Vonoprazan 5 mg group (N = 143)	132	92.3 [86.7, 96.1]	-0.9 [-7.0, 5.3]	$P = 0.0026$
Vonoprazan 10 mg group (N = 133)	123	92.5 [86.6, 96.3]	-0.7 [-6.9, 5.5]	$P = 0.0038$
Vonoprazan 20 mg group (N = 144)	136	94.4 [89.3, 97.6]	1.3 [-4.4, 7.0]	$P = 0.0006$
Vonoprazan 40 mg group (N = 134)	130	97.0 [92.5, 99.2]	3.8 [-1.3, 9.0]	$P < 0.0001$

a) Of the FAS, patients who received a diagnosis of Grade 0 or unevaluable according to LA classification for the results of endoscopy at the baseline (7 subjects in the LPZ 30 mg group, 5 subjects in the vonoprazan 5 mg group, 12 subjects in the vonoprazan 10 mg group, 10 subjects in the vonoprazan 20 mg group, 11 subjects in the vonoprazan 40 mg group) were excluded from the analysis.

b) Non-inferiority Cochran-Mantel-Haenszel test, non-inferiority margin of 10%, one-sided significance level of 2.5%, and the multiplicity of the test was adjusted in accordance with the closed testing procedure.

94 Patients who received a diagnosis of Grade A to D under the Los Angeles (LA) classification according to the endoscopic finding at the baseline of the study treatment (central assessment committee). Subjects with definitive diagnosis of Grade C or D were included to account for ≥30% of all the subjects.

95 Subjects with definitive diagnosis of Grade O under the LA classification according to the endoscopic finding at Week 4 (central assessment committee) were defined as those in the "state of being cured."

Adverse events occurred in 39.9% (59 of 148 subjects) of the vonoprazan 5 mg group; 42.8% (62 of 145 subjects) of the vonoprazan 10 mg group; 47.4% (73 of 154 subjects) of the vonoprazan 20 mg group; 37.9% (55 of 145 subjects) of the vonoprazan 40 mg group; and 43.9% (61 of 139 subjects) of the LPZ 30 mg group. Adverse drug reactions occurred in 6.1% (9 of 148 subjects) of the vonoprazan 5 mg group; 9.0% (13 of 145 subjects) of the vonoprazan 10 mg group; 10.4% (16 of 154 subjects) of the vonoprazan 20 mg group; 4.8% (7 of 145 subjects) of the vonoprazan 40 mg group; and 5.8% (8 of 139 subjects) of the LPZ 30 mg group. Adverse events and adverse drug reactions reported by ≥2% of subjects in any group were as shown in Table 37 and Table 38.

Table 37. Adverse events reported by ≥2% of subjects in any group

	LPZ 30 mg group (N = 139)		Vonoprazan 5 mg group (N = 148)		Vonoprazan 10 mg group (N = 145)		Vonoprazan 20 mg group (N = 154)		Vonoprazan 40 mg group (N = 145)	
	Incidence	N	Incidence	N	Incidence	N	Incidence	N	Incidence	N
Overall	43.9%	61	39.9%	59	42.8%	62	47.4%	73	37.9%	55
Nasopharyngitis	10.1%	14	8.1%	12	10.3%	15	9.7%	15	8.3%	12
Pharyngitis	1.4%	2	0.7%	1	1.4%	2	1.9%	3	2.1%	3
Gastroenteritis	2.9%	4	0%	0	2.1%	3	0.6%	1	0.7%	1
Diarrhoea	0.7%	1	1.4%	2	2.8%	4	2.6%	4	3.4%	5
Constipation	1.4%	2	0%	0	1.4%	2	3.2%	5	0.7%	1
Abdominal pain upper	2.2%	3	1.4%	2	1.4%	2	0.6%	1	0%	0
Upper respiratory tract inflammation	2.2%	3	0.7%	1	2.1%	3	0.6%	1	0.7%	1
Seasonal allergy	2.2%	3	1.4%	2	0%	0	1.3%	2	1.4%	2
Blood TG increased	2.2%	3	2.7%	4	2.1%	3	2.6%	4	2.1%	3
Blood CK increased	1.4%	2	2.0%	3	0%	0	1.9%	3	2.8%	4
Eosinophils increased	0.7%	1	0.7%	1	2.8%	4	0.6%	1	2.1%	3
Blood glucose increased	2.9%	4	0.7%	1	1.4%	2	0.6%	1	0.7%	1
Blood uric acid increased	2.2%	3	0.7%	1	2.1%	3	0%	0	0.7%	1
Protein urine present	0%	0	0%	0	2.1%	3	0%	0	0%	0

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Table 38. Adverse drug reactions reported by ≥2% of subjects inany group

	LPZ 30 mg group (N = 139)		Vonoprazan 5 mg group (N = 148)		Vonoprazan 10 mg group (N = 145)		Vonoprazan 20 mg group (N = 154)		Vonoprazan 40 mg group (N = 145)	
	Incidence	N	Incidence	N	Incidence	N	Incidence	N	Incidence	N
Overall	5.8%	8	6.1%	9	9.0%	13	10.4%	16	4.8%	7
Constipation	0%	0	0%	0	0%	0	2.6%	4	0.7%	1
Eosinophil count increased	0.7%	1	0.7%	1	2.1%	3	0%	0	0.7%	1

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No deaths were reported. Serious adverse events occurred in 0.7% (1 of 148 subjects, large intestine polyp) of the vonoprazan 5 mg group, 1.9% (3 of 154 subjects; urinary tract infection, putamen haemorrhage, and peripheral arterial occlusive disease in 1 subject each) of the vonoprazan 20 mg group, 1.4% (2 of 145 subjects; coronary artery stenosis and enterocolitis bacterial in 1 subject each) of the vonoprazan 40 mg group, and 0.7% (1 of 139 subjects, brain contusion/subdural haematoma) of the LPZ 30 mg group. A causal relationship to the study drug was ruled out for all events. Adverse events leading to study drug discontinuation occurred in 0.7% (1 of 148 subjects) of the vonoprazan 5 mg group, 3.4% (5 of 145 subjects) of the vonoprazan 10 mg group, 7.1% (11 of 154 subjects) of the vonoprazan 20 mg group, 1.4% (2 of 145 subjects) of the vonoprazan 40 mg group, and 2.9% (4 of 139 subjects) of the LPZ 30 mg group.

4.(iii).A.(2) Phase III study of the treatment for RE (5.3.5.1-2, Study TAK-438/CCT-002 [■ 20■ to ■ 20■])

A multi-center, randomized, active-controlled, double-blind, parallel-group study was conducted at 39 centers in Japan to investigate the efficacy and safety of vonoprazan in RE patients aged ≥20 years[96] (target sample size: 400 subjects in total; 200 subjects/group).

Vonoprazan 20 mg or LPZ 30 mg was to be orally administered once daily after breakfast for up to 8 weeks.[97] To patients with uncured RE at Week 8, vonoprazan 40 mg was to be furthermore administered orally once daily after breakfast up to another 8 weeks.[98]

All of the 409 subjects treated (207 subjects in the vonoprazan 20 mg group, 202 subjects in the LPZ 30 mg group) were included in the FAS and safety analysis set and the FAS was used for the primary efficacy analysis.

The RE cure rate[99] at Week 8, the primary endpoint, was as shown in Table 39. Non-inferiority of the vonoprazan group to the LPZ 30 mg group was verified ($P < 0.0001$, non-inferiority Farrington and Manning test,[100] one-sided significance level of 2.5%).

Table 39. RE cure rate at Week 8 (FAS)[a)]

Treatment group	No. of subjects with cured RE	Cure rate (%) [95% CI]	Difference from the LPZ 30 mg group (%) [95% CI]	*P* value[b)]
LPZ 30 mg group (N = 199)	190	95.5 [91.6, 97.9]	-	-
Vonoprazan 20 mg group (N = 205)	203	99.0 [96.5, 99.9]	3.5 [0.4, 6.7]	$P < 0.0001$

a) Of the FAS, patients who did not undergo endoscopy post-dose (2 subjects in the LPZ 30 mg group, 2 subjects in the vonoprazan 30 mg group) and patients who underwent endoscopy ≥15 days after the end of treatment (1 subject in the LPZ 30 mg group) were excluded from the analysis.
b) Non-inferiority Farrington and Manning test, non-inferiority margin of 10%, one-sided significance level of 2.5%

Adverse events occurred in 22.2% (46 of 207 subjects) of the vonoprazan 20 mg group and 22.3% (45 of 202 subjects) of the LPZ 30 mg group. Adverse drug reactions occurred in 6.8% (14 of 207 subjects) of the vonoprazan 20 mg group and 5.9% (12 of 202 subjects) of the LPZ 30 mg group. Adverse events reported by ≥2% of subjects in either group were as shown in Table 40. There were no adverse drug reactions reported by ≥2% in any group.

Table 40. Adverse events reported by ≥2% of subjects in either goup

	LPZ 30 mg group (N = 202)		Vonoprazan 20 mg group (N = 207)	
	Incidence	N	Incidence	N
Overall	22.3%	45	22.2%	46
Nasopharyngitis	4.0%	8	3.4%	7
Upper respiratory tract inflammation	2.0%	4	0.5%	1

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No deaths were reported. No serious adverse events occurred in the vonoprazan 20 mg group, while such events occurred in 1.5% (3 of 202 subjects; large intestine polyp, pelvic fracture/radius fracture, and hepatic encephalopathy [1 subject each]) of the LPZ 30 mg group, but a causal relationship to the study drug was ruled out for all events. Adverse events leading to study drug discontinuation occurred

96 Patients who received a diagnosis of Grade A to D under the LA classification according to the endoscopic finding at the baseline of the study treatment (assessed by the investigator or subinvestigator). Subjects with definitive diagnosis of Grade C or D were included to account for ≥30% of all the subjects.

97 The treatment was to be terminated when the endoscopy showed cure of symptoms at Week 2 or 4.

98 The treatment was to be terminated when the cure was confirmed at Week 4 of the additional treatment period.

99 Subjects with definitive diagnosis of Grade O under the LA classification according to the endoscopic finding by Week 8 (assessed by the investigator or subinvestigator) were defined as those cured.

100 *Statistics in Medicine.* 1990;9:1447-1454

in 1.0% (2 of 207 subjects) of the vonoprazan 20 mg group and 1.5% (3 of 202 subjects) of the LPZ 30 mg group.

4.(iii).A.(3) Phase III study of the maintenance therapy for RE (5.3.5.1-3, Study TAK-438/CCT-003 [[redacted] to [redacted]])

A multi-center, randomized, active-controlled, double-blind, parallel-group study was conducted at 55 centers in Japan to investigate the efficacy and safety of vonoprazan in patients who had RE cured by vonoprazan and were aged ≥20 years[101] (target sample size: 600 subjects in total; 200 subjects/group).

During the treatment period, vonoprazan 20 mg was to be orally administered once daily after breakfast up to 8 weeks, and during the maintenance period, vonoprazan 10 mg or 20 mg, or LPZ 15 mg was to be orally administered once daily after breakfast up to 24 weeks.[102]

Of the 611 subjects who completed the treatment period, 607 subjects (202 subjects in the 10 mg group, 204 subjects in the 20 mg group, 201 subjects in the LPZ group) were transferred to the maintenance period, and all of the 607 subjects were included in the FAS and safety analysis set, and the FAS was used for the primary efficacy analysis.

The RE recurrence rate[103] in Week 24 of the maintenance period, the primary endpoint, was as shown in Table 41. Non-inferiority of the vonoprazan 10 mg group and 20 mg group to the LPZ 15 mg group was verified ($P < 0.0001$ for either comparison, non-inferiority Farrington and Manning test, one-sided significance level of 2.5%, the multiplicity of the test adjusted in accordance with the closed testing procedure).

Table 41. RE recurrence rate at Week 24 of the maintenance period (FAS)[a)]

Treatment group	No. of subjects with recurrence	Recurrence rate (%) [95% CI]	Difference from the LPZ 15 mg group (%) [95% CI]	*P* value[b)]
LPZ 15 mg group (N = 196)	33	16.8 [11.9, 22.8]	-	-
Vonoprazan 10 mg group (N = 197)	10	5.1 [2.5, 9.1]	-11.8 [-17.8, -5.7]	$P < 0.0001$
Vonoprazan 20 mg group (N = 201)	4	2.0 [0.5, 5.0]	-14.8 [-20.4, -9.3]	$P < 0.0001$

a) Of the FAS, patients who did not undergo endoscopy post-dose (4 subjects in the LPZ 30 mg group, 4 subjects in the vonoprazan 10 mg group, 2 subjects in the vonoprazan 20 mg group) and patients who underwent endoscopy ≥15 days after the end of treatment (1 subject in the LPZ 30 mg group, 1 subject in the vonoprazan 10 mg group, 1 subject in the vonoprazan 20 mg group) were excluded from the analysis.
b) Non-inferiority Farrington and Manning test, non-inferiority margin of 10%, one-sided significance level of 2.5%, and the multiplicity of the test were adjusted in accordance with the closed testing procedure.

Adverse events during the maintenance period occurred in 54.0% (109 of 202 subjects) of the vonoprazan 10 mg group; 58.8% (120 of 204 subjects) of the vonoprazan 20 mg group; and 51.2% (103 of 201 subjects) of the LPZ 15 mg group. Adverse drug reactions occurred in 10.4% (21 of 202 subjects) of the vonoprazan 10 mg group; 10.3% (21 of 204 subjects) of the vonoprazan 20 mg group; and 11.4% (23 of 201 subjects) of the LPZ 15 mg group. Adverse events reported by ≥2% of subjects in any group were as shown in Table 42. Adverse drug reactions reported by ≥2% of subjects in any group were only diarrhoea (0.0% [0 of 202 subjects] of the vonoprazan 10 mg group, 0.5% [1 of 204 subjects] of the vonoprazan 20 mg group, 2.5% [5 of 201 subjects] of the LPZ 15 mg group).

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101 Patients who received diagnosis of Grade A to D under the LA classification according to the endoscopic finding at the baseline of the study treatment, received vonoprazan orally once daily at a dose of 20 mg for 2, 4, or 8 weeks in an open-label manner (treatment period), and then were endoscopically confirmed as being cured. Patients with definitive diagnosis of Grade C or D at the baseline were included to account for ≥15% of all the subjects.

102 For patients in whom recurrence of reflux esophagitis was endoscopically confirmed, the study was completed at the time of the confirmation.

103 Patients who received a diagnosis of Grade A to D under the LA classification according to the endoscopic finding (assessed by the investigator or subinvestigator) were defined as those with recurrence.

Table 42. Adverse events reported by ≥2% of subjects in any group (maintenance period)

	LPZ 15 mg group (N = 201)		Vonoprazan 10 mg group (N = 202)		Vonoprazan 20 mg group (N = 204)	
	Incidence	N	Incidence	N	Incidence	N
Overall	51.2%	103	54.0%	109	58.8%	120
Nasopharyngitis	13.9%	28	16.8%	34	13.2%	27
Gastroenteritis	0.5%	1	2.5%	5	2.5%	5
Bronchitis	1.0%	2	2.5%	5	0.0%	0
Periodontitis	0.0%	0	2.0%	4	0.5%	1
Diarrhoea	5.5%	11	3.0%	6	2.5%	5
Constipation	2.0%	4	1.0%	2	1.5%	3
Back pain	0.5%	1	1.5%	3	2.5%	5
Upper respiratory tract inflammation	1.5%	3	4.0%	8	2.0%	4
Seasonal allergy	1.0%	2	2.0%	4	1.0%	2
Blood TG increased	3.0%	6	0.5%	1	2.5%	5
Blood CK increased	1.0%	2	2.0%	4	2.9%	6
ALT increased	0.5%	1	1.5%	3	2.0%	4
Liver function test abnormal	0.5%	1	1.0%	2	2.0%	4
Fall	0.5%	1	4.0%	8	1.0%	2
Contusion	0.5%	1	2.5%	5	1.0%	2
Dizziness	0.5%	1	2.0%	4	1.0%	2

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No deaths were reported. Serious adverse events occurred in 2.5% of the vonoprazan 10 mg group (5 of 202 subjects; melaena, spinal compression fracture, dehydration, intentional self-injury, and renal artery stenosis in 1 subject each), 2.0% of the vonoprazan 20 mg group (4 of 204 subjects; atrial fibrillation, appendicitis, campylobacter gastroenteritis, and liver function test abnormal in 1 subject each), and 2.0% of the LPZ 15 mg group (4 of 201 subjects; aortic valve stenosis, sick sinus syndrome, diabetic retinopathy, and cervix carcinoma in 1 subject each). A causal relationship to the study drug could not be ruled out for liver function test abnormal and atrial fibrillation in 1 subject each in the vonoprazan 20 mg group.[104] Adverse events leading to study drug discontinuation occurred in 2.5% (5 of 202 subjects) of the vonoprazan 10 mg group, 3.9% (8 of 204 subjects) of the vonoprazan 20 mg group, and 4.0% (8 of 201 subjects) of the LPZ 15 mg group.

4.(iii).A.(4) Phase III long-term treatment study of the maintenance therapy for RE (5.3.5.2-1, Study TAK-438/OCT-001 [[redacted] to [redacted]])

A multi-center, randomized, single-blind,[105] parallel-group study was conducted at 39 centers in Japan to investigate the safety of long-term treatment with vonoprazan in patients aged ≥20 years who had been cured from RE by vonoprazan or LPZ[106] (target sample size: 300 subjects in total, 150 subjects/group).

Vonoprazan 10 mg or 20 mg was to be orally administered once daily after breakfast for up to 52 weeks.[107]

All of the 305 subjects treated (154 subjects in the vonoprazan 10 mg group, 151 subjects in the vonoprazan 20 mg group) were included in the FAS and safety analysis set, and the FAS was used for the primary efficacy analysis.

Adverse events occurred in 76.6% (118 of 154 subjects) of the vonoprazan 10 mg group and 78.8% (119 of 151 subjects) of the vonoprazan 20 mg group. Adverse drug reactions occurred in 9.7% (15 of 154 subjects) of the vonoprazan 10 mg group and 16.6% (25 of 151 subjects) of the vonoprazan 20 mg group.

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104 Both events of liver function test abnormal and atrial fibrillation resolved after 19 and 56 days of duration, respectively.

105 The study was to be conducted double-blind until the study data in all of the patients were fixed on Week 24 and then was to be continued open only to the sponsor.

106 Patients who completed Study CCT-002 with resolved reflux esophagitis confirmed endoscopically at Week 2, 4, or 8 in Study CCT-002

107 Patients terminated the study when recurrence of reflux esophagitis was endoscopically confirmed.

Adverse events and adverse drug reactions reported by ≥2% of subjects in either group were as shown in Table 43 and Table 44.

Table 43. Adverse events reported by ≥2% of subjects in either group

	Vonoprazan 10 mg group (N = 154)		Vonoprazan 20 mg group (N = 151)			Vonoprazan 10 mg group (N = 154)		Vonoprazan 20 mg group (N = 151)	
	Incidence	N	Incidence	N		Incidence	N	Incidence	N
Overall	76.6%	118	78.8%	119	Nausea	0.6%	1	2.0%	3
Nasopharyngitis	21.4%	33	28.5%	43	Back pain	3.9%	6	2.6%	4
Gastroenteritis	7.1%	11	6.0%	9	Osteoarthritis	3.9%	6	0%	0
Pharyngitis	5.8%	9	2.6%	4	Periarthritis	1.9%	3	2.0%	3
Bronchitis	1.9%	3	4.0%	6	Upper respiratory tract inflammation	4.5%	7	7.3%	11
Tinea pedis	0%	0	2.0%	3	Seasonal allergy	1.3%	2	2.0%	3
Tonsillitis	0%	0	2.0%	3	Insomnia	3.2%	5	4.6%	7
Gastric polyps	4.5%	7	4.6%	7	Blood CK increased	1.3%	2	4.6%	7
Enterocolitis	1.3%	2	3.3%	5	Liver function test abnormal	0.6%	1	2.0%	3
Gastritis	2.6%	4	0.7%	1	Hepatic function abnormal	0.6%	1	2.0%	3
Gastritis erosive	0.6%	1	4.0%	6	Fall	4.5%	7	2.6%	4
Constipation	2.6%	4	1.3%	2	Eczema	0.6%	1	4.6%	7
Diarrhoea	1.9%	3	2.0%	3	Dermatitis contact	0%	0	2.0%	3
Dental caries	0.6%	1	2.0%	3	Hypertension	1.9%	3	3.3%	5

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Table 44. Adverse drug reactions reported by ≥2% of subjects in either group

	Vonoprazan 10 mg group (N = 154)		Vonoprazan 20 mg group (N = 151)	
	Incidence	N	Incidence	N
Overall	9.7%	15	16.6%	25
Gastric polyps	0.6%	1	2.0%	3
Liver function test abnormal	0%	0	2.0%	3

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No deaths were reported. Serious adverse events occurred in 5.2% (8 of 154 subjects; age-related macular degeneration, large intestine polyp, pneumonia/peritonsillar abscess, gastroenteritis, osteomyelitis, diabetes mellitus/cerebral infarction, breast cancer, and malignant fibrous histiocytoma/schwannoma in 1 subject each) of the vonoprazan 10 mg group and 7.3% (11 of 151 subjects; pneumonia, pneumonia/pyrexia, thyroiditis subacute, aerophagia, biliary cirrhosis primary, enterocolitis bacterial, tendon rupture, spinal ligament ossification, myelodysplastic syndrome, cerebral infarction, and cubital tunnel syndrome in 1 subject each) of the vonoprazan 20 mg group. A causal relationship to the study drug could not be ruled out for malignant fibrous histiocytoma in the vonoprazan 10 mg group as well as pneumonia/pyrexia and thyroiditis subacute in 1 subject each of the vonoprazan 20 mg group.[108] Adverse events leading to study drug discontinuation occurred in 5.2% (8 of 154 subjects) of the vonoprazan 10 mg group and 7.9% (12 of 151 subjects) of the vonoprazan 20 mg group.

RE recurrence rate[103] in Weeks 24 and 52 is as shown in Table 45.

[108] All of the events of malignant fibrous histiocytoma, pneumonia, pyrexia, and thyroiditis subacute resolved after 148, 12, 31, and 49 days of duration, respectively.

Table 45. RE recurrence rate in Weeks 24 and 52 (FAS)

After the study treatment start	Treatment group	No. of subjects with recurrence	Recurrence rate (%) [95% CI]	Difference from the vonoprazan 10 mg group (%) [95% CI]
Week 24	Vonoprazan 10 mg group (N = 149)	9	6.0 [2.8, 11.2]	-
	Vonoprazan 20 mg group (N = 145)	6	4.1 [1.5, 8.8]	-1.9 [-6.9, 3.1]
Week 52	Vonoprazan 10 mg group (N = 149)	14	9.4 [5.2, 15.3]	-
	Vonoprazan 20 mg group (N = 145)	13	9.0 [4.9, 14.8]	-0.4 [-7.0, 6.2]

4.(iii).A.(5) Phase III study in patients with gastric ulcer (5.3.5.1-4, Study TAK-438/CCT-101 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A multi-center, randomized, active-controlled, double-blind, parallel-group study was conducted at 83 centers in Japan to investigate the efficacy and safety of vonoprazan in patients with gastric ulcer aged ≥20 years[109] (target sample size: 480 subjects in total; 240 subjects/group).

Vonoprazan 20 mg or LPZ 30 mg was to be orally administered once daily after breakfast for up to 8 weeks.[110]

All of the 482 subjects treated (244 subjects in the vonoprazan 20 mg group, 238 subjects in the LPZ 30 mg group) were included in the safety analysis set. Of these, 464 subjects (236 subjects in the vonoprazan 20 mg group, 228 subjects in the LPZ 30 mg group) were included in the FAS, and the FAS was used for the primary efficacy analysis, excluding 18 subjects (violation of the inclusion criteria [different from the target disease]).

The rate of gastric ulcer cure rate[111] at Week 8, the primary endpoint, was as shown in Table 46. Non-inferiority of the vonoprazan 20 mg group to the LPZ 30 mg group was verified (P = 0.0011, non-inferiority Farrington and Manning test, one-sided significance level of 2.5%).

Table 46. Gastric ulcer cure rate at Week 8 (FAS)[a)]

Treatment group	No. of subjects with cured gastric ulcer	Cure rate (%) [95% CI]	Difference from the LPZ 30 mg group (%) [95% CI]	P value[b)]
LPZ 30 mg group (N = 225)	211	93.8 [89.8, 96.6]	-	-
Vonoprazan 20 mg group (N = 231)	216	93.5 [89.5, 96.3]	-0.3 [-4.8, 4.2]	P = 0.0011

a) Of the FAS, patients who did not undergo endoscopy post-dose (3 subjects in the LPZ 30 mg group, 5 subjects in the vonoprazan 20 mg group) were excluded from the analysis.
b) Non-inferiority Farrington and Manning test, non-inferiority margin of 8%, one-sided significance level of 2.5%

Adverse events occurred in 26.6% (65 of 244 subjects) of the vonoprazan 20 mg group and 33.2% (79 of 238 subjects) of the LPZ 30 mg group. Adverse drug reactions occurred in 6.6% (16 of 244 subjects) of the vonoprazan 20 mg group and 5.9% (14 of 238 subjects) of the LPZ 30 mg group. Adverse events reported by ≥2% of subjects in either group were as shown in Table 47. Adverse drug reactions reported by ≥2% of subjects in either group were only constipation (2.0% [5 of 244 subjects] of the vonoprazan 20 mg group, 1.3% [3 of 238 subjects] of the LPZ 30 mg group).

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109 Patients with at least 1 lesion of gastric ulcer associated with white coat ≥5 mm in longitudinal diameter found endoscopically at the baseline of the study treatment

110 The study treatment was terminated when gastric ulcer was endoscopically diagnosed as cured in Week 2 or 4.

111 "Cure" was defined as a status where all the lesions of white coat related to gastric ulcer disappeared when checked endoscopically (assessed by the investigator or subinvestigator).

Table 47. Adverse events reported by ≥2% of subjects in either group

	LPZ 30 mg group (N = 238)		Vonoprazan 20 mg group (N = 244)	
	Incidence	N	Incidence	N
Overall	33.2%	79	26.6%	65
Nasopharyngitis	3.8%	9	2.9%	7
Abdominal pain upper	2.9%	7	3.3%	8
Constipation	1.7%	4	3.3%	8
Gastric ulcer	1.7%	4	2.9%	7
Abdominal discomfort	2.5%	6	1.6%	4
Diarrhoea	2.9%	7	0.8%	2
Vomiting	0%	0	2.0%	5

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No deaths were reported. Serious adverse events occurred in 2.5% (6 of 244 subjects; cardiac failure chronic, gastric ulcer/nephrotic syndrome, acute abdomen, gastric ulcer haemorrhage, contusion, and cerebral infarction in 1 subject each) of the vonoprazan 20 mg group and 1.7% (4 of 238 subjects; gastric ulcer, large intestine polyp, meningitis viral, and interstitial lung disease/pulmonary hypertension in 1 subject each) of the LPZ 30 mg group. A causal relationship to the study drug could not be ruled out for gastric ulcer and interstitial lung disease/pulmonary hypertension in 1 subject each of the LPZ 30 mg group.[112] Adverse events leading to study drug discontinuation occurred in 2.0% (5 of 244 subjects) of the vonoprazan 20 mg group and 0.8% (2 of 238 subjects) of the LPZ 30 mg group.

4.(iii).A.(6) Phase III study in patients with duodenal ulcer (5.3.5.1-5, Study TAK-438/CCT-102 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A multi-center, randomized, active-controlled, double-blind, parallel-group study was conducted at 76 centers in Japan to investigate the efficacy and safety of vonoprazan in patients with duodenal ulcer aged ≥20 years[113] (target sample size: 390 subjects in total; 195 subjects/group).

Vonoprazan 20 mg or LPZ 30 mg was to be orally administered once daily after breakfast for up to 6 weeks.[114]

Of all the 369 subjects treated (183 subjects in the vonoprazan 20 mg group, 186 subjects in the LPZ 30 mg group), 368 subjects (183 subjects in the vonoprazan 20 mg group, 185 subjects in the LPZ 30 mg group) were included in the safety analysis set, excluding 1 subject (critical protocol deviation). Of all the treated subjects, 366 subjects (182 subjects in the vonoprazan 20 mg group, 184 subjects in the LPZ 30 mg group) were included in the FAS, excluding 1 subject (critical protocol deviation) and 2 subjects (violation of the inclusion criteria [different from the target disease]). The FAS was used for the primary efficacy analysis.

The duodenal ulcer cure rate[115] at Week 6, the primary endpoint, was as shown in Table 48. Non-inferiority of the vonoprazan 20 mg group to the LPZ 30 mg group was not statistically verified (P = 0.0654, non-inferiority Farrington and Manning test, one-sided significance level of 2.5%).

[112] The event of gastric ulcer resolved after 110 days of duration. Both events of interstitial lung disease and pulmonary hypertension improved.

[113] Patients with at least 1 lesion of duodenal ulcer with white moss ≥5 mm in longitudinal diameter found endoscopically at the baseline of study treatment

[114] The study treatment was to be terminated when duodenal ulcer was endoscopically diagnosed as cured at Week 2 or 4.

[115] "Cure" was defined as a status where all the lesions of white moss related to duodenal ulcer disappeared when checked endoscopically (assessed by the investigator or subinvestigator).

Table 48. Duodenal ulcer cure rate at Week 6 (FAS)[a)]

Treatment group	No. of subjects with cured duodenal ulcer	Cure rate (%) [95% CI]	Difference from the LPZ 30 mg group (%) [95% CI]	*P* value[b)]
LPZ 30 mg group (N = 180)	177	98.3 [95.2, 99.7]	-	-
Vonoprazan 20 mg group (N = 178)	170	95.5 [91.3, 98.0]	-2.8 [-6.4, 0.7]	*P* = 0.0654

a) Of the FAS, patients who did not undergo endoscopy post-dose (4 subjects in the LPZ 30 mg group, 4 subjects in the vonoprazan 20 mg group) were excluded from the analysis.
b) Non-inferiority Farrington and Manning test, non-inferiority margin of 6%, one-sided significance level of 2.5%

Adverse events occurred in 34.4% (63 of 183 subjects) of the vonoprazan 20 mg group and 28.6% (53 of 185 subjects) of the LPZ 30 mg group. Adverse drug reactions occurred in 9.3% (17 of 183 subjects) of the vonoprazan 20 mg group and 4.9% (9 of 185 subjects) of the LPZ 30 mg group. Adverse events reported by ≥2% of subjects in either group are as shown in Table 49. There were no adverse drug reactions reported by ≥2% in any group.

Table 49. Adverse events reported by ≥2% of subjects in either group

	LPZ 30 mg group (N = 185)		Vonoprazan 20 mg group (N = 183)	
	Incidence	N	Incidence	N
Overall	28.6%	53	34.4%	63
Nasopharyngitis	6.5%	12	6.0%	11
Abdominal pain upper	3.8%	7	5.5%	10
Diarrhoea	2.7%	5	2.2%	4
Duodenal ulcer	1.1%	2	3.3%	6

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Death occurred in 1 subject (subarachnoid haemorrhage) of the vonoprazan 20 mg group and a causal relationship to the study drug could not be ruled out for the death.[116] Other than death, serious adverse events occurred in 2.7% (5 of 183 subjects; duodenal ulcer, duodenal ulcer haemorrhage, duodenal ulcer/gastrooesophageal reflux disease, pneumonia/sepsis, and haemoglobin decreased in 1 subject each) of the vonoprazan 20 mg group and 2.2% (4 of 185 subjects; pancreatitis acute, pharyngolaryngeal abscess, comminuted fracture, and duodenal neoplasm in 1 subject each) of the LPZ 30 mg group, but a causal relationship to the study drug was ruled out for all events. Adverse events leading to study drug discontinuation occurred in 2.7% (5 of 183 subjects) of the vonoprazan 20 mg group and 1.1% (2 of 185 subjects) of the LPZ 30 mg group.

4.(iii).A.(7) Phase III study for *Helicobacter pylori* eradication (5.3.5.1-6, Study TAK-438/CCT-401 [[redacted]])

A multi-center, randomized, active-controlled, double-blind,[117] parallel-group study was conducted at 46 centers in Japan to investigate the efficacy and safety of 3-drug combination therapy consisting of vonoprazan, AMPC, and CAM in patients with *H. pylori* positive[118] gastric ulcer scar or duodenal ulcer scar[119] aged ≥20 years (target sample size: 648 subjects in total[120]; 324 subjects/group[121]).

116 The subject experienced subarachnoid haemorrhage in the morning following the first dose of the study drug (vonoprazan 20 mg) and died. The subject received acetaminophen due to headache from 1 day before the study treatment. On the day of the study treatment, no abnormalities such as headache were observed. Blood pressure on the day of the study treatment was 138/87 mmHg.

117 The secondary eradication was to be open-label.

118 *H. pylori* positive was confirmed by one of the following tests performed before the start of study treatment: rapid urease test, culture method, ^{13}C-urea breath test, or fecal *H. pylori* antigen assay.

119 Patients who were endoscopically confirmed to have gastric or duodenal ulcer scar at the baseline of study treatment. Patients with a medical history of ulcer documentedin diagnostic interview or past medical records were considered eligible for the study, even if gastric or duodenal ulcer scar had disappeared.

120 The number of subjects for the secondary eradication was planned to be 50.

121 The target sample size at the baseline was set as 220 subjects for each group, and resetting of the number of blinded subjects as described in *Biom J.* 2007;49:903-916 was to be conducted when the number of subjects suitable for evaluating the *H. pylori* primary eradication rate at 4 weeks after the end of the primary eradication was estimated to reach 200. As a result, the resetting of the number of the subjects was performed, and it was changed to 324 subjects for each group.

Patients who failed to eradicate *H. pylori* in the primary eradication were to be transferred to the secondary eradication period. During each period, the drugs were to be orally administered twice daily for 7 days at the doses as shown in Table 50.

Table 50. Doses of the drugs

	Treatment group	Dose of each drug
Primary eradication period	Vonoprazan group	Vonoprazan 20 mg, AMPC 750 mg, and CAM 200 mg or 400 mg
	LPZ group	LPZ 30 mg, AMPC 750 mg, and CAM 200 mg or 400 mg
Secondary eradication period	Vonoprazan group	Vonoprazan 20 mg, AMPC 750 mg, and MNZ 250 mg

All of the 650 subjects treated during the primary eradication period were included in the FAS and safety analysis set of the primary eradication period, and the FAS was used for the primary efficacy analysis. All of the 50 subjects treated during the secondary eradication period were also included in the FAS and safety analysis set for the secondary eradication period, and the FAS was used for the primary efficacy analysis.

The *H. pylori* primary eradication rate[122] at 4 weeks after the end of the primary eradication treatment, the primary endpoint, was as shown in Table 51. Non-inferiority of the vonoprazan group to the LPZ group was verified ($P < 0.0001$, non-inferiority Farrington and Manning test, one-sided significance level of 2.5%).

Table 51. *H. pylori* primary eradication rate at 4 weeks after the end of the primary eradication treatment (FAS)[a)]

Treatment group	No. of subjects with eradication success	Eradication rate (%) [95% CI]	Difference from the LPZ 30 mg group (%) [95% CI]	*P* value[b)]
LPZ group (N = 320)	243	75.9 [70.9, 80.5]	-	-
Vonoprazan group (N = 324)	300	92.6 [89.2, 95.2]	16.7 [11.2, 22.1]	$P < 0.0001$

a) Of the FAS, patients who did not receive ^{13}C-urea breath test at all (1 subject in the LPZ 30 mg group, 5 subjects in the vonoprazan 20 mg group) were excluded from the analysis.
b) Non-inferiority Farrington and Manning test, non-inferiority margin of 10%, one-sided significance level of 2.5%

The *H. pylori* secondary eradication rate at 4 weeks after the end of the secondary eradication treatment [95% CI], the secondary endpoint, was 98.0% (49 of 50 subjects) [89.4%, 99.9%].

During the primary eradication period, adverse events occurred in 34.0% (112 of 329 subjects) of the vonoprazan group and 41.1% (132 of 321 subjects) of the LPZ mg group. Adverse drug reactions occurred in 20.4% (67 of 329 subjects) of the vonoprazan group and 24.6% (79 of 321 subjects) of the LPZ group. Adverse events and adverse drug reactions reported by ≥2% of subjects in either group during the primary eradication period were as shown in Table 52 and Table 53.

Table 52. Adverse events reported by ≥2% of subjects in either group (primary eradication period)

	LPZ group (N = 321)		Vonoprazan group (N = 329)	
	Incidence	N	Incidence	N
Overall	41.1%	132	34.0%	112
Diarrhoea	15.3%	49	12.5%	41
Nasopharyngitis	4.7%	15	5.5%	18
Dysgeusia	3.1%	10	4.0%	13

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122 The percentage of the subjects who were assessed as *H. pylori* negative by ^{13}C-urea breath test performed at 4 weeks after the end of the primary eradication

Table 53. Adverse drug reactions reported by ≥2% of subjects in either group (primary eradication period)

	LPZ group (N = 321)		Vonoprazan group (N = 329)	
	Incidence	N	Incidence	N
Overall	24.6%	79	20.4%	67
Diarrhoea	13.4%	43	10.6%	35
Dysgeusia	3.1%	10	4.0%	13

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Adverse events and adverse drug reactions during the secondary eradication period occurred in 30.0% (15 of 50 subjects) and 16.0% (8 of 50 subjects), respectively, of the subjects transferred to this period. Adverse events reported by ≥2% of the subjects during the secondary eradication period included diarrhoea, meteorism, nasopharyngitis, alanine aminotransferase increased, and aspartate aminotransferase increased (4.0% [2 of 50 subjects] each) as well as abdominal discomfort, abdominal pain, cheilitis, constipation, gastric mucosal lesion, gastrooesophageal reflux disease, appendicitis, pharyngitis, pseudomembranous colitis, postoperative ileus, blood triglycerides increased, electrocardiogram QT prolonged, gamma-glutamyltransferase increased, back pain, headache, and upper respiratory tract inflammation (2.0% [1 of 50 subjects] each). Adverse drug reactions reported by ≥2% of the subjects included diarrhoea, meteorism, alanine aminotransferase increased, and aspartate aminotransferase increased (4.0% [2 of 50 subjects] each) as well as abdominal discomfort, constipation, and electrocardiogram QT prolonged (2.0% [1 of 50 subjects] each).

No deaths occurred during either the primary or secondary eradication period. Serious adverse events during the primary eradication period occurred in 1.2% (4 of 329 subjects; acute myocardial infarction, gastric ulcer haemorrhage, cholangitis suppurative, and enteritis infectious in 1 subject each) of the vonoprazan group; and 0.6% (2 of 321 subjects; femoral neck fracture and pancreatic carcinoma in 1 subject each) of the LPZ group. A causal relationship to the study drug could not be ruled out for acute myocardial infarction in 1 subject of the vonoprazan group.[123] During the secondary eradication period, serious adverse events occurred in 2.0% (1 of 50 subjects; appendicitis/pseudomembranous colitis in 1 subject) of the subjects, but a causal relationship to the study drug was ruled out. Adverse events leading to study drug discontinuation occurred in 0.9% (3 of 329 subjects) of the vonoprazan group and 0.6% (2 of 321 subjects) of the LPZ group during the primary eradication, and such events did not occur during the secondary eradication period.

4.(iii).A.(8) Phase III study in patients with LDA ulcer (5.3.5.1-7, Study TAK-438/CCT-302 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A multi-center, randomized, active-controlled, double-blind, parallel-group study was conducted at 104 centers in Japan to investigate the efficacy and safety of vonoprazan in patients who had a medical history of gastric or duodenal ulcer,[124] had to take LDA for a long period of time,[125] and were aged ≥20 years (target sample size: 630 subjects in total; 210 subjects/group).

Vonoprazan 10 mg or 20 mg or LPZ 15 mg was to be administered orally once daily after breakfast for up to 24 weeks.[126]

All of the 621 subjects treated (202 subjects in the vonoprazan 10 mg group, 202 subjects in the vonoprazan 20 mg group, 217 subjects in the LPZ 15 mg group) were included in the FAS and safety analysis set, and the FAS was used for the primary efficacy analysis.

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123 The event of acute myocardial infarction resolved after 106 days of duration.

124 Patients who were confirmed to have ulcer scar by upper gastrointestinal endoscopy (assessed by the investigator or subinvestigator) performed at the baseline of study treatment or to have had ulcer (mucosal defect with white moss ≥3 mm) or ulcer scar by upper gastrointestinal endoscopy performed in the past

125 Patients who have to continue to take LDA (aspirin, 81-324 mg/day) to prevent thrombosis/embolizm due to ischaemic heart disease, ischaemic cerebrovascular disorder, etc. In principle, LDA type as well as dosage and administration were to remain unchanged during the study period.

126 The study treatment was terminated when recurrence of ulcer was endoscopically confirmed.

The recurrence rate[127] of gastric or duodenal ulcer in Week 24, the primary endpoint, was as shown in Table 54. Non-inferiority of either vonoprazan groups to the LPZ 15 mg group was verified ($P < 0.0001$ for either comparison, non-inferiority Farrington and Manning test, one-sided significance level of 2.5%, the multiplicity of the test adjusted in accordance with the closed testing procedure).

Table 54. Recurrence rate of gastric or duodenal ulcer in Week 24 (FAS)[a)]

Treatment group	No. of subjects with recurrence	Recurrence rate (%) [95% CI]	Difference from the LPZ 15 mg group (%) [95% CI]	*P* value[b)]
LPZ 15 mg group (N = 213)	6	2.8 [1.0, 6.0]	-	-
Vonoprazan 10 mg group (N = 197)	1	0.5 [0.0, 2.8]	-2.3 [-4.7, 0.1]	$P < 0.0001$
Vonoprazan 20 mg group (N = 196)	3	1.5 [0.3, 4.4]	-1.3 [-4.1, 1.5]	$P < 0.0001$

a) Of the FAS, patients who did not undergo endoscopy post-dose (2 subjects in the LPZ 15 mg group, 4 subjects in the vonoprazan 10 mg group, 4 subjects in the vonoprazan 20 mg group) and patients who received diagnosis of gastric or duodenal ulcer at the baseline endoscopy through the central assessment committee, (2 subjects in the LPZ 15 mg group, 1 subject in the vonoprazan 10 mg group, 2 subjects in the vonoprazan 20 mg group) were excluded from the analysis.

b) Non-inferiority Farrington and Manning test, non-inferiority margin of 8.7%, one-sided significance level of 2.5%, and the multiplicity of the test was adjusted in accordance with the closed testing procedure.

Adverse events occurred in 71.3% (144 of 202 subjects) of the vonoprazan 10 mg group, 75.7% (153 of 202 subjects) of the vonoprazan 20 mg group, and 67.7% (147 of 217 subjects) of the LPZ 15 mg group. Adverse drug reactions occurred in 10.4% (21 of 202 subjects) of the vonoprazan 10 mg group, 16.3% (33 of 202 subjects) of the vonoprazan 20 mg group, and 17.5% (38 of 217 subjects) of the LPZ 15 mg group. Adverse events and adverse drug reactions reported by ≥2% of subjects in any group were as shown in Table 55 and Table 56.

127 "Recurrence of ulcer" was defined as the case where a mucosal defect with white moss ≥3 mm was confirmed endoscopically by the central assessment committee.

Table 55. Adverse events reported by ≥2% of subjects in any group

	LPZ 15 mg group (N = 217)		Vonoprazan 10 mg group (N = 202)		Vonoprazan 20 mg group (N = 202)	
	Incidence	N	Incidence	N	Incidence	N
Overall	67.7%	147	71.3%	144	75.7%	153
Nasopharyngitis	17.1%	37	14.9%	30	20.3%	41
Pharyngitis	2.8%	6	1.5%	3	1.5%	3
Gastroenteritis	0.9%	2	1.0%	2	2.5%	5
Periodontitis	0.9%	2	1.0%	2	2.5%	5
Constipation	4.6%	10	5.0%	10	6.9%	14
Diarrhoea	6.0%	13	4.0%	8	5.4%	11
Dental caries	1.8%	4	2.0%	4	1.5%	3
Gastric polyps	3.2%	7	1.0%	2	1.0%	2
Back pain	0.5%	1	3.0%	6	3.0%	6
Osteoarthritis	0.9%	2	1.5%	3	2.0%	4
Periarthritis	0.5%	1	2.0%	4	1.5%	3
Pain in extremity	0.9%	2	0.0%	0	2.5%	5
Upper respiratory tract inflammation	2.8%	6	4.0%	8	2.5%	5
Rhinitis allergic	0.5%	1	1.5%	3	2.5%	5
Oedema peripheral	0.9%	2	2.0%	4	1.5%	3
Seasonal allergy	1.4%	3	2.0%	4	1.0%	2
Blood CK increased	3.2%	7	2.0%	4	4.5%	9
Blood TG increased	1.4%	3	3.0%	6	1.5%	3
γ-GT increased	1.4%	3	2.0%	4	2.0%	4
Blood iron decreased	0.9%	2	2.5%	5	1.5%	3
Blood glucose increased	0.5%	1	1.5%	3	2.5%	5
Fall	3.7%	8	3.0%	6	1.0%	2
Contusion	2.8%	6	1.5%	3	0.5%	1
Diabetes mellitus	4.1%	9	1.5%	3	3.5%	7
Dehydration	0.5%	1	2.0%	4	0.5%	1
Eczema	2.3%	5	4.0%	8	1.5%	3
Hypertension	2.8%	6	2.0%	4	3.0%	6

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Table 56. Adverse drug reactions reported by ≥2% of subjects in any group

	LPZ 15 mg group (N = 217)		Vonoprazan 10 mg group (N = 202)		Vonoprazan 20 mg group (N = 202)	
	Incidence	N	Incidence	N	Incidence	N
Overall	17.5%	38	10.4%	21	16.3%	33
Constipation	2.3%	5	1.0%	2	3.0%	6
Diarrhoea	3.2%	7	0.5%	1	0.5%	1
Blood iron decreased	0%	0	2.0%	4	1.0%	2

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No deaths were reported. Serious adverse events occurred in 9.9% (20 of 202 subjects) of the vonoprazan 10 mg group; 9.9% (20 of 202 subjects) of the vonoprazan 20 mg group; and 6.5% (14 of 217 subjects) of the LPZ 15 mg group (Table 57). A causal relationship to the study drug could not be ruled out for enterocolitis, gastric cancer, and oral fibroma in 1 subject each of the vonoprazan 20 mg group as well as pancreatitis acute and renal failure acute in 1 subject each of the LPZ 15 mg group.[128] Adverse events leading to study drug discontinuation occurred in 4.0% (8 of 202 subjects) of the vonoprazan 10 mg group; 4.5% (9 of 202 subjects) of the vonoprazan 20 mg group; and 6.0% (13 of 217 subjects) of the LPZ 15 mg group.

[128] All the events of enterocolitis, gastric cancer, and oral fibroma in the vonoprazan 20 mg group resolved after 10, 85, and 85 days of duration, respectively. Both events of pancreatitis acute and renal failure acute in the LPZ 15 mg group resolved after 26 and 121 days of duration, respectively.

Table 57. Serious adverse events

Treatment group	Incidence (N)	Event term	
Vonoprazan 10 mg group (N = 202)	9.9% (20)	2 subjects	Angina pectoris
		1 subject each	Anaemia, angina pectoris, renal impairment, and peripheral arterial occlusive disease; peripheral arterial occlusive disease; cardiac failure; atrial fibrillation; cardiac failure congestive; ileus; pneumonia; herpes zoster; nasopharyngitis; contusion; lower limb fracture; blood pressure increased; dehydration; gastric cancer; adenocarcinoma gastric; bladder cancer; carotid artery stenosis and cerebral infarction; calculus urinary
Vonoprazan 20 mg group (N = 202)	9.9% (20)	3 subjects	Gastric cancer
		2 subjects each	Coronary artery stenosis, diabetes mellitus, oesophageal carcinoma
		1 subject each	Angina pectoris; ventricular tachycardia and chest discomfort; enterocolitis; pneumonia; bacterial infection; coronary artery restenosis; foot fracture; spinal compression fracture and convulsion; oral fibroma; altered state of consciousness; peripheral arterial occlusive disease
LPZ 15 mg group (N = 217)	6.5% (14)	1 subject each	Coronary artery stenosis; cardiac failure, enterocolitis haemorrhagic, and pneumonia; myocardial ischaemia; cataract; macular degeneration; ileus; large intestine polyp; pancreatitis acute and respiratory disorder; cholangitis; gastroenteritis; diabetes mellitus; calculus ureteric; renal failure acute and prostatitis; pneumothorax

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4.(iii).A.(9) Phase III long-term study in patients with LDA ulcer (5.3.5.1-9, Study TAK-438/OCT-302 [[redacted] to [redacted]])

A multi-center, randomized, active-controlled, single-blind,[129] parallel-group study was conducted at 99 centers in Japan to investigate the safety of vonoprazan in patients who completed Study CCT-302[130] (target sample size: 450 subjects in total; 150 subjects per group).

Vonoprazan 10 mg or 20 mg or LPZ 15 mg was to be orally administered once daily after breakfast and the duration of treatment was to be 28 to 80 weeks.[131]

Of all the 621 subjects treated in Study CCT-302, a total of 439 subjects (152 subjects in the vonoprazan 10 mg group, 135 subjects in the vonoprazan 20 mg group, 152 subjects in the LPZ 15 mg group) were transferred to this study, and all of the 439 subjects received the study drug. In the FAS and safety analysis set of this study, 621 subjects (202 subjects in the vonoprazan 10 mg group, 202 subjects in the vonoprazan 20 mg group, 217 subjects in the LPZ 15 mg group) were included as done in Study CCT-302. The FAS was used for the primary efficacy analysis.

Regarding safety,[132] adverse events occurred in 87.6% (177 of 202 subjects) of the vonoprazan 10 mg group; 87.1% (176 of 202 subjects) of the vonoprazan 20 mg group; and 84.8% (184 of 217 subjects) of the LPZ 15 mg group. Adverse drug reactions occurred in 16.3% (33 of 202 subjects) of the vonoprazan 10 mg group; 19.3% (39 of 202 subjects) of the vonoprazan 20 mg group; and 24.4% (53 of 217 subjects) of the LPZ 15 mg group. Adverse events and adverse drug reactions reported by ≥2% of subjects in any group are as shown in Table 58 and Table 59.

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129 Study CCT-302 was to be conducted double-blind until unblinding and then the study was continued to be conducted single-blind as OCT-302, keeping the study drug unkown to the study centers until the end of the study.

130 Patients in whom non-recurrence of gastric or duodenal ulcer was endoscopically confirmed in Week 24 in Study CCT-302

131 The duration of treatment is 52 to 104 weeks from the first dose of the study drug in Study CCT-302. The treatment was terminated when the recurrence of ulcer was confirmed.

132 The safety analysis was performed using pooled data from this study and data from Study CCT-302.

Table 58. Adverse events reported by ≥2% of subjects in any group

	LPZ 15 mg group (N = 217)		Vonoprazan 10 mg group (N = 202)		Vonoprazan 20 mg group (N = 202)	
	Incidence	N	Incidence	N	Incidence	N
Overall	84.8%	184	87.6%	177	87.1%	176
Nasopharyngitis	31.3%	68	29.7%	60	31.2%	63
Gastroenteritis	2.8%	6	5.0%	10	4.0%	8
Bronchitis	1.8%	4	4.0%	8	4.0%	8
Pharyngitis	3.7%	8	3.0%	6	2.5%	5
Influenza	1.4%	3	3.5%	7	2.5%	5
Periodontitis	1.4%	3	1.5%	3	4.5%	9
Oesophageal candidiasis	1.4%	3	0.5%	1	2.0%	4
Pneumonia	0.9%	2	0.5%	1	2.5%	5
Angina pectoris	0.5%	1	2.0%	4	1.5%	3
Cataract	3.7%	8	0.5%	1	1.5%	3
Diarrhoea	12.0%	26	7.4%	15	9.4%	19
Constipation	7.4%	16	6.4%	13	8.4%	17
Dental caries	2.8%	6	3.5%	7	1.5%	3
Gastric polyps	3.7%	8	2.5%	5	1.5%	3
Abdominal pain upper	1.8%	4	2.5%	5	2.0%	4
Haemorrhoids	3.7%	8	2.0%	4	0.5%	1
Large intestine polyp	2.3%	5	2.0%	4	1.5%	3
Enterocolitis	0.5%	1	2.5%	5	2.0%	4
Abdominal discomfort	0.5%	1	2.5%	5	1.0%	2
Periodontal disease	0.5%	1	2.5%	5	0.5%	1
Back pain	2.3%	5	4.0%	8	7.9%	16
Arthralgia	3.7%	8	3.5%	7	2.0%	4
Osteoarthritis	2.8%	6	3.5%	7	3.0%	6
Myalgia	1.4%	3	2.0%	4	2.0%	4
Pain in extremity	0.9%	2	1.5%	3	3.0%	6
Spinal osteoarthritis	2.8%	6	0.5%	1	2.0%	4
Periarthritis	0.5%	1	2.0%	4	2.0%	4
Gastric cancer	0.5%	1	1.0%	2	2.0%	4
Headache	3.2%	7	2.0%	4	2.0%	4
Benign prostatic hyperplasia	1.4%	3	2.0%	4	2.0%	4
Upper respiratory tract inflammation	4.6%	10	5.9%	12	6.4%	13
Rhinitis allergic	1.8%	4	2.5%	5	3.0%	6
Oedema peripheral	1.4%	3	2.5%	5	3.5%	7
Seasonal allergy	3.2%	7	3.5%	7	4.0%	8
Blood CK increased	4.6%	10	4.0%	8	5.4%	11
Blood TG increased	2.3%	5	4.0%	8	1.5%	3
γ-GT increased	1.8%	4	2.5%	5	2.5%	5
Blood glucose increased	1.4%	3	2.0%	4	2.5%	5
Blood iron decreased	0.9%	2	3.0%	6	2.0%	4
Fall	6.0%	13	5.4%	11	4.0%	8
Contusion	6.5%	14	3.5%	7	3.5%	7
Diabetes mellitus	4.6%	10	3.5%	7	4.0%	8
Dehydration	1.8%	4	2.0%	4	0.5%	1
Hypoglycaemia	0.9%	2	1.0%	2	2.5%	5
Eczema	3.2%	7	5.0%	10	2.5%	5
Hypertension	3.2%	7	4.0%	8	5.0%	10

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Table 59. Adverse drug reactions reported by ≥2% of subjects in any group

	LPZ 15 mg group (N = 217)		Vonoprazan 10 mg group (N = 202)		Vonoprazan 20 mg group (N = 202)	
	Incidence	N	Incidence	N	Incidence	N
Overall	24.4%	53	16.3%	33	19.3%	39
Constipation	2.8%	6	1.0%	2	3.0%	6
Diarrhoea	4.6%	10	1.0%	2	0.5%	1
Blood iron decreased	0%	0	2.0%	4	1.5%	3

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Death occurred in 1 subject (cardiac failure) of the vonoprazan 10 mg group, and a causal relationship to the study drug was ruled out for the death. Serious adverse events other than the death occurred in 15.8% (32 of 202 subjects) of the vonoprazan 10 mg group; 15.8% (32 of 202 subjects) of the vonoprazan 20 mg group; and 14.7% (32 of 217 subjects) of the LPZ 15 mg group (Table 60). A causal relationship to the study drug could not be ruled out for pancreatitis acute/diabetic nephropathy, large intestine polyp, cholelithiasis, and thrombotic cerebral infarction in 1 subject each of the vonoprazan 10 mg group, gastric cancer in 2 subjects and enterocolitis and oral fibroma in 1 subject each of the vonoprazan 20 mg group as well as pancreatitis acute, adenocarcinoma of the cervix, and renal failure acute in 1 subject each of the LPZ 15 mg group.[133] Adverse events leading to study drug discontinuation occurred in 7.9% (16 of 202 subjects) of the vonoprazan 10 mg group; 7.4% (15 of 202 subjects) of the vonoprazan 20 mg group; and 9.2% (20 of 217 subjects) of the LPZ 15 mg group.

[133] All the events of pancreatitis acute, large intestine polyp, cholelithiasis, and diabetic nephropathy in the vonoprazan 10 mg group resolved after 73, 80, 36, and 71 days of duration, respectively. The event of thrombotic cerebral infarction in the vonoprazan 10 mg group was found to be improved. All the events of gastric cancer in 2 subjects, enterocolitis, and oral fibroma in the vonoprazan 20 mg group resolved after 85, 168, 4, and 85 days of duration, respectively. All the events of pancreatitis acute, adenocarcinoma of the cervix, and renal failure acute in the LPZ group resolved after 26, 127, and 121 days of duration, respectively.

Table 60. Serious adverse events other than deaths

Treatment group	Incidence (N)	Event	
Vonoprazan 10 mg group (N = 202)	15.8% (32)	3 subjects	Angina pectoris
		2 subjects each	Large intestine polyp; gastric cancer
		1 subject each	Blood pressure increased, pancreatitis acute, convulsion, and diabetic nephropathy; anaemia, angina pectoris, renal impairment, and peripheral arterial occlusive disease; peripheral arterial occlusive disease; cardiac failure congestive; atrial fibrillation; prinzmetal angina and diabetes mellitus; diabetes mellitus; cataract; ileus; colitis ischaemic; cholangitis; pneumonia; herpes zoster; nasopharyngitis; contusion; lower limb fracture; dehydration and influenza; influenza; angina pectoris and diabetes mellitus inadequate control; adenocarcinoma gastric; bladder cancer; lung neoplasm malignant; carotid artery stenosis and cerebral infarction; thrombotic cerebral infarction; calculus urinary; cholelithiasis
Vonoprazan 20 mg group (N = 202)	15.8% (32)	4 subjects	Gastric cancer
		3 subjects	Diabetes mellitus
		2 subjects each	Angina pectoris; influenza; oesophageal carcinoma
		1 subject each	Cardiac failure; pneumonia; pneumonia and pleuropericarditis; ventricular tachycardia, chest discomfort, and intercostal neuralgia; enterocolitis; coronary artery stenosis and mallory-weiss syndrome; cataract and cardiac failure acute; coronary artery stenosis; cataract; bacterial infection; pyelonephritis; coronary artery restenosis; foot fracture; spinal compression fracture and convulsion; tooth fracture; oral fibroma; altered state of consciousness; asthma; peripheral arterial occlusive disease
LPZ 15 mg group (N = 217)	14.7% (32)	3 subjects	Coronary artery stenosis
		2 subjects	Renal failure acute and prostatitis
		1 subject each	Angina pectoris; cardiac failure, enterocolitis haemorrhagic, and pneumonia; cardiac failure congestive; myocardial infarction; myocardial ischaemia; cataract; macular degeneration; large intestine polyp; ileus; pancreatitis acute and respiratory disorder; cholangitis; bile duct stone; cholecystitis acute and joint dislocation; gastroenteritis; femur fracture; traumatic intracranial haemorrhage; diabetes mellitus; lumbar spinal stenosis; gastric cancer; adenocarcinoma of the cervix; small cell lung cancer; putamen haemorrhage; transient ischaemic attack; calculus ureteric and carotid artery stenosis; pneumothorax; aortic dissection; hypotension

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Regarding efficacy,[134] the recurrence rate of gastric or duodenal ulcer127 was as shown in Table 61.

Table 61. Recurrence rate of gastric or duodenal ulcer (FAS)

After the study treatment start[a)]		LPZ 15 mg group (N = 217)	Vonoprazan 10 mg group (N = 202)	Vonoprazan 20 mg group (N = 202)
Week 52	No. of subjects with recurrence	6	1	3
	Recurrence rate (%) [95% CI]	2.8 [1.0, 6.0]	0.5 [0.0, 2.8]	1.5 [0.3, 4.4]
	Difference from the LPZ 15 mg group (%) [95% CI]	-	-2.3 [-4.7, 0.1]	-1.3 [-4.1, 1.5]
Week 76	No. of subjects with recurrence	7	1	3
	Recurrence rate (%) [95% CI]	3.3 [1.3, 6.7]	0.5 [0.0, 2.8]	1.5 [0.3, 4.4]
	Difference from the LPZ 15 mg group (%) [95% CI]	-	-2.8 [-5.4, -0.2]	-1.8 [-4.7, 1.2]
Week 104	No. of subjects with recurrence	7	1	3
	Recurrence rate (%) [95% CI]	3.3 [1.3, 6.7]	0.5 [0.0, 2.8]	1.5 [0.3, 4.4]
	Difference from the LPZ 15 mg group (%) [95% CI]	-	-2.8 [-5.4, -0.2]	-1.8 [-4.7, 1.2]

a) Total treatment period including that in Study CCT-302

[134] The efficacy analysis was performed using pooled data from this study and data from Study CCT-302.

4.(iii).A.(10) Phase III long-term treatment study in patients with LDA ulcer (5.3.5.2-2, Study TAK-438/OCT-304 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A multi-center, uncontrolled, open-label study was conducted at 12 centers in Japan to investigate the safety of vonoprazan in patients who had a medical history of gastric or duodenal ulcer,[124] had to take LDA for a long period of time, and were aged ≥20 years[125] (target sample size: 160 subjects).

Vonoprazan 20 mg was to be orally administered once daily after breakfast for up to 24 weeks.[135]

All of the 27 subjects treated[136] were included in the FAS and safety analysis set, and the FAS was used for the primary efficacy analysis.

Adverse events occurred in 77.8% (21 of 27 subjects), and adverse events reported by ≥2 subjects were haemorrhoids and nasopharyngitis at 11.1% each (3 of 27 subjects) as well as hepatic steatosis and diabetes mellitus at 7.4% each (2 of 27 subjects). Adverse drug reactions occurred in 3.7% (1 of 27 subjects, liver function test abnormal).

No deaths were reported. Serious adverse events occurred in 3.7% (1 of 27 subjects, bile duct stone), but a causal relationship to the study drug was ruled out for the event. Adverse events leading to study drug discontinuation occurred in 14.8% (4 of 27 subjects).

The recurrence rate127 of gastric or duodenal ulcer in Week 24 [95% CI] was 0.0% [0.0%, 13.2%] (0 of 26 subjects).

4.(iii).A.(11) Phase III study in patients with NSAID ulcer (5.3.5.1-8, Study TAK-438/CCT-301 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A multi-center, randomized, active-controlled, double-blind, parallel-group study was conducted at 129 centers in Japan to investigate the efficacy and safety of vonoprazan in patients who had a medical history of gastric or duodenal ulcer,[124] had to receive NSAID for a long period of time,[137] and were aged ≥20 years (target sample size: 630 subjects in total; 210 subjects/group).

Vonoprazan 10 mg or 20 mg or LPZ 15 mg was to be orally administered once daily after breakfast for up to 24 weeks.[138]

Of all the 641 subjects treated (218 subjects in the vonoprazan 10 mg group, 212 subjects in the vonoprazan 20 mg group, 211 subjects in the LPZ 15 mg group), 640 subjects (218 subjects in the vonoprazan 10 mg group, 212 subjects in the vonoprazan 20 mg group, 210 subjects in the LPZ 15 mg group) excluding 1 subject (critical violation of GCP[139]) were included in the FAS and safety analysis set, and the FAS was used for the primary efficacy analysis.

The recurrence rate[127] of gastric or duodenal ulcer in Week 24, the primary endpoint, was as shown in Table 62. Non-inferiority of either vonoprazan group to the LPZ 15 mg group was verified ($P < 0.0001$ for either comparison, non-inferiority Farrington and Manning test, one-sided significance level of 2.5%, the multiplicity of the test adjusted in accordance with the closed testing procedure).

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135 The study treatment was terminated when recurrence of ulcer was endoscopically confirmed.

136 The study was terminated earlier before its target sample size was reached, because its objective was to collect data from a total of 300 subjects treated for 6 months including those in Study CCT-302.

137 Patients who have to continue receiving NSAID (including aspirin ≥1000 mg/day) to control pain due to rheumatoid arthritis, osteoarthritis, etc. In principle, the type of NSAID as well as its dosage and administration were to remain unchanged during the study period.

138 The study treatment was terminated when recurrence of ulcer was endoscopically confirmed.

139 Study initiated by a physician who was not under contract

Table 62. Recurrence rate of gastric or duodenal ulcer in Week 24 (FAS)[a)]

Treatment group	No. of subjects with recurrence	Recurrence rate (%) [95% CI]	Difference from the LPZ 15 mg group (%) [95% CI]	*P* value[b)]
LPZ 15 mg group (N = 199)	11	5.5 [2.8, 9.7]	-	-
Vonoprazan 10 mg group (N = 209)	7	3.3 [1.4, 6.8]	-2.2 [-6.2, 1.8]	$P < 0.0001$
Vonoprazan 20 mg group (N = 203)	7	3.4 [1.4, 7.0]	-2.1 [-6.1, 2.0]	$P < 0.0001$

a) Of the FAS, patients who did not undergo endoscopy post-dose (9 subjects in the LPZ 15 mg group, 3 subjects in the vonoprazan 10 mg group, 7 subjects in the vonoprazan 20 mg group) and patients who received diagnosis of gastric or duodenal ulcer at the baseline endoscopy (central assessment committee) (2 subjects in the LPZ 15 mg group, 6 subjects in the vonoprazan 10 mg group, 2 subjects in the vonoprazan 20 mg group) were excluded from the analysis.

b) Non-inferiority Farrington and Manning test, non-inferiority margin of 8.3%, one-sided significance level of 2.5%, and the multiplicity of the test was adjusted in accordance with the closed testing procedure.

Adverse events occurred in 71.6% (156 of 218 subjects) of the vonoprazan 10 mg group; 71.7% (152 of 212 subjects) of the vonoprazan 20 mg group; and 76.7% (161 of 210 subjects) of the LPZ 15 mg group. Adverse drug reactions occurred in 15.6% (34 of 218 subjects) of the vonoprazan 10 mg group; 17.5% (37 of 212 subjects) of the vonoprazan 20 mg group; and 14.3% (30 of 210 subjects) of the LPZ 15 mg group. Adverse events and adverse drug reactions reported by ≥2% of subjects in any group are as shown in Table 63 and Table 64, respectively.

Table 63. Adverse events reported by ≥2% of subjects in any group

	LPZ 15 mg group (N = 210)		Vonoprazan 10 mg group (N = 218)		Vonoprazan 20 mg group (N = 212)	
	Incidence	N	Incidence	N	Incidence	N
Overall	76.7%	161	71.6%	156	71.7%	152
Nasopharyngitis	18.6%	39	22.9%	50	18.4%	39
Gastroenteritis	2.9%	6	1.8%	4	2.8%	6
Pharyngitis	3.3%	7	0.5%	1	1.4%	3
Bronchitis	1.0%	2	2.8%	6	0.5%	1
Diarrhoea	5.2%	11	3.7%	8	5.2%	11
Constipation	2.4%	5	5.0%	11	0.9%	2
Stomatitis	1.9%	4	4.1%	9	1.9%	4
Dental caries	1.9%	4	2.3%	5	0.9%	2
Abdominal pain upper	0.5%	1	2.3%	5	0%	0
Back pain	1.9%	4	1.4%	3	4.2%	9
Rheumatoid arthritis	4.3%	9	0.9%	2	1.9%	4
Periarthritis	0.5%	1	2.3%	5	1.4%	3
Pain in extremity	0.5%	1	0.9%	2	2.4%	5
Upper respiratory tract inflammation	2.9%	6	1.8%	4	5.2%	11
Rhinitis allergic	1.9%	4	0.9%	2	2.4%	5
Seasonal allergy	1.0%	2	2.3%	5	2.8%	6
Blood CK increased	3.8%	8	3.2%	7	3.3%	7
Diabetes mellitus	0.5%	1	0.9%	2	2.8%	6
Contusion	5.7%	12	4.6%	10	4.2%	9
Fall	4.8%	10	5.0%	11	4.7%	10
Procedural haemorrhage	0.5%	1	3.7%	8	2.4%	5
Eczema	1.9%	4	3.2%	7	1.9%	4
Dermatitis contact	1.4%	3	0.9%	2	3.3%	7

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Table 64. Adverse drug reactions reported by ≥2% of subjects in any group

	LPZ 15 mg group (N = 210)		Vonoprazan 10 mg group (N = 218)		Vonoprazan 20 mg group (N = 212)	
	Incidence	N	Incidence	N	Incidence	N
Overall	14.3%	30	15.6%	34	17.5%	37
Diarrhoea	2.9%	6	0.9%	2	0.9%	2
Constipation	1.4%	3	2.3%	5	0.5%	1

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Death occurred in 1 subject (cardiac tamponade due to aortic dissection) of the vonoprazan 20 mg group, but a causal relationship to the study drug was ruled out. Other than the death, serious adverse events occurred in 4.1% (9 of 218 subjects) of the vonoprazan 10 mg group; 5.2% (11 of 212 subjects) of the vonoprazan 20 mg group; and 4.8% (10 of 210 subjects) of the LPZ 15 mg group (Table 65). A causal relationship to the study drug could not be ruled out for aortic valve incompetence in 1 subject of the vonoprazan 10 mg group and muscular weakness in 1 subject of the vonoprazan 20 mg group.[140] Adverse events leading to study drug discontinuation occurred in 2.3% (5 of 218 subjects) of the vonoprazan 10 mg group; 7.1% (15 of 212 subjects) of the vonoprazan 20 mg group; and 5.7% (12 of 210 subjects) of the LPZ 15 mg group.

Table 65. Serious adverse events other than death

Treatment group	Incidence (N)	Event term	
Vonoprazan 10 mg group (N = 218)	4.1% (9)	1 subject each	Aortic valve incompetence, haemorrhoids, procedural haemorrhage, subdural haematoma, hypoglycaemia, breast cancer, neuralgia, syncope, thrombophlebitis
Vonoprazan 20 mg group (N = 212)	5.2% (11)	1 subject each	Impaired healing and spinal compression fracture; cholangitis and cholecystitis; gastroenteritis; femoral neck fracture; lumbar spinal stenosis; muscular weakness; spinal osteoarthritis; cerebral haemorrhage; cervical myelopathy; dizziness postural; interstitial lung disease
LPZ 15 mg group (N = 210)	4.8% (10)	1 subject each	Anal skin tags; hepatitis E; intentional overdose and altered state of consciousness; road traffic accident and renal injury; back pain; acute myeloid leukaemia; gastric cancer; cerebral haemorrhage; myelopathy; interstitial lung disease

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4.(iii).A.(12) Phase III extension study in patients with NSAID ulcer (5.3.5.1-10, Study TAK-438/OCT-301 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A multi-center, randomized, active-controlled, single-blind,[141] parallel-group study was conducted at 117 centers in Japan to investigate the safety of vonoprazan in patients who completed Study CCT-301[142] (target sample size: 420 subjects in total; 140 subjects per group).

Vonoprazan 10 mg or 20 mg or LPZ 15 mg was to be orally administered once daily after breakfast and the duration of treatment was 28 to 80 weeks.[143]

Of all the 641 subjects treated in Study CCT-301, 406 subjects (148 subjects in the vonoprazan 10 mg group, 137 subjects in the vonoprazan 20 mg group, 121 subjects in the LPZ 15 mg group) were transferred to this study, and all of the 406 subjects received the study drug. In the FAS and safety analysis set of this study, 640 subjects (218 subjects in the vonoprazan 10 mg group, 212 subjects in the vonoprazan 20 mg group, 210 subjects in the LPZ 15 mg group) were included as done in Study CCT-301. The FAS was used for the primary efficacy analysis.

Regarding safety,[144] adverse events occurred in 84.4% (184 of 218 subjects) of the vonoprazan 10 mg group; 82.5% (175 of 212 subjects) of the vonoprazan 20 mg group; and 88.1% (185 of 210 subjects) of the LPZ 15 mg group. Adverse drug reactions occurred in 17.4% (38 of 218 subjects) of the vonoprazan 10 mg group; 17.5% (37 of 212 subjects) of the vonoprazan 20 mg group; and 19.0% (40 of 210 subjects) of the LPZ 15 mg group. Adverse events and adverse drug reactions reported by ≥2% of subjects in any group are as shown in Table 66 and Table 67, respectively.

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[140] Both events of aortic valve incompetence in the vonoprazan 10 mg group and muscular weakness in the vonoprazan 20 mg group resolved after 121 and 119 days of duration, respectively.

[141] The Study CCT-301 was conducted double-blind until unblinding and then the study was continued to be conducted single-blind, keeping the study drug unkown to the study centers until the end of the study.

[142] Patients in whom non-recurrence of gastric or duodenal ulcer was endoscopically confirmed in Week 24 in Study CCT-301

[143] The duration of treatment is 52 to 104 weeks from the first dose of the study drug in Study CCT-301. The treatment was terminated when the recurrence of the ulcer was confirmed.

[144] The safety analysis was performed using pooled data from this study and data from Study CCT-301.

Table 66. Adverse events reported by ≥2% of subjects in any group

	LPZ 15 mg group (N = 210)		Vonoprazan 10 mg group (N = 218)		Vonoprazan 20 mg group (N = 212)	
	Incidence	N	Incidence	N	Incidence	N
Overall	88.1%	185	84.4%	184	82.5%	175
Nasopharyngitis	29.0%	61	32.1%	70	27.8%	59
Gastroenteritis	4.8%	10	4.6%	10	3.3%	7
Pharyngitis	3.8%	8	2.8%	6	1.9%	4
Bronchitis	1.0%	2	4.6%	10	3.3%	7
Influenza	1.4%	3	1.8%	4	2.4%	5
Cystitis	0.5%	1	1.8%	4	2.4%	5
Enteritis infectious	1.9%	4	2.3%	5	0.5%	1
Dry eye	1.9%	4	0.9%	2	2.4%	5
Conjunctivitis	0.5%	1	2.3%	5	1.4%	3
Diarrhoea	6.7%	14	5.0%	11	7.1%	15
Constipation	2.4%	5	6.9%	15	3.3%	7
Stomatitis	3.3%	7	5.0%	11	1.9%	4
Dental caries	5.2%	11	2.8%	6	1.9%	4
Gastric polyps	2.4%	5	1.8%	4	1.9%	4
Gastrooesophageal reflux disease	2.4%	5	1.8%	4	1.9%	4
Nausea	1.9%	4	2.3%	5	1.9%	4
Haemorrhoids	1.0%	2	2.3%	5	0.9%	2
Abdominal pain upper	1.0%	2	2.8%	6	0.0%	0
Oedema peripheral	1.0%	2	3.2%	7	2.8%	6
Back pain	2.9%	6	3.2%	7	6.1%	13
Rheumatoid arthritis	4.8%	10	2.8%	6	2.8%	6
Osteoarthritis	3.8%	8	2.8%	6	3.3%	7
Arthralgia	2.9%	6	1.8%	4	3.8%	8
Periarthritis	1.0%	2	2.3%	5	2.4%	5
Spinal osteoarthritis	1.0%	2	1.8%	4	2.8%	6
Pain in extremity	0.5%	1	2.3%	5	2.4%	5
Lumbar spinal stenosis	0.0%	0	0.5%	1	2.8%	6
Dizziness	2.4%	5	3.2%	7	0.9%	2
Headache	1.4%	3	1.4%	3	2.4%	5
Insomnia	1.9%	4	2.8%	6	1.4%	3
Upper respiratory tract inflammation	3.3%	7	5.5%	12	6.6%	14
Rhinitis allergic	2.9%	6	2.3%	5	3.8%	8
Seasonal allergy	3.8%	8	3.7%	8	7.1%	15
Blood CK increased	5.2%	11	4.1%	9	3.3%	7
Blood iron decreased	2.4%	5	1.8%	4	1.9%	4
Blood TG increased	1.9%	4	1.8%	4	2.4%	5
Blood pressure increased	1.0%	2	1.4%	3	2.4%	5
Diabetes mellitus	1.0%	2	0.9%	2	2.8%	6
Fall	8.6%	18	10.1%	22	8.5%	18
Contusion	9.5%	20	7.8%	17	6.6%	14
Ligament sprain	2.9%	6	3.7%	8	2.4%	5
Procedural haemorrhage	1.4%	3	4.1%	9	3.3%	7
Road traffic accident	2.4%	5	1.4%	3	0.5%	1
Spinal compression fracture	0.0%	0	2.3%	5	1.4%	3
Procedural complication	0.5%	1	2.3%	5	0.5%	1
Hypertension	2.9%	6	1.4%	3	2.8%	6
Eczema	5.7%	12	4.6%	10	3.8%	8
Dermatitis contact	2.9%	6	3.7%	8	5.7%	12

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Table 67. Adverse drug reactions reported by ≥2% of subjects in any group

	LPZ 15 mg group (N = 210)		Vonoprazan 10 mg group (N = 218)		Vonoprazan 20 mg group (N = 212)	
	Incidence	N	Incidence	N	Incidence	N
Overall	19.0%	40	17.4%	38	17.5%	37
Diarrhoea	2.9%	6	1.4%	3	0.9%	2
Constipation	1.4%	3	2.3%	5	0.5%	1

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No deaths occurred except for 1 subject in the vonoprazan 20 mg group in Study CCT-301. Other than the death, serious adverse events occurred in 8.3% (18 of 218 subjects) of the vonoprazan 10 mg group; 13.7% (29 of 212 subjects) of the vonoprazan 20 mg group; and 8.6% (18 of 210 subjects) of the LPZ 15 mg group (Table 68). A causal relationship to the study drug could not be ruled out for aortic valve incompetence and putamen haemorrhage in 1 subject each of the vonoprazan 10 mg group and subcutaneous abscess and muscular weakness in 1 subject each of the vonoprazan 20 mg group.[145]

Table 68. Serious adverse events other than death

Treatment group	Incidence (N)	Event term	
Vonoprazan 10 mg group (N = 218)	8.3% (18)	1 subject each	Angina pectoris and procedural haemorrhage; aortic valve incompetence; colitis ischaemic; diverticulitis intestinal haemorrhagic; haemorrhoids; oesophageal dysplasia; herpes virus infection and cerebral infarction; spinal compression fracture; patella fracture; ligament rupture; subdural haematoma and cubital tunnel syndrome; hypoglycaemia; breast cancer; neuralgia; putamen haemorrhage; syncope; calculus ureteric; thrombophlebitis
Vonoprazan 20 mg group (N = 212)	13.7% (29)	2 subjects each	Intervertebral disc protrusion, lumbar spinal stenosis, interstitial lung disease
		1 subject each	Cardiac failure chronic; sudden hearing loss and vertigo; cataract and glaucoma; intestinal obstruction; large intestine polyp; impaired healing and spinal compression fracture; spinal compression fracture; cholangitis and cholecystitis; gastroenteritis; pneumonia mycoplasmal and spinal osteoarthritis; subcutaneous abscess; patella fracture; femoral neck fracture; snake bite; osteoarthritis; muscular weakness; periarthritis; rheumatoid arthritis; spinal osteoarthritis and gastric cancer; cerebral haemorrhage; cervical myelopathy; dizziness postural; subarachnoid haemorrhage
LPZ 15 mg group (N = 210)	8.6% (18)	2 subjects	Osteoarthritis
		1 subject each	Anal skin tags; enterocolitis; hepatitis E; intentional overdose and altered state of consciousness; road traffic accident and renal injury; occult blood positive; intervertebral disc protrusion; back pain; gastric cancer; acute myeloid leukaemia; pharyngeal neoplasm; cerebral haemorrhage; myelopathy; interstitial lung disease; pneumothorax; varicose vein

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Regarding efficacy,[146] the recurrence rate of gastric or duodenal ulcer[127] was as shown in Table 69.

[145] The event of aortic valve incompetence in the vonoprazan 10 mg group resolved after 121 days of duration. The event of putamen haemorrhage in the same group occurred on Day 328 of the study treatment and then resolved (after 255 days of duration) with sequelae. The subject was receiving warfarin for atrial fibrillation and experienced blood pressure increased (157/100 mmHg) 3 weeks before the event. Both events of subcutaneous abscess and muscular weakness in the vonoprazan 20 mg group resolved after 62 and 119 days of duration, respectively.

[146] The efficacy analysis was performed using pooled data from this study and data from Study CCT-301.

Table 69. Recurrence rate of gastric or duodenal ulcer (FAS)

After the study treatment start[a)]		LPZ 15 mg group (N = 199)	Vonoprazan 10 mg group (N = 209)	Vonoprazan 20 mg group (N = 203)
Week 52	No. of subjects with recurrence	14	8	11
	Recurrence rate (%) [95% CI]	7.0 [3.9, 11.5]	3.8 [1.7, 7.4]	5.4 [2.7, 9.5]
	Difference from the LPZ 15 mg group (%) [95% CI][a)]	-	-3.2 [-7.6, 1.2]	-1.6 [-6.3, 3.1]
Week 76	No. of subjects with recurrence	15	8	12
	Recurrence rate (%) [95% CI]	7.5 [4.3, 12.1]	3.8 [1.7, 7.4]	5.9 [3.1, 10.1]
	Difference from the LPZ 15 mg group (%) [95% CI][a)]	-	-3.7 [-8.2, 0.8]	-1.6 [-6.5, 3.3]
Week 104	No. of subjects with recurrence	15	8	12
	Recurrence rate (%) [95% CI]	7.5 [4.3, 12.1]	3.8 [1.7, 7.4]	5.9 [3.1, 10.1]
	Difference from the LPZ 15 mg group (%) [95% CI]	-	-3.7 [-8.2, 0.8]	-1.6 [-6.5, 3.3]

a) Total treatment period including that in Study CCT-301

4.(iii).A.(13) Phase III long-term treatment study in patients with NSAID ulcer (5.3.5.2-3, Study TAK-438/OCT-303 [[redacted] to [redacted]])

A multi-center, uncontrolled, open-label study was conducted at 13 centers in Japan to investigate the safety of vonoprazan in patients who had a medical history of gastric or duodenal ulcer,[124] had to receive NSAID for a long period of time, and were aged ≥20 years[137] (target sample size: 175 subjects).

Vonoprazan 20 mg was to be orally administered once daily after breakfast for up to a maximum of 24 weeks.[147]

All of the 30 subjects treated[148] were included in the FAS and safety analysis set, and the FAS was used for the primary efficacy analysis.

Adverse events occurred in 73.3% (22 of 30 subjects), and adverse events reported by ≥2 subjects were nasopharyngitis at 30.0% (9 of 30 subjects), and diarrhoea, chest pain, oral herpes, muscle spasms, and upper respiratory tract inflammation at 6.7% each (2 of 30 subjects). Adverse drug reactions occurred in 10.0% (3 of 30 subjects; constipation, diarrhoea, and blood iron decreased in 1 subject each).

No deaths were reported. Serious adverse events occurred in 3.3% (1 of 30 subjects, colitis ischaemic), but a causal relationship to the study drug was ruled out for the event.

The recurrence rate127 of gastric or duodenal ulcer at Week 24 [95% CI] was 3.6% (1 of 28 subjects) [0.1%, 18.3%].

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Efficacy

Based on the review in the following sections 4.(iii).B.(1).1) to 4.(iii).B.(1).6), PMDA considers that the submitted data have demonstrated the efficacy of vonoprazan in the treatment and maintenance therapy for RE, treatment for gastric ulcer and duodenal ulcer, adjunct to *H. pylori* eradication, and prevention of recurrent gastric or duodenal ulcer during LDA or NSAID administration.

A final evaluation on the efficacy of vonoprazan will be made, taking account of comments raised in the Expert Discussion.

147 The study treatment was terminated when recurrence of ulcer was endoscopically confirmed.

148 The study was terminated earlier before the target sample size was reached, because its objective was to collect data from a total of 300 subjects treated for 6 months including those in Study CCT-301.

4.(iii).B.(1).1) RE

(a) Treatment for RE

i) RE cure rate at Week 8

The RE cure rate at Week 8 in the FAS, the primary endpoint in Study CCT-002, was as shown in Table 39 [see "4.(iii).A.(2) Phase III study of the treatment for RE"]. Non-inferiority of the vonoprazan 20 mg group to the LPZ 30 mg group was verified. Based on the above, PMDA considers that the efficacy of vonoprazan at 20 mg in the treatment for RE was demonstrated.

ii) RE cure rate by patient characteristic

The results of analysis on the RE cure rate at Week 8 in Study CCT-002 in each subgroup stratified according to age, gender, baseline RE severity under LA classification, presence or absence of *H. pylori* infection, and CYP2C19 genotype are as shown in Table 70. PMDA confirmed that in each subgroup, the RE cure rate at Week 8 in the vonoprazan 20 mg group did not tend to be inferior to that in the LPZ 30 mg group.

Table 70. RE cure rate at Week 8 in each subgroup in Study CCT-002 (FAS)

Stratification factor	Category	LPZ 30 mg group (N = 199)	Vonoprazan 20 mg group (N = 205)
Age	<65 years	97.0% (129/133)	99.2% (128/129)
	≥65 years and <75 years	92.0% (46/50)	98.0% (49/50)
	≥75 years	93.8% (15/16)	100.0% (26/26)
Gender	Male	96.7% (148/153)	98.5% (135/137)
	Female	91.3% (42/46)	100.0% (68/68)
LA classification at the baseline	Grade A and B	100.0% (127/127)	99.2% (129/130)
	Grade C and D	87.5% (63/72)	98.7% (74/75)
H. pylori infection	Presence	94.4% (17/18)	97.0% (32/33)
	Absence	95.6% (173/181)	99.4% (171/172)
CYP2C19 genotype	EM	94.5% (155/164)	98.9% (179/181)
	PM	100.0% (35/35)	100.0% (24/24)

(b) Maintenance therapy for RE

i) Recurrence rate of RE

In Study CCT-003, the recurrence rate of RE in Week 24 of the maintenance period in the FAS, the primary endpoint, was as shown in Table 41 [see "4.(iii).A.(3). Phase III study of the maintenance therapy for RE"]. Non-inferiority of the vonoprazan 10 mg group and 20 mg group to the LPZ 15 mg group was verified. The recurrence rate of RE at Week 24 and 52 in Study OCT-001 was as shown in Table 45 [see "4.(iii).A.(4) Phase III long-term treatment study of the maintenance therapy for RE"]. In either vonoprazan 10 mg group or 20 mg group, the recurrence rate of RE did not tend to increase remarkably with the increasing treatment period of vonoprazan. Based on the above, PMDA considers that the efficacy of vonoprazan at 10 mg and 20 mg in the maintenance therapy for RE was demonstrated.

ii) Recurrence rate of RE by patient characteristic

The results of analysis on the recurrence rate of RE at Week 24 of the maintenance period in Study CCT-003 in each subgroup stratified according to age, gender, baseline RE severity under LA classification, presence or absence of *H. pylori* infection, CYP2C19 genotype, presence or absence of oesophageal hiatal hernia, and body mass index at the baseline were as shown in Table 71. PMDA confirmed that in each subgroup, the recurrence rate of RE at Week 24 in the vonoprazan 10 mg group or vonoprazan 20 mg group did not tend to be inferior to that in the LPZ 30 mg group.

Table 71. Recurrence rate of RE at Week 24 in each subgroup in Study CCT-003 (FAS)

Stratification factor	Category	LPZ 15 mg group (N = 196)	Vonoprazan 10 mg group (N = 197)	Vonoprazan 20 mg group (N = 201)
Age	<65 years	14.4% (19/132)	4.3% (6/139)	0.0% (0/136)
	≥65 years and <75 years	21.7% (10/46)	7.0% (3/43)	7.0% (3/43)
	≥75 years	22.2% (4/18)	6.7% (1/15)	4.5% (1/22)
Gender	Male	13.9% (19/137)	6.3% (10/159)	1.3% (2/159)
	Female	23.7% (14/59)	0.0% (0/38)	4.8% (2/42)
LA classification at baseline	Grade A and B	11.0% (17/155)	3.1% (5/159)	1.3% (2/158)
	Grade C and D	39.0% (16/41)	13.2% (5/38)	4.7% (2/43)
H. pylori infection	Presence	3.7% (1/27)	2.7% (1/37)	0.0% (0/22)
	Absence	18.9% (32/169)	5.6% (9/160)	2.2% (4/179)
CYP2C19 genotype	EM	19.6% (31/158)	5.4% (9/166)	1.8% (3/168)
	PM	5.3% (2/38)	3.2% (1/31)	3.0% (1/33)
Oesophageal hiatal hernia	Presence (≥2 cm)	38.7% (12/31)	11.9% (5/42)	4.3% (2/46)
	Presence (<2 cm)	14.9% (15/101)	4.1% (4/98)	0.9% (1/112)
	Absence	9.4% (6/64)	1.8% (1/57)	2.4% (1/42)
BMI	<18.5 kg/m^2	0.0% (0/1)	0.0% (0/3)	0.0% (0/0)
	≥18.5 kg/m^2 and <25.0 kg/m^2	9.9% (11/111)	3.6% (4/110)	2.8% (3/109)
	≥25.0 kg/m^2	26.2% (22/84)	7.1% (6/84)	1.1% (1/92)

4.(iii).B.(1).2) Gastric ulcer

(a) Gastric ulcer cure rate at Week 8

The gastric ulcer cure rate at Week 8 in the FAS, the primary endpoint in Study CCT-101, was as shown in Table 46 [see "4.(iii).A.(5) Phase III study in patients with gastric ulcer"]. Non-inferiority of the vonoprazan 20 mg group to the LPZ 30 mg group was verified. Based on the above, PMDA considers that the efficacy of vonoprazan at 20 mg in the treatment for gastric ulcer was demonstrated.

(b) Gastric ulcer cure rate by patient characteristic

The results of analysis on the gastric ulcer cure rate at Week 8 in Study CCT-101 in each subgroup stratified according to age, gender, use of LDA or NSAID (excluding external medicines) at the onset of the concerned ulcer, presence or absence of *H. pylori* infection, and CYP2C19 genotype were as shown in Table 72. PMDA confirmed that in each subgroup, the gastric ulcer cure rate until Week 8 in the vonoprazan 20 mg group did not tend to be inferior to that in the LPZ 30 mg group.

Table 72. Cure rate until Week 8 in each subgroup in Study CCT-101 (FAS)

Stratification factor	Category	LPZ 30 mg group (N = 225)	Vonoprazan 20 mg group (N = 231)
Age	<65 years	95.3% (143/150)	95.7% (156/163)
	≥65 years and <75 years	93.8% (45/48)	89.6% (43/48)
	≥75 years	85.2% (23/27)	85.0% (17/20)
Gender	Males	93.8% (151/161)	95.5% (150/157)
	Females	93.8% (60/64)	89.2% (66/74)
Use of LDA or NSAID at the onset of the concerned ulcer	Presence (previously used)	87.5% (14/16)	93.8% (15/16)
	Presence (used at the baseline)	88.9% (24/27)	85.0% (17/20)
	Absence	95.1% (173/182)	94.4% (184/195)
H. pylori infection	Presence	95.1% (176/185)	95.0% (189/199)
	Absence	87.5% (35/40)	84.4% (27/32)
CYP2C19 genotype	EM	94.3% (182/193)	94.7% (180/190)
	PM	90.6% (29/32)	90.0% (36/40)

4.(iii).B.(1).3) Duodenal ulcer

(a) Duodenal ulcer cure rate at Week 6

The duodenal ulcer cure rate until Week 6 in the FAS, the primary endpoint in Study CCT-102, was as shown in Table 48 [see "4.(iii).A.(6) Phase III study in patients with duodenal ulcer"]. Non-inferiority of the vonoprazan 20 mg group to the LPZ 30 mg group was not statistically verified.

The applicant explained the failure to statisticaly verify the vonoprazan 20 mg group is non-inferior to the LPZ 30 mg group in the FAS as follows:
In Study CCT-102, the ulcer was not cured in 8 subjects in the vonoprazan 20 mg group, of whom 1 subject completed the 6-week treatment, and 7 subjects discontinued the treatment[149]; and not cured in 3 subjects in the LPZ 30 mg group, of whom 1 subject completed the 6-week treatment and 2 subjects discontinued the treatment.[150] More patients in the vonoprazan 20 mg group than in the LPZ 30 mg group discontinued the treatment irrespective of the drug effect. The short period of study treatment, 1 to 18 days, in these discontinued subjects have possibly contributed to the uncured status.

The analysis result on the cure rate was possibly affected by the larger number of discontinued subjects with shorter study treatment period in the vonoprazan 20 mg group than that in the LPZ 30 mg group. Not only the secondary analysis in the per protocol set (PPS)[151] but also the additional analysis of patients who completed the study treatment in the FAS confirmed the non-inferiority of the vonoprazan 20 mg group to the LPZ 30 mg group (Table 73). The analyses in the FAS, PPS, and a part of the patients of the FAS who completed the study treatment were performed excluding a particular category of the patients. Such exclusion possibly compromised the comparability. A sensitivity analysis was therefore additionally performed by regarding the patients excluded from the FAS as those with uncured ulcer. As a result, the difference [95% CI] between the vonoprazan 20 mg group and LPZ 30 mg group was -2.8 [-7.3, 1.8], which was comparable to the result of the analysis in the FAS (Table 73).

Based on the above, the duodenal ulcer cure rate in the vonoprazan 20 mg group was not clinically different from that in the LPZ 30 mg group.

Table 73. Duodenal ulcer cure rate at Week 6 in each analysis set in Study CCT-102

	Treatment group	No. of subjects with cured duodenal ulcer	Cure rate (%) [95% CI]	Difference from the LPZ 30 mg group (%) [95% CI]	*P* value[c)]
FAS[a)]	LPZ 30 mg group (N = 180)	177	98.3 [95.2, 99.7]	-	-
	Vonoprazan 20 mg group (N = 178)	170	95.5 [91.3, 98.0]	-2.8 [-6.4, 0.7]	*P* = 0.0654
PPS	LPZ 30 mg group (N = 176)	174	98.9 [96.0, 99.9]	-	-
	Vonoprazan 20 mg group (N = 173)	168	97.1 [93.4, 99.1]	-1.8 [-4.7, 1.2]	*P* = 0.0171
FAS (patients who completed the study treatment)	LPZ 30 mg group (N = 178)	177	99.4 [96.9, 100.0]	-	-
	Vonoprazan 20 mg group (N = 171)	170	99.4 [96.8, 100.0]	-0.0 [-1.6, 1.6]	*P* = 0.0008
FAS[b)] (sensitivity analysis)	LPZ 30 mg group (N = 184)	177	96.2 [92.3, 98.5]	-	-
	Vonoprazan 20 mg group (N = 182)	170	93.4 [88.8, 96.5]	-2.8 [-7.3, 1.8]	*P* = 0.0960

a) Of the FAS, patients who did not undergo endoscopy post-dose (4 subjects in the LPZ 30 mg group, 4 subjects in the vonoprazan 20 mg group) were excluded from the analysis.
b) The patients excluded from the primary analysis in the FAS were considered as patients with uncured ulcer.
c) Non-inferiority Farrington and Manning test, one-sided significance level of 2.5%

PMDA considers as follows:

149 Pretreatment event or adverse event (a causal relationship to the study drug was ruled out in any event) in 3 subjects, unable to follow-up in 2 subjects, critical protocol deviation in 1 subject, and spontaneous discontinuation in 1 subject

150 Critical protocol deviation, 1 subject; and abnormal laboratory finding at the baseline of the study treatment, 1 subject

151 Analysis set included all the subjects in the FAS except for 3 subjects (violation of the inclusion/exclusion criteria; 2 subjects in the vonoprazan 20 mg group, 1 subject in the LPZ 30 mg group), 1 subject (violation of the dosing regimen of the study drug; 1 subject in the vonoprazan 20 mg group), 13 subjects (violation of the prohibited concomitant drugs; 6 subjects in the vonoprazan 20 mg group, 7 subjects in the LPZ 30 mg group), and 8 subjects (not subjected to endoscopy; 4 subjects in the vonoprazan 20 mg group, 4 subjects in the LPZ 30 mg group).

The primary analysis in the FAS did not statistically verify non-inferiority of the vonoprazan 20 mg group to the LPZ 30 mg group, but the cure rate [95% CI] in the vonoprazan 20 mg group was 95.5% [91.3, 98.0], indicating clinically sufficient efficacy. The analyses in the PPS and in a part of the patients of the FAS who completed the study treatment were performed to exclude the effect of the study treatment discontinuation and demonstrated that the lower limit of 95% confidence interval of the difference between the vonoprazan 20 mg group and the LPZ 30 mg group was above -6%, although it should be noted that these analyses were performed as the secondary and additional analyses. Furthermore, the sensitivity analysis was performed by regarding the patients excluded from the FAS as patients with uncured ulcer. As a result, the point estimate of the difference between the vonoprazan 20 mg group and the LPZ 30 mg group and the lower limit of the 95% confidence interval was -2.8% and -7.3%, respectively, which were comparable to the results of the primary analysis in the FAS. The lower limit of 95% confidence interval of the difference between these groups was not considerably lower than -6%. Non-inferiority of vonoprazan to LPZ has also been verified in treatment for the gastric-acid-related diseases such as gastric ulcer listed in this application, demonstrating its efficacy. Based on the above points, the ulcer cure effect on duodenal ulcer in the vonoprazan 20 mg group did not tend to be clinically significantly inferior to that in the LPZ 30 mg group. PMDA therefore considered that vonoprazan has an efficacy in patients with duodenal ulcer as well. A final decision will be made, taking account of comments raised in the Expert Discussion.

(b) Duodenal ulcer cure rate by patient characteristic

The results of the analysis on the duodenal ulcer cure rate at Week 6 in Study CCT-102 in each subgroup stratified according to age, gender, use of LDA or NSAID (excluding external medicines) at the onset of the concerned ulcer, presence or absence of *H. pylori* infection, CYP2C19 genotype, and size of the duodenal ulcer were as shown in Table 74. PMDA confirmed that in each subgroup, the duodenal ulcer cure rate at Week 6 in the vonoprazan 20 mg group did not tend to be clearly inferior to that in the LPZ 30 mg group.

Table 74. Duodenal ulcer cure rate at Week 6 in each subgroup in Study CCT-102 (FAS)

Stratification factor	Category	LPZ 30 mg group (N = 180)	Vonoprazan 20 mg group (N = 178)
Age	<65 years	98.7% (151/153)	96.0% (145/151)
	≥65 years and <75 years	94.4% (17/18)	90.5% (19/21)
	≥75 years	100.0% (9/9)	100.0% (6/6)
Gender	Male	97.4% (112/115)	95.0% (113/119)
	Female	100.0% (65/65)	96.6% (57/59)
Use of LDA or NSAID at the onset of the concerned ulcer	Presence (previously used)	100.0% (11/11)	84.6% (11/13)
	Presence (used at the baseline)	100.0% (16/16)	92.3% (12/13)
	Absence	98.0% (150/153)	96.7% (147/152)
H. pylori infection	Presence	97.8% (133/136)	95.9% (142/148)
	Absence	100.0% (44/44)	93.3% (28/30)
CYP2C19 genotype	EM	98.6% (144/146)	95.3% (141/148)
	PM	97.1% (33/34)	96.7% (29/30)
Ulcer size	Very small (<5 mm)	- (0/0)	- (0/0)
	Small (≥5 mm and <10 mm)	97.6% (122/125)	96.2% (127/132)
	Medium (≥10 mm and <20 mm)	100.0% (49/49)	95.1% (39/41)
	Large (≥20 mm and <30 mm)	100.0% (2/2)	80.0% (4/5)
	Very large (≥30 mm)	100.0% (4/4)	- (0/0)

4.(iii).B.(1).4) Adjunct to *H. pylori* eradication

(a) *H. pylori* eradication rate

The *H. pylori* primary eradication rate at 4 weeks after the end of the primary eradication treatment, the primary endpoint in Study CCT-401, was as shown in Table 51 [see "4.(iii).A.(7) Phase III study for *Helicobacter pylori* eradication"]. Non-inferiority of the vonoprazan group to the LPZ group was verified. In this study, the *H. pylori* secondary eradication rate at 4 weeks after the end of the secondary eradication treatment [95% CI], the secondary endpoint, was 98.0% (49 of 50 subjects) [89.4%, 99.9%].

Based on the above, PMDA considers that the efficacy of vonoprazan in the *H. pylori* primary and secondary eradication has been demonstrated.

(b) Eradication rate by patient characteristic

The results of analysis on the *H. pylori* primary eradication rate at 4 weeks after the end of the primary eradication treatment in Study CCT-401 in each subgroup stratified according to age, gender, CYP2C19 genotype, the dose of CAM, and the minimum inhibitory concentration (MIC) against *H. pylori* (AMPC [combined[152]], CAM [combined152]) are as shown in Table 75. PMDA confirmed that in each of these subgroups, the *H. pylori* primary eradication rate in the vonoprazan group did not tend to be inferior to that in the LPZ group.

Table 75. *H. pylori* primary eradication rate at 4 weeks after the end of the primary eradication treatment in each subgroup in Study CCT-401 (FAS)

Stratification factor	Category	LPZ group (N = 320)	Vonoprazan group (N = 324)
Age	<65 years	74.3% (185/249)	93.0% (226/243)
	≥65 years and <75 years	83.9% (52/62)	91.3% (63/69)
	≥75 years	66.7% (6/9)	91.7% (11/12)
Gender	Male	81.9% (158/193)	93.3% (180/193)
	Female	66.9% (85/127)	91.6% (120/131)
CYP2C19 genotype	EM	75.0% (204/272)	92.9% (250/269)
	PM	81.3% (39/48)	90.9% (50/55)
Dose of CAM	200 mg/dose	78.7% (129/164)	93.3% (152/163)
	400 mg/dose	73.1% (114/156)	91.9% (148/161)
MIC against *H. pylori* AMPC (combined)	≤0.03 μg/mL	80.6% (183/227)	94.0% (220/234)
	>0.03 μg/mL	58.9% (43/73)	87.3% (62/71)
	Unmeasurable	89.5% (17/19)	94.7% (18/19)
MIC against *H. pylori* CAM (combined)	≤0.5 μg/mL	97.3% (180/185)	97.6% (200/205)
	≥1 μg/mL	40.0% (46/115)	82.0% (82/100)
	Unmeasurable	89.5% (17/19)	94.7% (18/19)

4.(iii).B.(1).5) Prevention of recurrent gastric or duodenal ulcer during LDA treatment

(a) Recurrence of gastric or duodenal ulcer

In Study CCT-302, the recurrence rate of gastric or duodenal ulcer at Week 24 in the FAS, the primary endpoint, was as shown in Table 54 [see "4.(iii).A.(8) Phase III study in patients with LDA ulcer"]. Non-inferiority of the vonoprazan 10 mg group and 20 mg group to the LPZ 15 mg group was verified. Recurrence of gastric or duodenal ulcer at Weeks 52 to 104 in Study OCT-302 was as shown in Table 61 [see "4.(iii).A.(9) Phase III long-term study in patients with LDA ulcer"]. In either vonoprazan 10 mg group or 20 mg group, the recurrence rate did not tend to increase with the increasing treatment period of vonoprazan. Based on the above, PMDA considers that the efficacy of vonoprazan at 10 mg and 20 mg in prevention of recurrent gastric or duodenal ulcer during the LDA treatment has been demonstrated.

(b) Haemorrhagic lesion

Development of a haemorrhagic lesion in gastric or duodenal ulcer during the LDA treatment can raise clinically significant issues. PMDA therefore investigated the incidence of haemorrhagic lesions in the stomach and duodenum. The incidence of haemorrhagic lesions in the stomach and duodenum at Week 12 and Week 24 in Study CCT-302 was as shown in Table 76. No haemorrhagic lesions developed in either the vonoprazan 10 mg group or vonoprazan 20 mg group.

[152] MIC in the vestibular mid curvatura ventriculi major or MIC in the upper corpus curvatura ventriculi major, whichever is greater

Table 76. Incidence of haemorrhagic lesions in Weeks 12 and 24 in Study CCT-302 (FAS)

After the study treatment start		LPZ 15 mg group (N = 209)	Vonoprazan 10 mg group (N = 196)	Vonoprazan 20 mg group (N = 194)
Week 12	No. of subjects with haemorrhagic lesions	4	0	0
	Incidence (%) [95% CI]	1.9 [0.5, 4.8]	0.0 [0.0, 1.9]	0.0 [0.0, 1.9]
	Difference from the LPZ 15 mg group (%) [95% CI]	-	-1.9 [-3.8, -0.1]	-1.9 [-3.8, -0.1]
Week 24	No. of subjects with haemorrhagic lesions	6	0	0
	Incidence (%) [95% CI]	2.9 [1.1, 6.1]	0.0 [0.0, 1.9]	0.0 [0.0, 1.9]
	Difference from the LPZ 15 mg group (%) [95% CI]	-	-2.9 [-5.1, -0.6]	-2.9 [-5.1, -0.6]

(c) Recurrence rate of gastric ulcer or duodenal ulcer by patient characteristic

The results of analysis on the recurrence rate of gastric ulcer or duodenal ulcer at Week 24 in Study CCT-302 in each subgroup stratified according to age, presence or absence of *H. pylori* infection, CYP2C19 genotype, smoking history, drinking habit, and concomitant use of oral antithrombotic drug were as shown in Table 77. PMDA confirmed that in each subgroup, the recurrence rate of gastric or duodenal ulcer in Week 24 in the vonoprazan 10 mg group or the vonoprazan 20 mg group did not tend to be inferior to that in the LPZ 15 mg group. In any patient stratum, no considerable difference was observed in the recurrence rate of gastric or duodenal ulcer between the vonoprazan 10 mg group and the vonoprazan 20 mg group.

Table 77. Recurrence rate of gastric ulcer or duodenal ulcer at Week 24 in each subgroup in Study CCT-302 (FAS)

Stratification factor	Category	LPZ 15 mg group (N = 213)	Vonoprazan 10 mg group (N = 197)	Vonoprazan 20 mg group (N = 196)
Age	<65 years	1.4% (1/69)	1.9% (1/53)	0.0% (0/50)
	≥65 years and <75 years	2.2% (2/90)	0.0% (0/91)	2.0% (2/99)
	≥75 years	5.6% (3/54)	0.0% (0/53)	2.1% (1/47)
H. pylori infection	Presence	2.3% (2/86)	0.0% (0/83)	0.0% (0/79)
	Absence	3.3% (4/123)	0.9% (1/114)	2.6% (3/116)
CYP2C19 genotype	EM	2.7% (5/184)	0.6% (1/162)	1.3% (2/155)
	PM	3.6% (1/28)	0.0% (0/35)	2.4% (1/41)
Smoking history	Presence	1.8% (3/165)	0.6% (1/155)	1.9% (3/155)
	Absence	6.3% (3/48)	0.0% (0/42)	0.0% (0/41)
Drinking habit	Presence	1.7% (2/119)	0.8% (1/126)	0.9% (1/117)
	Absence	4.3% (4/94)	0.0% (0/71)	2.5% (2/79)
Concomitant use of oral antithrombotic drug	Presence	2.2% (2/91)	0.0% (0/83)	2.5% (2/79)
	Absence	3.3% (4/122)	0.9% (1/114)	0.9% (1/117)

4.(iii).B.(1).6) Prevention of recurrent gastric or duodenal ulcer during NSAID treatment

(a) Recurrent gastric or duodenal ulcer

In Study CCT-301, the recurrence rate of gastric ulcer or duodenal ulcer at Week 24 in the FAS, the primary endpoint, was as shown in Table 62 [see "4.(iii).A.(11) Phase III study in patients with NSAID ulcer"]. Non-inferiority of the vonoprazan 10 mg group and 20 mg group to the LPZ 15 mg group was verified. Recurrence of gastric ulcer or duodenal ulcer at Weeks 52 to 104 in Study OCT-301 was as shown in Table 69 [see "4.(iii).A.(12) Phase III extension study in patients with NSAID ulcer"]. In either vonoprazan 10 mg group or 20 mg group, the recurrence rate did not tend to increase with the increasing treatment period of vonoprazan. Based on the above, PMDA considers that the efficacy of vonoprazan at 10 mg and 20 mg in prevention of recurrent gastric or duodenal ulcer during the NSAID treatment was demonstrated.

(b) Haemorrhagic lesion

Development of a haemorrhagic lesion in gastric or duodenal ulcer during the NSAID treatment can raise clinically significant issues. PMDA therefore investigated the incidence of haemorrhagic lesions in the stomach and duodenum. The incidence of haemorrhagic lesions in the stomach and duodenum in

Weeks 12 and 24 in Study CCT-301 was as shown in Table 78. No considerable difference was observed in incidence of haemorrhagic lesions between the vonoprazan 10 mg group or the vonoprazan 20 mg group and the LPZ 15 mg group.

Table 78. Incidence of haemorrhagic lesions in Weeks 12 and 24 in Study CCT-301 (FAS)

After the study treatment start		LPZ 15 mg group (N = 200)	Vonoprazan 10 mg group (N = 210)	Vonoprazan 20 mg group (N = 199)
Week 12	Cumulative number of subjects developing haemorrhagic lesions	4	2	2
	Cumulative incidence (%) [95% CI]	2.0 [0.5, 5.0]	1.0 [0.1, 3.4]	1.0 [0.1, 3.6]
	Difference from the LPZ 15 mg group (%) [95% CI]	-	-1.0 [-3.4, 1.3]	-1.0 [-3.4, 1.4]
Week 24	Cumulative number of subjects developing haemorrhagic lesions	4	3	2
	Cumulative incidence (%) [95% CI]	2.0 [0.5, 5.0]	1.4 [0.3, 4.1]	1.0 [0.1, 3.6]
	Difference from the LPZ 15 mg group (%) [95% CI]	-	-0.6 [-3.1, 1.9]	-1.0 [-3.4, 1.4]

(c) Recurrence rate of gastric ulcer or duodenal ulcer by patient characteristic

The results of analysis on the recurrence rate of gastric ulcer or duodenal ulcer at Week 24 in Study CCT-301 in each subgroup stratified according to age, presence or absence of *H. pylori* infection, CYP2C19 genotype, smoking history, drinking habit, use of oral steroid formulation, and Modified Lanza Score[153] during the screening period were as shown in Table 79. PMDA confirmed that in each subgroup, the recurrence rate of gastric ulcer or duodenal ulcer at Week 24 in the vonoprazan 10 mg group or the vonoprazan 20 mg group did not tend to be inferior to that in the LPZ 15 mg group. In any patient stratum, no considerable difference was observed in the recurrence rate of gastric or duodenal ulcer between the vonoprazan 10 mg group and the vonoprazan 20 mg group.

Table 79. Recurrence rate of gastric ulcer or duodenal ulcer at Week 24 in each subgroup in Study CCT-301 (FAS)

Stratification factor	Category	LPZ 15 mg group (N = 199)	Vonoprazan 10 mg group (N = 209)	Vonoprazan 20 mg group (N = 203)
Age	<65 years	5.4% (5/93)	2.3% (2/88)	2.2% (2/91)
	≥65 years and <75 years	4.7% (3/64)	3.9% (3/76)	3.0% (2/66)
	≥75 years	7.1% (3/42)	4.4% (2/45)	6.5% (3/46)
H. pylori infection	Presence	5.5% (4/73)	3.9% (3/76)	3.2% (2/63)
	Absence	5.6% (7/124)	3.0% (4/132)	3.6% (5/140)
CYP2C19 genotype	EM	5.6% (9/160)	2.5% (4/160)	2.9% (5/172)
	PM	5.1% (2/39)	6.1% (3/49)	6.5% (2/31)
Smoking history	Presence	8.3% (9/109)	3.8% (4/106)	3.3% (4/120)
	Absence	2.2% (2/90)	2.9% (3/103)	3.6% (3/83)
Drinking habit	Presence	8.0% (7/87)	0.9% (1/106)	4.1% (4/97)
	Absence	3.6% (4/112)	5.8% (6/103)	2.8% (3/106)
Use of oral steroid formulation	Presence	6.8% (3/44)	6.5% (3/46)	3.3% (1/30)
	Absence	5.2% (8/155)	2.5% (4/163)	3.5% (6/173)
Modified Lanza Score (screening period)	<1	3.0% (4/132)	0.0% (0/121)	0.7% (1/135)
	≥1	10.4% (7/67)	8.0% (7/88)	8.8% (6/68)

(d) Recurrence rate of gastric ulcer or duodenal ulcer by NSAID type

NSAIDs frequently used in Study CCT-301 included celecoxib, loxoprofen, meloxicam, and diclofenac. Data on the recurrence rate of gastric ulcer or duodenal ulcer at Week 24 were stratified according to presence or absence of the use of these 4 drugs, and the results were as shown in Table 80. PMDA

[153] Modified Lanza Score (gastric submucosal injury): 0, No haemorrhage or erosions observed; 1, One haemorrhage or erosion; 2, 2 to 5 haemorrhages or erosions observed in 1 localized gastric area; 3, Haemorrhages or erosions observed in 2 gastric areas or ≥6 haemorrhages or erosions observed in 1 gastric area; 4, Haemorrhages or erosions observed in ≥3 gastric areas.
The area indicates cardia fundus, upper, mid, and lower gastric corpus, gastric angle, and pyloric antral zone.

confirmed that in the subgroups of subjects who concomitantly received celecoxib or loxoprofen, the recurrence rate of gastric ulcer or duodenal ulcer at Week 24 in the vonoprazan 10 mg group or the vonoprazan 20 mg group did not tend to be inferior to that in the LPZ 15 mg group. The number of subjects who concomitantly received meloxicam or diclofenac was as small as approximately 20, making an adequate investigation difficult.

Table 80. Recurrence rate of gastric ulcer or duodenal ulcer at Week 24 by type of concomitant NSAIDs in Study CCT-301 (FAS)

Type of NSAIDs		LPZ 15 mg group (N = 199)	Vonoprazan 10 mg group (N = 209)	Vonoprazan 20 mg group (N = 203)
COX-2 selective inhibitor (celecoxib) use	Presence	4.2% (2/48)	1.6% (1/62)	1.5% (1/67)
	Absence	6.0% (9/151)	4.1% (6/147)	4.4% (6/136)
Loxoprofen use	Presence	6.9% (5/72)	1.3% (1/76)	4.5% (3/66)
	Absence	4.7% (6/127)	4.5% (6/133)	2.9% (4/137)
Meloxicam use	Presence	5.0% (1/20)	0.0% (0/25)	0.0% (0/21)
	Absence	5.6% (10/179)	3.8% (7/184)	3.8% (7/182)
Diclofenac use	Presence	0.0% (0/20)	13.6% (3/22)	11.1% (2/18)
	Absence	6.1% (11/179)	2.1% (4/187)	2.7% (5/185)

4.(iii).B.(2) Safety

Based on the review in the following 4.(iii).B.(2).1) to 4.(iii).B.(2).4), PMDA has concluded that the safety of vonoprazan is acceptable as long as appropriate cautions are provided using the safety information of the existing proton pump inhibitors (PPIs) as a reference, although attention should be paid to events such as hypergastrinaemia. PMDA, however, considers that it is necessary to collect further information on the following matters through post-marketing surveillance, etc.: safety of long-term administration of vonoprazan; safety in the elderly; hypergastrinaemia, hyperplasia and metaplasia in the gastric mucosal epithelium, or neuroendocrine tumor associated with vonoprazan administration; fracture; and safety of concomitant use of vonoprazan with clopidogrel.

A final decision on the safety of vonoprazan will be made, taking account of comments raised in the Expert Discussion.

4.(iii).B.(2).1) Adverse events in clinical studies

(a) Adverse events

There were neither adverse events nor adverse drug reactions with the incidence in the vonoprazan group was at least 5% higher than that in the LPZ group in any of the phase III studies [see "*4.(iii).A Summary of the submitted data*"].

Serious adverse events in each of the phase III studies were as shown in Table 81. Adverse events reported in the vonoprazan group included those of which a causal relationship to the study drug could not be ruled out, but when compared to LPZ neither events nor trends specific to vonoprazan were observed. In terms of the outcome, all of the events resolved or were resolving except for subarachnoid haemorrhage (death) in the vonoprazan 20 mg group in Study CCT-102 and putamen haemorrhage (with sequelae) in the vonoprazan 10 mg group in Study OCT-301.116·145

Table 81. Serious adverse events in Phase III studies

Study population	Study	Treatment group	No. of subjects with event	Names of adverse events
Treatment for RE	CCT-002	LPZ 30 mg group	1 subject each	Large intestine polyp; pelvic fracture and radius fracture; hepatic encephalopathy
		Vonoprazan 20 mg group	0 subjects	None
Maintenance therapy for RE	CCT-003	LPZ 15 mg group	1 subject each	Aortic valve stenosis, sick sinus syndrome, diabetic retinopathy, cervix carcinoma
		Vonoprazan 10 mg group	1 subject each	Melaena, spinal compression fracture, dehydration, intentional self-injury, renal artery stenosis
		Vonoprazan 20 mg group	1 subject each	Atrial fibrillation, appendicitis, campylobacter gastroenteritis, liver function test abnormal
	OCT-001	Vonoprazan 10 mg group	1 subject each	Age-related macular degeneration; large intestine polyp; pneumonia and peritonsillar abscess; gastroenteritis; osteomyelitis; diabetes mellitus and cerebral infarction; breast cancer; malignant fibrous histiocytoma and schwannoma
		Vonoprazan 20 mg group	1 subject each	Pneumonia; pyrexia and pneumonia; thyroiditis subacute; aerophagia; biliary cirrhosis primary; enterocolitis bacterial; tendon rupture; spinal ligament ossification; myelodysplastic syndrome; cerebral infarction; cubital tunnel syndrome
Gastric ulcer	CCT-101	LPZ 30 mg group	1 subject each	Gastric ulcer; large intestine polyp; meningitis viral; interstitial lung disease and pulmonary hypertension
		Vonoprazan 20 mg group	1 subject each	Cardiac failure chronic; gastric ulcer and nephrotic syndrome; acute abdomen; gastric ulcer haemorrhage; contusion; cerebral infarction
Duodenal ulcer	CCT-102	LPZ 30 mg group	1 subject each	Pancreatitis acute, pharyngolaryngeal abscess, comminuted fracture, duodenal neoplasm
		Vonoprazan 20 mg group	1 subject each	Subarachnoid haemorrhage; duodenal ulcer; duodenal ulcer haemorrhage; duodenal ulcer and gastrooesophageal reflux disease; pneumonia and sepsis; haemoglobin decreased
H. pylori eradication	CCT-401	LPZ group	1 subject each	Femoral neck fracture, pancreatic carcinoma
		Vonoprazan group	1 subject each	Primary eradication period: Acute myocardial infarction; gastric ulcer haemorrhage; cholangitis suppurative; enteritis infectious Secondary eradication period: Appendicitis and pseudomembranous colitis
LDA ulcer	CCT-302 + OCT-302	LPZ 15 mg group	1 subject each except for coronary artery stenosis, and renal failure acute and prostatitis	Coronary artery stenosis (3 subjects); renal failure acute and prostatitis (2 subjects); angina pectoris; cardiac failure, enterocolitis haemorrhagic, and pneumonia; cardiac failure congestive; myocardial infarction; myocardial ischaemia; cataract; macular degeneration; large intestine polyp; ileus; pancreatitis acute and respiratory disorder; cholangitis; bile duct stone; cholecystitis acute and joint dislocation; gastroenteritis; femur fracture; traumatic intracranial haemorrhage; diabetes mellitus; lumbar spinal stenosis; gastric cancer; adenocarcinoma of the cervix; small cell lung cancer; putamen haemorrhage; transient ischaemic attack; calculus ureteric and carotid artery stenosis; pneumothorax; aortic dissection; hypotension; cholelithiasis
		Vonoprazan 10 mg group	1 subject each except for angina pectoris, gastric cancer, and large intestine polyp	Angina pectoris (3 subjects); large intestine polyp (2 subjects); gastric cancer (2 subjects); blood pressure increased, pancreatitis acute, convulsion, and diabetic nephropathy; anaemia, angina pectoris, renal impairment, and peripheral arterial occlusive disease; peripheral arterial occlusive disease; cardiac failure congestive; atrial fibrillation; prinzmetal angina and diabetes mellitus; diabetes mellitus; cataract; ileus; colitis ischaemic; cholangitis; pneumonia; herpes zoster; nasopharyngitis; contusion; lower limb fracture; dehydration and influenza; influenza; angina pectoris and diabetes mellitus inadequate control; adenocarcinoma gastric; bladder cancer; lung neoplasm malignant; carotid artery stenosis and cerebral infarction; thrombotic cerebral infarction; calculus urinary

		Vonoprazan 20 mg group	1 subject each except for gastric cancer, diabetes mellitus, angina pectoris, influenza, and oesophageal carcinoma	Gastric cancer (4 subjects); diabetes mellitus (3 subjects); angina pectoris (2 subjects); influenza (2 subjects); oesophageal carcinoma (2 subjects); cardiac failure; pneumonia; pneumonia and pleuropericarditis; ventricular tachycardia, chest discomfort, and intercostal neuralgia; enterocolitis; coronary artery stenosis and mallory-weiss syndrome; cataract and cardiac failure acute; coronary artery stenosis; cataract; bacterial infection; pyelonephritis; coronary artery restenosis; foot fracture; spinal compression fracture and convulsion; tooth fracture; oral fibroma; altered state of consciousness; asthma; peripheral arterial occlusive disease
	OCT-304	Vonoprazan 20 mg group	1 subject	Bile duct stone
NSAID ulcer	CCT-301 + OCT-301	LPZ 15 mg group	1 subject each except for osteoarthritis	Osteoarthritis (2 subjects); anal skin tags; enterocolitis; hepatitis E; intentional overdose and altered state of consciousness; road traffic accident and renal injury; occult blood positive; intervertebral disc protrusion; back pain; gastric cancer; acute myeloid leukaemia; pharyngeal neoplasm; cerebral haemorrhage; myelopathy; interstitial lung disease; pneumothorax; varicose vein
		Vonoprazan 10 mg group	1 subject each	Angina pectoris and procedural haemorrhage; aortic valve incompetence; colitis ischaemic; diverticulitis intestinal haemorrhagic; haemorrhoids; oesophageal dysplasia; herpes virus infection and cerebral infarction; spinal compression fracture; patella fracture; ligament rupture; subdural haematoma and cubital tunnel syndrome; hypoglycaemia; breast cancer; neuralgia; putamen haemorrhage; syncope; calculus ureteric; thrombophlebitis
		Vonoprazan 20 mg group	1 subject each except for intervertebral disc protrusion, lumbar spinal stenosis, and interstitial lung disease	Intervertebral disc protrusion (2 subjects); lumbar spinal stenosis (2 subjects); interstitial lung disease (2 subjects); cardiac failure chronic; sudden hearing loss and vertigo; cataract and glaucoma; intestinal obstruction; large intestine polyp; impaired healing and spinal compression fracture; spinal compression fracture; cholangitis and cholecystitis; gastroenteritis; pneumonia mycoplasmal and spinal osteoarthritis; subcutaneous abscess; patella fracture; femoral neck fracture; snake bite; osteoarthritis; muscular weakness; periarthritis; rheumatoid arthritis; spinal osteoarthritis and gastric cancer; cerebral haemorrhage; cervical myelopathy; dizziness postural; subarachnoid haemorrhage
	OCT-303	Vonoprazan 20 mg group	1 subject	Colitis ischaemic

(b) Adverse events during the long-term treatment

The incidences of adverse events by number of treatment days in the Long-term Treatment Studies OCT-001, OCT-301, and OCT-302, were as shown in Table 82 to Table 84. PMDA considers that the incidence of adverse events did not tend to clearly increase with the increasing treatment period of vonoprazan in any study. It is, however, necessary to collect further information on the safety of the long-term treatment of vonoprazan in routine clinical use through post-marketing surveillance etc.

Table 82. Incidence of adverse events by treatment days in Study OCT-001

Number of days after the treatment start	Vonoprazan 10 mg group	Vonoprazan 20 mg group
1 to 84 days	43.5% (67/154)	43.0% (65/151)
85 to 168 days	32.2% (46/143)	40.4% (57/141)
169 to 253 days	37.5% (51/136)	45.0% (58/129)
254 to 365 days	34.9% (45/129)	39.2% (49/125)
≥366 days	15.0% (3/20)	5.9% (1/17)
Overall treatment period	76.6% (118/154)	78.8% (119/151)

Table 83. Incidence of adverse events by time of onset in Study OCT-301

Number of days after the treatment start	LPZ 15 mg group	Vonoprazan 10 mg group	Vonoprazan 20 mg group
1 to 84 days	58.1% (122/210)	49.1% (107/218)	54.7% (116/212)
85 to 168 days	46.6% (88/189)	51.2% (106/207)	47.4% (92/194)
169 to 252 days	48.9% (66/135)	44.6% (75/168)	53.9% (83/154)
253 to 336 days	50.4% (59/117)	56.0% (79/141)	47.0% (63/134)
337 to 420 days	36.3% (41/113)	37.0% (51/138)	24.2% (31/128)
421 to 504 days	33.3% (15/45)	33.3% (18/54)	33.3% (16/48)
505 to 588 days	14.8% (4/27)	21.4% (6/28)	39.1% (9/23)
589 to 672 days	33.3% (1/3)	100.0% (1/1)	25.0% (1/4)
673 to 756 days	0.0% (0/1)	- (0/0)	- (0/0)
Overall treatment period	88.1% (185/210)	84.4% (184/218)	82.5% (175/212)

Table 84. Incidence of adverse events by time of onset in Study OCT-302

Number of days after the treatment start	LPZ 15 mg group	Vonoprazan 10 mg group	Vonoprazan 20 mg group
1 to 84 days	47.5% (103/217)	46.5% (94/202)	56.9% (115/202)
85 to 168 days	46.9% (97/207)	52.6% (101/192)	51.8% (100/193)
169 to 252 days	45.5% (80/176)	47.3% (78/165)	48.0% (73/152)
253 to 336 days	50.0% (75/150)	46.7% (70/150)	42.5% (57/134)
337 to 420 days	29.9% (43/144)	34.5% (50/145)	35.9% (47/131)
421 to 504 days	31.4% (16/51)	22.6% (14/62)	17.9% (10/56)
505 to 588 days	13.3% (2/15)	20.0% (3/15)	22.2% (2/9)
589 to 672 days	0.0% (0/1)	0.0% (0/2)	0.0% (0/1)
673 to 756 days	- (0/0)	0.0% (0/1)	- (0/0)
Overall treatment period	84.8% (184/217)	87.6% (177/202)	87.1% (176/202)

(c) Adverse events in the elderly

The incidences of adverse events by age of the subject (<65 years, ≥65 years and <75 years, ≥75 years) in each of the phase III studies were as shown in Table 85. The incidence of adverse events by age tended to slightly increase in proportion to age in the vonoprazan 10 mg group and the vonoprazan 20 mg group in Studies CCT-003 and OCT-001 and in the vonoprazan 20 mg group in Studies CCT-302 and OCT-302, but such consistent trend was not observed in other studies. The incidence of adverse events by age in the vonoprazan group did not tend to be considerably different from that in the LPZ group.

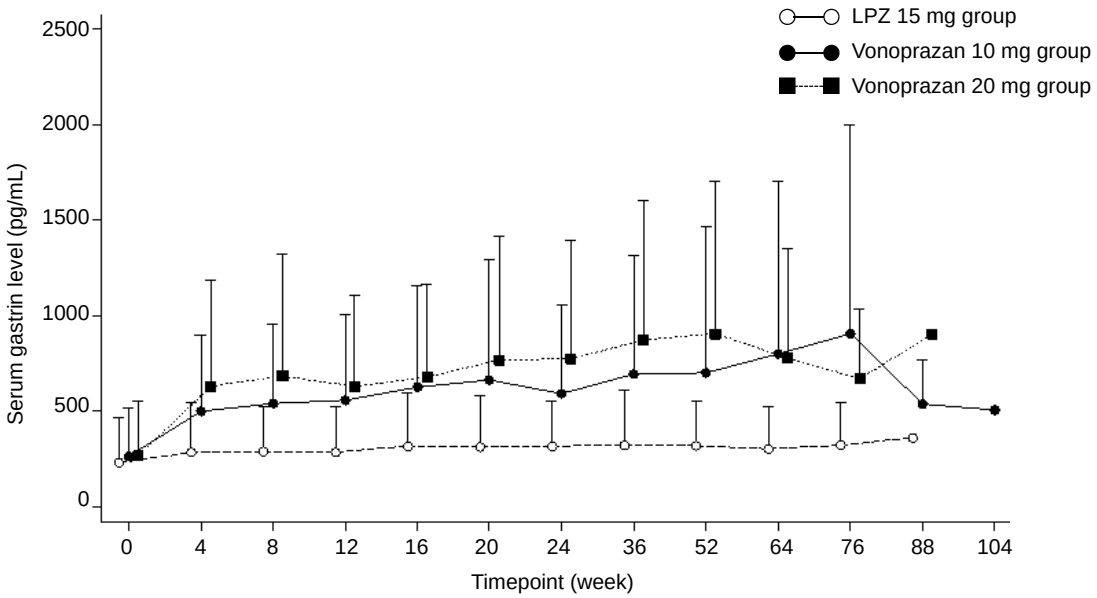
At present, PMDA considers that no significant safety concerns in the elderly have been raised, but it is necessary to provide cautions to ensure careful administration of vonoprazan to the elderly as well as to collect further information on the safety in the elderly through post-marketing surveillance etc., because in Studies CCT-003 and OCT-001, the incidence of adverse events in the elderly tended to be higher than that in the non-elderly, and the number of subjects aged ≥75 years in particular was limited in each phase III study.

Table 85. Incidence of adverse events by age in each phase III study

Study population	Study	Treatment group	<65 years	≥65 years and <75 years	≥75 years
Treatment for RE	CCT-002	LPZ 30 mg group	20.1% (27/134)	23.5% (12/51)	35.3% (6/17)
		Vonoprazan 20 mg group	23.1% (30/130)	21.6% (11/51)	19.2% (5/26)
Maintenance therapy for RE	CCT-003	LPZ 15 mg group	49.3% (67/136)	59.6% (28/47)	44.4% (8/18)
		Vonoprazan 10 mg group	50.0% (71/142)	60.5% (26/43)	70.6% (12/17)
		Vonoprazan 20 mg group	56.8% (79/139)	60.5% (26/43)	68.2% (15/22)
	OCT-001	Vonoprazan 10 mg group	74.7% (71/95)	77.8% (35/45)	85.7% (12/14)
		Vonoprazan 20 mg group	74.8% (77/103)	81.8% (27/33)	100.0% (15/15)
Gastric ulcer	CCT-101	LPZ 30 mg group	35.0% (55/157)	38.0% (19/50)	16.1% (5/31)
		Vonoprazan 20 mg group	26.0% (44/169)	31.5% (17/54)	19.0% (4/21)
Duodenal ulcer	CCT-102	LPZ 30 mg group	24.4% (38/156)	60.0% (12/20)	33.3% (3/9)
		Vonoprazan 20 mg group	35.1% (54/154)	28.6% (6/21)	37.5% (3/8)
H. pylori eradication	CCT-401 (primary eradication period)	LPZ group	40.4% (101/250)	45.2% (28/62)	33.3% (3/9)
		Vonoprazan group	32.4% (80/247)	39.1% (27/69)	38.5% (5/13)
LDA ulcer	CCT-302 + OCT-302	LPZ 15 mg group	87.0% (60/69)	81.5% (75/92)	87.5% (49/56)
		Vonoprazan 10 mg group	88.9% (48/54)	86.3% (82/95)	88.7% (47/53)
		Vonoprazan 20 mg group	81.1% (43/53)	87.1% (88/101)	93.8% (45/48)
	OCT-304	Vonoprazan 20 mg group	77.8% (7/9)	85.7% (6/7)	72.7% (8/11)
NSAID ulcer	CCT-301 + OCT-301	LPZ 15 mg group	89.5% (85/95)	87.1% (61/70)	86.7% (39/45)
		Vonoprazan 10 mg group	82.8% (77/93)	81.8% (63/77)	91.7% (44/48)
		Vonoprazan 20 mg group	87.5% (84/96)	77.6% (52/67)	79.6% (39/49)
	OCT-303	Vonoprazan 20 mg group	81.8% (9/11)	62.5% (5/8)	72.7% (8/11)

4.(iii).B.(2).2) Serum gastrin level

Figure 1 shows changes of serum gastrin levels in Study OCT-302, a long-term treatment study. From Week 4 to Week 88, the serum gastrin levels were higher in both the vonoprazan 10 mg group and the vonoprazan 20 mg group than in the LPZ 15 mg group from, and those in the vonoprazan 20 mg group tended to be slightly higher than those in the vonoprazan 10 mg group. Similar trends were observed in both Studies OCT-301 and OCT-001.



No. of subjects (N)													
LPZ 15 mg group	213	216	215	209	206	203	199	151	144	51	16	1	0
Vonoprazan 10 mg group	202	200	197	196	188	188	186	149	146	63	18	2	1
Vonoprazan 20 mg group	201	202	196	194	190	186	186	133	130	58	13	1	0

Figure 1. Changes of serum gastrin levels (mean + SD) (Study OCT-302)

The applicant explained the increased serum gastrin levels in response to vonoprazan and its consequence (development of neuroendocrine tumor etc.) as follows:
Although in any phase III study, the serum gastrin level increased over time in a vonoprazan-dose dependent manner, changes in serum gastrin levels after the end of treatment in Studies CCT-101 and CCT-102 showed that the increased serum gastrin level returned to a level within the normal range at 2 to 8 weeks after the end of the treatment.

Gastric mucosal specimens available in Studies CCT-003 and OCT-001 were subjected to histopathological examinations (Table 86, Table 87). Morphometrical examinations showed no remarkable changes in cell density of epithelial cells in the fundic gland mucosa between before and after the treatment in any dose group in either study. Data on the density of neuroendocrine cells (Grimelius positive cells, Chromogranin A positive cells, Synaptophysin positive cells) in the fundic gland and the percent positive cells (ratio of the positive cell count to the total epithelial cell count) showed an increase or increasing trend of Grimelius positive cells in all dose group including the LPZ 15 mg group in Study CCT-003 but no remarkable changes in the other cell types between before and after the treatment. No new development of hyperplasia, metaplasia, or neuroendocrine cell tumor was histologically observed in the fundic gland mucosal epithelium following administration of vonoprazan.

Based on the above, the effect of the increased serum gastrin level in response to vonoprazan on the fundic gland mucosal epithelial cells was considered comparable to that in response to LPZ. There are no reports indicating a clear relationship of LPZ with gastric neuroendocrine cell tumor in the clinical experience of LPZ. As with LPZ, vonoprazan is therefore considered unlikely to be related to development of gastric neuroendocrine cell tumor even if the increased serum gastrin level in response to vonoprazan is continued for a long period of time.

Table 86. Results of gastric mucosal histopathological examination in Study CCT-003

Item	Timepoint	LPZ 15 mg group (N = 201)			Vonoprazan 10 mg group (N = 202)			Vonoprazan 20 mg group (N = 204)		
		N	Percent positive cells[a] (%)	Cell density (/mm^2)	N	Percent positive cells[a] (%)	Cell density (/mm^2)	N	Percent positive cells[a] (%)	Cell density (/mm^2)
Epithelial cells	Baseline	28	-	1579.8 ± 483.1	29	-	1822.0 ± 318.8	28	-	1736.9 ± 394.3
	Week 24	24	-	1625.5 ± 268.9	26	-	1714.2 ± 430.4	28	-	1544.3 ± 474.4
Grimelius positive cells	Baseline	28	4.5 ± 2.0	71.6 ± 40.0	29	3.8 ± 2.7	70.5 ± 55.6	28	3.8 ± 2.2	65.6 ± 37.8
	Week 24	24	6.6 ± 1.3	106.1 ± 26.8	26	6.2 ± 1.5	107.4 ± 38.6	28	5.9 ± 2.1	94.3 ± 42.6
Chromogranin A positive cells	Baseline	28	8.7 ± 4.7	135.0 ± 66.2	29	7.1 ± 4.3	125.2 ± 72.5	28	8.0 ± 4.6	134.8 ± 70.7
	Week 24	24	8.3 ± 1.2	135.4 ± 29.6	26	7.5 ± 1.9	130.6 ± 45.9	28	7.6 ± 2.1	119.6 ± 50.4
Synaptophysin positive cells	Baseline	28	11.2 ± 3.9	173.0 ± 70.0	29	9.8 ± 4.8	172.8 ± 81.2	28	11.1 ± 6.0	183.2 ± 90.8
	Week 24	24	9.9 ± 2.4	158.4 ± 37.2	26	9.2 ± 1.9	155.3 ± 44.9	28	9.2 ± 3.0	144.9 ± 61.7
Ki-67 (MIB-1) positive cells	Baseline	28	10.4 ± 7.6	144.3 ± 81.9	29	6.2 ± 4.1	110.4 ± 66.2	28	8.3 ± 4.5	132.3 ± 55.1
	Week 24	24	7.2 ± 3.6	114.2 ± 50.4	26	6.9 ± 3.2	109.5 ± 40.8	28	7.5 ± 3.5	105.4 ± 48.5

Mean ± SD

a) Percent positive cells: Positive cell count/total epithelial cell count × 100

Table 87. Results of gastric mucosal histopathological examination in Study OCT-001

Item	Timepoint	Vonoprazan 10 mg group (N = 154)			Vonoprazan 20 mg group (N = 151)		
		N	Percent positive cells[a] (%)	Cell density (/mm^2)	N	Percent positive cells[a] (%)	Cell density (/mm^2)
Epithelial cells	Baseline	32	-	1700.8 ± 333.4	33	-	1864.5 ± 305.0
	Week 24	32	-	1579.8 ± 415.8	30	-	1733.4 ± 326.2
	Week 52	27	-	1644.7 ± 436.7	28	-	1673.2 ± 473.7
Grimelius positive cells	Baseline	32	3.7 ± 2.9	61.7 ± 46.2	33	4.7 ± 2.6	85.4 ± 47.6
	Week 24	32	4.8 ± 2.2	79.6 ± 42.9	30	5.5 ± 1.8	93.9 ± 31.4
	Week 52	27	6.3 ± 2.1	102.6 ± 40.1	28	5.6 ± 1.6	92.7 ± 31.0
Chromogranin A positive cells	Baseline	32	6.7 ± 3.7	112.0 ± 57.1	33	8.2 ± 3.9	150.3 ± 70.0
	Week 24	32	5.6 ± 3.0	92.4 ± 56.0	30	6.6 ± 2.8	111.0 ± 47.2
	Week 52	27	7.4 ± 2.1	119.9 ± 40.3	28	6.7 ± 2.1	109.2 ± 34.4
Synaptophysin positive cells	Baseline	32	10.1 ± 4.5	165.3 ± 58.7	33	10.0 ± 4.5	181.1 ± 75.3
	Week 24	32	8.9 ± 3.6	134.9 ± 52.4	30	8.8 ± 2.1	149.9 ± 33.6
	Week 52	27	8.6 ± 1.5	139.1 ± 38.9	28	8.2 ± 2.4	134.2 ± 41.1
Ki-67 (MIB-1) positive cells	Baseline	32	8.3 ± 6.5	142.5 ± 113.0	33	8.4 ± 4.7	153.7 ± 89.1
	Week 24	32	7.9 ± 5.7	111.9 ± 48.3	30	5.4 ± 2.6	90.7 ± 41.7
	Week 52	27	7.9 ± 4.7	118.6 ± 49.5	28	7.0 ± 3.7	105.3 ± 40.3

Mean ± SD

a) Percent positive cells: Positive cell count/total epithelial cell count × 100

PMDA considers as follows:

At the gastric mucosal histopathological examinations, no new development of hyperplasia, metaplasia, or neuroendocrine cell tumor was observed in the fundic gland mucosal epithelium during the observation period in Study CCT-003 or OCT-001. The serum gastrin levels increased over time in the vonoprazan 10 mg group and the vonoprazan 20 mg group and persistently remained higher compared to the LPZ 15 mg group. At present, the risk associated with continuously high serum gastrin levels following long-term administration of vonoprazan, such as development of neuroendocrine tumor, remains unclear. Therefore, the information that the serum gastrin levels tended to be higher in the vonoprazan group than in the LPZ group in clinical studies should be appropriately provided to healthcare providers in clinical settings. It is also necessary to collect further information on hypergastrinaemia and the development of hyperplasia, metaplasia, or neuroendocrine tumor in the gastric mucosal epithelium following vonoprazan treatment through post-marketing surveillance, and appropriately provide the information to healthcare providers in clinical settings when new beneficial findings become available.

4.(iii).B.(2).3) Effects on the fracture

It is indicated that the existing PPIs possibly increase the fracture risk, and the package insert of LPZ also includes cautions against fracture.

The incidence of adverse events related to fracture in long-term treatment studies of vonoprazan was as shown in Table 88. No considerable difference was observed in incidence of such events between the vonoprazan 10 mg group or the vonoprazan 20 mg group and the LPZ 15 mg group.

Table 88. Incidence of adverse events related to fracture in Studies OCT-001, OCT-302, and OCT-301

Study	LPZ 15 mg group	Vonoprazan 10 mg group	Vonoprazan 20 mg group
OCT-001	-	0.6% (1/154) Foot fracture	0.7% (1/151) Radius fracture
OCT-302	1.4% (3/217) Hand fracture, radius fracture, femur fracture	3.5% (7/202) Foot fracture (3 subjects), spinal compression fracture (2 subjects), lower limb fracture, rib fracture	2.5% (5/202) Spinal compression fracture (2 subjects), foot fracture, humerus fracture, spinal fracture
OCT-301	2.4% (5/210) Rib fracture (2 subjects), foot fracture, humerus fracture, neck fracture	3.7% (8/218) Spinal compression fracture (4 subjects); rib fracture; spinal compression fracture, rib fracture, and hand fracture; patella fracture	4.2% (9/212) Spinal compression fracture (3 subjects), rib fracture, foot fracture, hand fracture, patella fracture, fractured coccyx, femoral neck fracture

Unless otherwise specially indicated in paretheses after the name of an adverse event, the event is the one experienced by1subject.

PMDA considers as follows:

Regarding the relationship between PPIs and the increased risk of fracture, it has been reported that the risk of fracture possibly increases slightly in the elderly receiving them at a high dose or for a long period of time ≥1 year.[154,155,156] Although the relationship between PPIs and fracture has not been clearly concluded, the risk of fracture associated with vonoprazan cannot be ruled out as with the existing PPIs, because a reasonable mechanism of action in which the inhibited acid secretion leads to increased gastric pH, consequently affecting absorption of calcium has been indicated as a contributory factor. Therefore, caution against fracture should be included in the package insert as done for LPZ. It is also necessary to collect further information on fracture through post-marketing surveillance etc.

4.(iii).B.(2).4) Concomitant use with clopidogrel

Patients treated with LDA have ischaemic heart disease or ischaemic cerebrovascular disorder as an underlying disease and thus possibly use clopidogrel sulfate (clopidogrel), an antiplatelet drug, concomitantly with LDA. In the package insert of omeprazole, one of the existing PPIs, caution against concomitant use with clopidogrel is included, indicating a decreased effect of clopidogrel, because omeprazole inhibits CYP2C19, which is involved in metabolism of clopidogrel, potentially leading to decreased blood concentration of the active metabolite of clopidogrel.[157] Vonoprazan is also shown to inhibit CYP2C19 in a time-dependent manner *in vitro* [see "4.(ii).A.(1).4).(e) CYP inhibition"].

The incidence of cardiovascular adverse events in Studies CCT-302, OCT-302, and OCT-304 in patients requiring long-term LDA treatment was as shown below.

In Study CCT-302, cardiovascular adverse events occurred in 1.0% (2 of 202 subjects; lacunar infarction, cerebral infarction) of the vonoprazan 10 mg group and 0.5% (1 of 217 subjects, lacunar infarction) of the LPZ 15 mg group, and no such events occurred in the vonoprazan 20 mg group. In Study OCT-302, they occurred in 1.5% (3 of 202 subjects; lacunar infarction, cerebral infarction, thrombotic cerebral infarction) of the vonoprazan 10 mg group and 1.8% (4 of 217 subjects; lacunar infarction in 2 subjects, myocardial infarction and putamen haemorrhage in 1 subject each) of the LPZ 15 mg group, and no

154 *JAMA.* 2006;296:2947-2953, *BMJ*.2012;344:e372(doi:10.1136/bmj.e372)

155 FDA Drug Safety Communication: Possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors. (2011)

156 EMA: PhVWP Monthly report on safety concerns, guidelines and general matters. Publication No. EMA/CHMP/PhVWP/183322/. (2012)

157 *J Am Coll Cardiol.* 2008;51:256-260

such events occurred in the vonoprazan 20 mg group. No cardiovascular adverse events occurred in Study OCT-304. No cardiovascular deaths occurred in either Study CCT-302 or OCT-302, and none of the patients with cardiovascular adverse events used clopidogrel concomitantly.

PMDA considers it unnecessary to provide cautions against concomitant use of vonoprazan with clopidogrel in the package insert at present, because no particularly significant events associated with the concomitant use are included in the submitted clinical study data. PMDA, however, considers that it is necessary to collect further information on the safety of concomitant use of vonoprazan with clopidogrel through post-marketing surveillance etc., because the number of patients concomitantly treated with clopidogrel in the clinical studies was limited,[158] and it cannot be completely ruled out that the drug interaction possibly occurs due to the time-dependent inhibitory effect of vonoprazan against CYP2C19 in the clinical settings.

4.(iii).B.(3) Indication

The non-inferiority of vonoprazan to LPZ was verified in phase III studies in RE patients, patients with gastric ulcer, patients requiring *H. pylori* eradication, and patients who had a medical history of gastric or duodenal ulcer and had to receive LDA or NSAID for a long period of time [see "4.(iii).B.(1) Efficacy"]. In a phase III study in patients with duodenal ulcer, non-inferiority of vonoprazan to LPZ was not statistically verified, but the cure rate [95% CI] in the vonoprazan 20 mg group was 95.5% [91.3, 98.0], showing clinically sufficient efficacy as described in "4.(iii).B.(1).3) Duodenal ulcer." PMDA therefore considers it possible to accept the efficacy of vonoprazan in patients with duodenal ulcer. Regarding the safety, PMDA considers that significant issues are unlikely to occur for any indication at present, although more attention should be paid to increased serum gastrin levels than LPZ [see "4.(iii).B.(2) Safety"].

Based on the above, PMDA considers the proposed indications of vonoprazan that follow are appropriate: gastric ulcer; duodenal ulcer; reflux esophagitis; prevention of recurrent gastric or duodenal ulcer associated with low-dose aspirin administration; prevention of recurrent gastric or duodenal ulcer during non-steroidal anti-inflammatory drug administration; as well as an adjunct to *Helicobacter pylori* eradication in gastric ulcer, duodenal ulcer, gastric mucosa-associated lymphatic tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, the stomach after endoscopic resection of early stage gastric cancer, or *Helicobacter pylori* gastritis.

A final decision on the indications of vonoprazan will be made, taking account of comments raised in the Expert Discussion.

4.(iii).B.(4) Dosage and administration

Based on the review in the following sections 4.(iii).B.(4).1) to 4.(iii).B.(4).7), PMDA considers it acceptable to set the dosage and administration for each indication in accordance with those employed in Japanese phase III studies. A final decision on the dosage and administration of vonoprazan will be made, taking account of not only review results for each indication but also comments raised in the Expert Discussion.

4.(iii).B.(4).1) Rationale for setting the dosage and administration in Japanese phase III studies

The applicant explained the doses in phase III studies of vonoprazan as follows:
The LPZ dose used in the control group as the therapeutic dose for RE, was the same dose used for the treatment of gastric or duodenal ulcer, and half of this dose was used for the maintenance therapy of RE and the prevention of recurrent LDA or NSAID ulcer. Twice the therapeutic dose of RE (the therapeutic dose for RE twice daily) was used as the dose for an adjunct to *H. pylori* eradication therapy.

In a Japanese phase I multiple-dose study (Study CPH-002), vonoprazan was administered once daily to Japanese healthy adult male subjects at a dose of 10 to 40 mg for 7 days to investigate pH 3 HTR, pH

[158] Number of subjects treated concomitantly with clopidogrel in Study CCT-302, 45 of 202 subjects in the vonoprazan 10 mg group, 36 of 202 subjects in the vonoprazan 20 mg group, 39 of 217 subjects in the LPZ 15 mg group; in Study OCT-302, 45 of 202 subjects in the vonoprazan 10 mg group, 36 of 202 subjects in the vonoprazan 20 mg group, 41 of 217 subjects in the LPZ 15 mg group

4 HTR, and pH 5 HTR[159] [Table 22, see "4.(ii).A.(3) Japanese phase I multiple-dose study"]. As a result, sufficient inhibition against acid secretion was observed for 24 hours at the doses of ≥10 mg of vonoprazan.

In a phase II dose-finding study in RE patients (Study CCT-001), non-inferiority of the vonoprazan 5 mg group, 10 mg group, 20 mg group, and 40 mg group to the LPZ 30 mg group was verified in terms of the "RE cure rate at Week 4," the primary endpoint. Furthermore, the cure rate at Week 4 in the patients with severe RE of Grade C/D under LA classification assessed during the observation period was 87.3%, 86.4%, 100.0%, 96.0%, and 87.0% in the vonoprazan 5 mg group, 10 mg group, 20 mg group, and 40 mg group, and the LPZ 30 mg group, respectively. The cure rate in the ≥20 mg vonoprazan groups was higher than that in the LPZ 30 mg group, and the cure rate between the vonoprazan 20 mg group and 40 mg group was comparable. The incidence of adverse events was largely comparable among the dose groups. Based on the above data on the efficacy and safety, the clinical recommended dose of vonoprazan in treatment for RE was set at 20 mg as the daily dose.

Based on the above, the investigational dose chosen was 20 mg in Studies CCT-101 (gastric ulcer) and CCT-102 (duodenal ulcer), equivalent to the therapeutic dose for RE, a representative acid-related disease. In Studies CCT-003 and OCT-001 (maintenance therapy for RE), Studies CCT-302 and OCT-302 (prevention of recurrent LDA ulcer) as well as Studies CCT-301 and OCT-301 (prevention of recurrent NSAID ulcer), the investigational dose chosen was 10 mg and 20 mg, a half of and equivalent to the therapeutic dose for RE, because they were considered most likely to become the clinical recommended doses. Furthermore, in Study CCT-401 (adjunct to *H. pylori* eradication), the investigational dose was set at twice the therapeutic dose for RE (twice daily at a dose of 20 mg, the therapeutic dose for RE).

PMDA considers that there are no particular problems with vonoprazan dose-finding in phase III studies for each indication.

4.(iii).B.(4).2) RE

(a) Treatment for RE

The proposed dosage and administration of vonoprazan in treatment for RE was set as the following: the usual dose of 20 mg is administered once daily for up to 4 weeks; and if there is a lack of efficacy, the treatment may be extended to a maximum of 8 weeks.

The applicant explained the reason for the above dose and administration as follows:
In Study CCT-002 in RE patients, non-inferiority of the vonoprazan 20 mg group to the LPZ 30 mg group was verified in terms of the cure rate at Week 8, the primary endpoint [Table 39, see "4.(iii).A.(2) Phase III study of the treatment for RE"]. The cure rate at Week 4 was as shown in Table 89. The difference [95% CI] between the cure rate at Week 4 in the vonoprazan 20 mg group and that at Week 8 in the LPZ 30 mg group was 1.1% [-2.7, 4.9], suggesting that the efficacy of vonoprazan 20 mg once daily for 4 weeks was not inferior to that of LPZ 30 mg once daily for 8 weeks.[160] It was therefore considered appropriate to determine the usual treatment period of vonoprazan as up to 4 weeks.

[159] The parameters of pH 3 HTR and pH 4 HTR have been reported to affect therapeutic outcomes of peptic ulcer (gastric or duodenal ulcer) and gastroesophageal reflux disease, respectively (*Dig Dis Sci.* 1995;40:24S-49S, *Arch Intern Med.* 1999;159:649-657.).

[160] In treatment for RE, LPZ may be administered for up to 8 weeks.

Table 89. RE cure rate at Week 4 and Week 8 in Study CCT-002 (FAS)[a)]

After the study treatment start	Treatment group	No. of subjects with cured RE	Cure rate (%) [95% CI]	Difference from the LPZ 30 mg group (%) [95% CI]
Week 4	LPZ 30 mg group (N = 199)	184	92.5 [87.9, 95.7]	-
	Vonoprazan 20 mg group (N = 205)	198	96.6 [93.1, 98.6]	4.1 [-0.3, 8.6]
Week 8	LPZ 30 mg group (N = 199)	190	95.5 [91.6, 97.9]	-
	Vonoprazan 20 mg group (N = 205)	203	99.0 [96.5, 99.9]	3.5 [0.4, 6.7]

a) Of the FAS, patients who did not undergo endoscopy post-dose (2 subjects in the LPZ 30 mg group, 2 subjects in the vonoprazan 30 mg group) and patients who underwent endoscopy ≥15 days after the end of treatment (1 subject in the LPZ 30 mg group) were excluded from the analysis.

The applicant considered that vonoprazan may be administered for up to 8 weeks if there is a lack of efficacy, because in Studies CCT-001 and CCT-002, some patients in whom RE remained uncured at Week 4 was cured at Week 8, and there were no particular safety issues in patients who received vonoprazan once daily at a dose of 20 mg for 8 weeks.

Considering that shorter treatment period is desirable in addition to the applicant explanation above, PMDA has concluded that there are no particular problems to determine the dosage and administration of vonoprazan for RE as follows: the usual dose of 20 mg is administered once daily for 4 weeks; and if there is a lack of efficacy, the treatment may be extended to a maximum of 8 weeks.

(b) Maintenance therapy for RE

The proposed dosage and administration of vonoprazan in the maintenance therapy for RE was as follows: the usual dose of 10 mg or 20 mg is administered once daily.

The applicant explained the reason for the above regimen as follows:
In Study CCT-003, designed for patients in whom RE was confirmed endoscopically to be cured, non-inferiority of the vonoprazan 10 mg group and the vonoprazan 20 mg group to the LPZ 15 mg group was verified in terms of the RE recurrence rate at Week 24 of the maintenance period, i.e., the primary endpoint. Based on the central assessment of the endoscopic findings on RE, a difference [two-sided 95% CI] between the vonoprazan 20 mg group and the vonoprazan 10 mg group was -3.6% [-6.5, -0.6], of which the upper limit of the two-sided 95% confidence interval was below 0. The results of the subgroup analysis [Table 71, see "4.(iii).B.(1).1).(b).ii) Recurrence rate of RE by patient characteristic"] suggested usefulness of vonoprazan at a dose of 20 mg in patients with severe baseline RE under LA classification (Grade C/D) and patients with *H. pylori* negative and esophageal hiatal hernia who were deemed to have enhanced gastric acid secretion or have a high risk of acid reflux. The applicant, therefore, considered that the dose of 20 mg was recommended for these patients. In the above subgroup analysis, the RE recurrence rate in the vonoprazan 20 mg group tended to be lower than that in the vonoprazan 10 mg group in all the subgroups except for patients aged ≥65 years and <75 years, female patients, and patients without esophageal hiatal hernia. Therefore, for patients with repeated recurrence and relapse irrespective of the patient characteristics, vonoprazan at a dose of 20 mg was recommended.

During the maintenance period of Study CCT-003 and in Study OCT-001, no particular safety issues were observed in patients who received vonoprazan once daily at a dose of 10 mg or 20 mg.

Based on the above, the following dosage and administration of vonoprazan are considered appropriate for the maintenance therapy for RE: the dosage of 10 mg or 20 mg is administered once daily, and the dosage should be chosen in consideration of the patient characteristics etc.

PMDA considers as follows:
In Study CCT-003, non-inferiority of the vonoprazan 10 mg group and the vonoprazan 20 mg group to the LPZ 15 mg group was verified in terms of the "recurrence rate at Week 24 of the maintenance period,"

the primary endpoint. In the subgroups of the patients with severe baseline RE under LA classification (Grade C/D) and patients with *H. pylori* negative and esophageal hiatal hernia who were deemed to have enhanced gastric acid secretion or have a high risk of acid reflux, the recurrence rate of RE in the vonoprazan 20 mg group tended to be generally lower than that in the vonoprazan 10 mg group, suggesting clinical usefulness of vonoprazan at a dose of 20 mg, although it should be noted that this tendency was derived from the subgroup analysis.

On the other hand, no considerable differences have been observed in the safety between the vonoprazan 10 mg group and the 20 mg group, but the serum gastrin level tended to be slightly higher in the vonoprazan 20 mg group than in the 10 mg group. Caution is needed for the matter in the maintenance therapy for RE in which vonoprazan is administered for a long period of time.

In consideration of the above matters and desirable state in which unnecessary drug exposure is avoided wherever possible, PMDA has concluded that it is acceptable to determine the main dosage and administration of vonoprazan in the maintenance therapy for RE as follows: the dosage of 10 mg is administered once daily, and if there is a lack of efficacy, the dose of 20 mg may be administered once daily. Still, a final decision will be made, taking account of comments raised in the Expert Discussion.

4.(iii).B.(4).3) Gastric ulcer

In Study CCT-101 in patients with gastric ulcer, the efficacy of vonoprazan was demonstrated, and no particular safety issues were raised. PMDA has thus concluded that there are no particular problems to determine the following dosage and administration of vonoprazan in patients with gastric ulcer as employed in Study CCT-101: the dose of 20 mg is administered once daily usually for up to 8 weeks.

4.(iii).B.(4).4) Duodenal ulcer

In Study CCT-102 in patients with duodenal ulcer, the efficacy of vonoprazan was demonstrated, and no particular safety issues were raised. PMDA has thus concluded that there are no particular problems to determine the following dosage and administration of vonoprazan in patients with duodenal ulcer as employed in Study CCT-102: the dose of 20 mg is administered once daily usually for up to 6 weeks.

4.(iii).B.(4).5) Adjunct to *H. pylori* eradication

In Study CCT-401 in *H. pylori* positive patients, the efficacy of vonoprazan was demonstrated, and no particular safety issues were raised. PMDA has thus concluded that there are no particular problems to determine the following dosage and administration of vonoprazan in *H. pylori* positive patients as employed in Study CCT-401: the dose of 20 mg is administered twice daily for 7 days.

4.(iii).B.(4).6) Prevention of recurrent gastric or duodenal ulcer during LDA treatment

In Study CCT-302 in patients who had a medical history of gastric or duodenal ulcer and had to receive LDA for a long period of time, the efficacy of vonoprazan was demonstrated at both doses of 10 mg and 20 mg without differences between the doses. Regarding safety, the trend of adverse events in the vonoprazan 10 mg group was comparable to that in the vonoprazan 20 mg group in Studies CCT-302, OCT-302, and OCT-304. No particular safety issues were raised in either group.

Based on the above data, PMDA has concluded that there are no particular problems to determine the following dosage and administration of vonoprazan for prevention of recurrent gastric or duodenal ulcer during the LDA treatment: the low dose of 10 mg is administered once daily.

4.(iii).B.(4).7) Prevention of recurrent gastric or duodenal ulcer during NSAID treatment

In Study CCT-301 in patients who had a medical history of gastric or duodenal ulcer and had to receive NSAID for a long period of time, the efficacy of vonoprazan was demonstrated at both doses of 10 mg and 20 mg without differences between the doses. Regarding safety, the trend of adverse events in the vonoprazan 10 mg group was comparable to that in the vonoprazan 20 mg group in Studies CCT-301, OCT-301, and OCT-303. No particular safety issues were raised in either group.

Based on the above data, PMDA has concluded that there are no particular problems to set the following dosage and administration of vonoprazan for prevention of recurrent gastric or duodenal ulcer during the NSAID treatment: the low dose of 10 mg is administered once daily.

4.(iii).B.(5) Clinical positioning

Non-inferiority of vonoprazan to LPZ was verified in phase III studies in RE patients, patients with gastric ulcer, patients requiring *H. pylori* eradication, and patients who had a medical history of gastric or duodenal ulcer and had to receive LDA or NSAID for a long term [see "4.(iii).B.(1) Efficacy"]. In a phase III study in patients with duodenal ulcer, non-inferiority of vonoprazan to LPZ was not statistically verified, but as described in "4.(iii).B.(1).3) Duodenal ulcer," PMDA considers it possible to accept the efficacy of vonoprazan in patients with duodenal ulcer. Regarding the safety, PMDA considers that no major problems are likely to occur for any indication at present, although more attention should be paid to increased serum gastrin levels when administering vonoprazan than when administering LPZ [see "4.(iii).B.(2) Safety"]. Based on the above, PMDA considers that positioning of vonoprazan in the treatment and maintenance therapy for RE, treatment for gastric ulcer and duodenal ulcer, an adjunct to *H. pylori* eradication, and prevention of recurrent gastric or duodenal ulcer during LDA or NSAID administration is comparable to that of LPZ, and therefore vonoprazan can be a new therapeutic option of a PPI for these indications.

4.(iii).B.(6) Post-marketing investigations

The applicant explained as follows:

The use-results surveys will be conducted for treatments for gastric ulcer, duodenal ulcer, or RE as shown in Table 90 and for 3-drug combination therapy including vonoprazan for *H. pylori* eradication as shown in Table 91. The specified drug use-results surveys on long-term treatment will be conducted for the maintenance therapy for RE as shown in Table 92 as well as for prevention of recurrent gastric or duodenal ulcer during the LDA treatment and during the NSAID treatment as shown in Table 93 and Table 94, respectively.

Table 90. Outline of use-results survey (treatment for gastric ulcer, duodenal ulcer, and RE) (draft)

Objective	To investigate the safety and efficacy of vonoprazan in patients with gastric ulcer, duodenal ulcer, and RE in routine clinical use
Survey method	Central registry system
Patients surveyed	Patients with gastric ulcer, duodenal ulcer, or RE
Target sample size	3000 patients (≥500 patients each with gastric ulcer or duodenal ulcer, ≥1000 patients with RE)
Survey period	2 years and 2 months (registration period, 2 years)
Observation period	Gastric ulcer, 8 weeks; duodenal ulcer, 6 weeks; RE, 8 weeks
Main survey items	• Patient characteristics (gender, age, disease to be treated, medical history, complications, presence or absence of *H. pylori* infection, etc.) • Administration status of vonoprazan (daily dose, treatment period, reason for treatment discontinuation) • Administration status of concomitant drugs (presence or absence of concomitant drugs, names of drugs to be concomitantly administered, treatment objective) • Efficacy (endoscopy, improvement of symptoms) • Liver function test values • Adverse events (date of onset, seriousness, vonoprazan treatment completed or discontinued, outcome, causal relationship to vonoprazan, etc.) (detailed information on the hepatic impairment and gastrointestinal infection due to *Clostridium difficile* [CD] will be collected at the time of onset)

Table 91. Outline of use-results survey (adjunct to *H. pylori* eradication) (draft)

Objective	To investigate the safety and efficacy of vonoprazan in patients who are undergoing *H. pylori* eradication with the 3-drug combination therapy including vonoprazan in routine clinical use
Survey method	Central registry system
Patients surveyed	The following patients who are undergoing *H. pylori* eradication with the 3-drug combination therapy including vonoprazan • Patients who are undergoing *H. pylori* eradication by the primary eradication regimen for the first time • Patients who have failed in *H. pylori* eradication with AMPC, CAM, and PPIs including vonoprazan and undergoing the secondary eradication regimen
Target sample size	500 patients
Survey period	1 year and 8 months (registration period, 1 year and 6 months)
Observation period	From the start of the treatment to eradication assessment (eradication should be assessed between 4 weeks to ≤2 months after the end of eradication regimen)
Main survey items	• Patient characteristics (gender, age, primary disease to be treated with *H. pylori* eradication, previous *H. pylori* eradication regimens, time of diagnosis of *H. pylori* infection and diagnosis method, medical history, complication, etc.) • Administration status of vonoprazan and antimicrobial drugs (drug name, daily dose, duration of 3-drug eradication therapy, reason for discontinuing 3-drug eradication therapy) • Administration status of concomitant drugs other than antimicrobial agents (presence or absence of concomitant drugs, drug name, treatment objective) • Efficacy (*H. pylori* eradication assessment [examination method, date of examination, assessment results]) • Liver function test values • Adverse events (date of onset, seriousness, 3-drug eradication therapy completed or discontinued, outcome, causal relationship to the 3-drug eradication therapy, etc.) (detailed information on the hepatic impairment and gastrointestinal infection due to CD will be collected at the time of onset)

Table 92. Outline of specified drug use-results survey on long-term use (maintenance therapy for RE) (draft)

Objective	To investigate the safety and efficacy of vonoprazan in a long-term administration as a maintenance therapy for RE under use conditions in routine medical practice
Survey method	Central registry system
Patients surveyed	Patients who receive vonoprazan as the maintenance therapy for RE for a longperiod
Target sample size	1000 (300 subjects who have received vonoprazan for 12 months)
Survey period	2 years and 6 months (registration period, 1 year and 6 months)
Observation period	12 months
Main survey items	• Patient characteristics (gender, age, medical history, complication, presence or absence of *H. pylori* infection, etc.) • Administration status of vonoprazan (daily dose, treatment period, reason for discontinuing treatment) • Administration status of concomitant drugs (presence or absence of concomitant drugs, drug name, treatment objective) • Efficacy (endoscopy, improvement of symptoms) • Liver function test values • Serum gastrin level • Adverse events (date of onset, seriousness, vonoprazan treatment completed or discontinued, outcome, causal relationship to vonoprazan, etc.) (detailed information on the hepatic impairment, fracture, and gastrointestinal infection due to CD, as well as tumors such as gastric carcinoid and gastric adenoma will be collected at the time of onset)

Table 93. Outline of specified drug use-results survey on long-term use (prevention of recurrent LDA ulcer) (draft)

Objective	To investigate the safety and efficacy following long-term treatment with vonoprazan in patients on LDA under use conditions in routine medical practice
Survey method	Central registry system
Patients surveyed	Patients who have been continuing to receive LDA to prevent thrombogenesis/embolization, have a medical history of gastric or duodenal ulcer, and have to receive vonoprazan for a long period to prevent its recurrence. Excluding patients who have gastric ulcer, duodenal ulcer, or active upper gastrointestinal haemorrhage at the baseline of vonoprazan treatment.
Target sample size	1000 patients (300 patients who have received vonoprazan for 12 months)
Survey period	3 years (registration period, 2 years)
Observation period	12 months
Main survey items	• Patient characteristics (gender, age, disease to be treated with LDA, medical history, complications, presence or absence of *H. pylori* infection, etc.) • Administration status of vonoprazan (daily dose, treatment period, reason for treatment discontinuation) • Administration status of LDA (drug name, daily dose, treatment period) • Administration status of concomitant drugs other than LDA (presence or absence of concomitant drugs, drug name, treatment objective) • Efficacy (presence or absence in development of gastric or duodenal ulcer and gastric or duodenal haemorrhagic lesion after the start of the vonoprazan treatment, etc.) • Liver function test values • Serum gastrin level • Adverse events (date of onset, seriousness, vonoprazan treatment completed or discontinued, outcome, causal relationship to vonoprazan, etc.) (detailed information on the hepatic impairment, fracture, and gastrointestinal infection due to CD, as well as tumors such as gastric carcinoid and gastric adenoma will be collected at the time of onset)

Table 94. Outline of specified drug use-results survey on long-term use (prevention of recurrent NSAID ulcer) (draft)

Objective	To investigate the safety and efficacy of long-term treatment with vonoprazan in patients on NSAID under use conditions in routine medical practice
Survey method	Central registry system
Patients surveyed	Patients who continued to receive NSAID (except for LDA) to control pain associated with rheumatoid arthritis, osteoarthritis, etc., have a medical history of gastric or duodenal ulcer, and have to receive vonoprazan for a long period to prevent its recurrence. Excluding patients who have gastric ulcer, duodenal ulcer, or active upper gastrointestinal haemorrhage at the baseline of vonoprazan treatment.
Target sample size	1000 patients (300 patients who have received vonoprazan for 12 months)
Survey period	3 years (registration period, 2 years)
Observation period	12 months
Main survey items	• Patient characteristics (gender, age, disease to be treated with NSAID, medical history, complication, presence or absence of *H. pylori* infection, etc.) • Administration status of vonoprazan (daily dose, treatment period, reason for treatment discontinuation) • Administration status of NSAID (drug name, daily dose, treatment period) • Administration status of concomitant drugs other than NSAID (presence or absence of concomitant use, drug name, treatment objective) • Efficacy (presence or absence in development of gastric or duodenal ulcer and gastric or duodenal haemorrhagic lesion after the start of vonoprazan treatment, etc.) • Liver function test values • Serum gastrin level • Adverse events (date of onset, seriousness, vonoprazan treatment completed or dicontinued, outcome, causal relationship to vonoprazan, etc.) (detailed information on the hepatic impairment, fracture, and gastrointestinal infection due to CD, as well as tumors such as gastric carcinoid and gastric adenoma will be collected at the time of onset)

PMDA considers that it is necessary to collect the following information through post-marketing surveillance. A final decision on details of the survey plans will be made, taking account of comments raised in the Expert Discussion.

- Administration status of clopidogrel as well as presence or absence of cardiovascular and cerebrovascular events in patients receiving LDA

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1-1, 5.3.5.1-3, 5.3.5.1-4, 5.3.5.1-5, 5.3.5.1-6, 5.3.5.1-7, 5.3.5.1-8). As a result, PMDA concluded that the clinical studies as a whole were performed in compliance with GCP, and there should be no problem with conducting a regulatory review based on the submitted application documents. The following finding was recognized in some of the study centers and thus informed to the head of the study centers as a matter to be improved, although it did not considerably affect the overall evaluation of the studies.

[Matter to be improved]
Study centers

- Protocol deviations (noncompliance with the timing of the clinical laboratory tests, noncompliance with the provisions related to prohibited concomitant drugs)

IV. Overall Evaluation

Based on the submitted data, PMDA considers as follows:
The efficacy of vonoprazan is demonstrated in patients with gastric ulcer, duodenal ulcer, or reflux esophagitis; in prevention of the recurrence of gastric ulcer or duodenal ulcer associated with the low-dose aspirin administration; in prevention of the recurrence of gastric ulcer or duodenal ulcer during non-steroidal anti-inflammatory drug administration; as well as in adjunct to *Helicobacter pylori* eradication in gastric ulcer, duodenal ulcer, gastric mucosa-associated lymphatic tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, the stomach after endoscopic resection of early stage gastric cancer, or *Helicobacter pylori* gastritis, and the safety is acceptable. Vonoprazan is a PPI that inhibits acid secretion by inhibiting H^+,K^+-ATPase in gastric mucosal parietal cells in a reversible and potassium-competitive manner, unlike the existing PPIs, providing a new therapeutic option for the above indications, and is considered to have a clinical significance. Vonoprazan may be approved if it can be concluded based on the comments on the efficacy, safety, indications, dosage and administration, and post-marketing investigations from the Expert Discussion that there are no particular problems.

Review Report (2)

November 10, 2014

I. Product Submitted for Registration

[Brand name]	Takecab Tablets 10 mg, Takecab Tablets 20 mg
[Non-proprietary name]	Vonoprazan Fumarate
[Name of applicant]	Takeda Pharmaceutical Company Limited
[Date of application]	February 28, 2014

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc., concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by the Pharmaceuticals and Medical Devices Agency" (PMDA Administration Rule No. 8/2008 dated December 25, 2008).

(1) Efficacy

Non-inferiority of vonoprazan fumarate (hereinafter referred to as vonoprazan) to lansoprazole (LPZ) was verified in terms of the primary endpoint in phase III studies in treatment and maintenance therapy for reflux esophagitis (RE), gastric ulcer, an adjunct to *Helicobacter pylori* (*H. pylori*) eradication, and prevention of recurrent gastric or duodenal ulcer associated with the low-dose aspirin (LDA) treatment and during the non-steroidal anti-inflammatory drug (NSAID) treatment. PMDA has therefore concluded that the efficacy of vonoprazan is demonstrated for these indications.

Regarding the efficacy of vonoprazan in patients with duodenal ulcer, the duodenal ulcer cure rate at Week 6, the primary endpoint, in Study CCT-102 was as shown in Table 48 [see "Review Report (1), 4.(iii).A.(6) Phase III study in patients with duodenal ulcer"]. Non-inferiority of the vonoprazan 20 mg group to the LPZ 30 mg group was not statistically verified. Based on the following points, however, the ulcer cure effect on duodenal ulcer in the vonoprazan 20 mg group did not tend to be clinically significantly inferior to that in the LPZ 30 mg group. PMDA therefore considered that vonoprazan has efficacy in patients with duodenal ulcer as well.

- The cure rate [95% CI] in the vonoprazan 20 mg group was 95.5% [91.3, 98.0], indicating clinically sufficient efficacy.

- The secondary and additional analyses were performed in the per protocol set (PPS) and in the patients who completed the study treatment in the full analysis set (FAS), respectively, to exclude the effect of the study treatment discontinuation [Table 73, see "4.(iii).B.(1).3).(a) Duodenal ulcer cure rate at Week 6" of the Review Report (1)] and the results showed that the lower limit of 95% confidence interval of the difference between the vonoprazan 20 mg group and the LPZ 30 mg group was above -6%.

- As a result of the sensitivity analysis performed by regarding the patients excluded from the FAS as patients with a recurrence, the difference between the vonoprazan 20 mg group and the LPZ 30 mg group and the lower limit of the 95% confidence interval were -2.8% and -7.3%, respectively [Table 73, see "4.(iii).B.(1).3).(a) Duodenal ulcer cure rate at Week 6" of the Review Report (1)], which were comparable to the results of the primary analysis in the FAS. The lower limit of 95% confidence interval of the difference between these groups would not be considerably lower than -6%.

- In treatment for the gastric-acid-related diseases such as gastric ulcer listed in this application, non-inferiority of vonoprazan to LPZ has been verified.

The above conclusion of PMDA was supported by the expert advisors.

(2) Safety

PMDA considers as follows:

The safety of vonoprazan is acceptable as long as appropriate cautions are provided using the safety information of the existing proton pump inhibitors (PPIs) as a reference, because incidences of adverse events and adverse drug reactions in the vonoprazan group did not tend to be clearly higher than those in the LPZ group in each phase III study; of the serious adverse events, neither events nor trends of onsets specific to the vonoprazan group were observed in comparison with the LPZ group; and the incidence of adverse events did not tend to clearly increase with the increasing treatment period of vonoprazan in each long-term treatment study. However, it is necessary to collect further information on the safety of long-term treatment with vonoprazan, safety in the elderly, fracture, and safety of concomitant use of vonoprazan with clopidogrel through post-marketing surveillance, etc.

In addition, the serum gastrin levels increased over time in the vonoprazan 10 mg group and the vonoprazan 20 mg group and remained higher for a long period, compared with the LPZ 15 mg group in each long-term treatment study. At present, the risk associated with the continuously high serum gastrin levels following long-term treatment with vonoprazan, such as development of neuroendocrine tumor, remains unclear. Therefore, the information that the serum gastrin levels tended to be higher in the vonoprazan group than in the LPZ group in clinical studies should be appropriately provided to the healthcare providers in clinical settings. It is also necessary to collect further information on development of hypergastrinaemia and neuroendocrine tumor following administration of vonoprazan through post-marketing surveillance, etc.

The above conclusion of PMDA was supported by the expert advisors, and the following comment was raised:

- At present, the risk associated with the continuously high serum gastrin levels following long-term treatment with vonoprazan, such as development of neuroendocrine tumor, remains unclear. Patients who receive vonoprazan for a long period of time should be carefully monitored by periodical endoscopy, etc.

In consideration of the above comment of the expert advisor, PMDA requested the applicant to provide cautions that patients who receive long-term treatment with vonoprazan should be carefully monitored by periodical endoscopy, etc., in the package insert, to which the applicant responded appropriately, and PMDA accepted the response.

(3) Indication

Based on the review results for the efficacy and safety, PMDA considers that the proposed indications of vonoprazan that follow are appropriate: treatment of gastric ulcer, duodenal ulcer, or reflux esophagitis; prevention of recurrent gastric or duodenal ulcer associated with low-dose aspirin administration; and prevention of recurrent gastric or duodenal ulcer associated with non-steroidal anti-inflammatory drug administration; as well as adjunct therapy to *Helicobacter pylori* eradication in gastric or duodenal ulcer, gastric mucosa-associated lymphatic tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, the stomach after endoscopic resection of early stage gastric cancer, or *Helicobacter pylori* gastritis.

The above conclusion of PMDA was supported by the expert advisors. PMDA has therefore concluded that the following “Indications” and “Precautions for indications” for vonoprazan may be included in the package insert in accordance with the applicant’s proposal.

[Indications]

- Treatment of gastric ulcer, duodenal ulcer, or reflux esophagitis; prevention of recurrent gastric or duodenal ulcer associated with low-dose aspirin administration; and prevention of recurrent gastric or duodenal ulcer associated with non-steroidal anti-inflammatory drug administration

- Adjunct to *Helicobacter pylori* eradication in the following:
  Gastric ulcer, duodenal ulcer, gastric mucosa-associated lymphatic tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, the stomach after endoscopic resection of early stage gastric

cancer, or *Helicobacter pylori* gastritis

[Precautions for indications]
For prevention of recurrent gastric or duodenal ulcer associated with low-dose aspirin administration
Vonoprazan should be administered to patients who continue receiving low-dose aspirin to prevent thrombogenesis/embolization. A medical history of gastric or duodenal ulcer should be checked before starting administration of vonoprazan.

For prevention of recurrent gastric or duodenal ulcer associated with non-steroidal anti-inflammatory drug administration
Vonoprazan should be administered to patients who continue receiving NSAID to control pain associated with rheumatoid arthritis, osteoarthritis, etc. A medical history of gastric or duodenal ulcer should be checked before starting administration of vonoprazan.

For adjunct therapy to *Helicobacter pylori* eradication
(1) The efficacy of *Helicobacter pylori* eradication in patients with advanced gastric MALT lymphoma has not been established.
(2) For patients with idiopathic thrombocytopenic purpura, the *Helicobacter pylori* eradication should be performed only in patients who are considered eligible for the eradication therapy in light of the guideline, etc.
(3) The efficacy of the *Helicobacter pylori* eradication for treatment of the stomach after endoscopic resection of early stage gastric cancer has been established, but not for other therapies for prevention of gastric cancer development.
(4) Before vonoprazan is administered to patients with *Helicobacter pylori* gastritis, the patients should be checked that they are *Helicobacter pylori* positive and endoscopically that they are affected by *Helicobacter pylori* gastritis.

(4) Dosage and administration
Based on the review results on the efficacy and safety, PMDA considers it appropriate to set the dosage and administration for gastric ulcer, duodenal ulcer, and adjunct therapy to *H. pylori* eradication in accordance with the corresponding conditions in the relevant phase III studies.

PMDA has accepted that the vonoprazan treatment period for RE is set at 4 weeks in principle, and if response to the initial course of treatment is inadequate, the treatment period may be extended up to 8 weeks, because Study CCT-002 suggested that the efficacy following once-daily administration of vonoprazan 20 mg for 4 weeks was not inferior to that following once-daily administration of LPZ 30 mg for 8 weeks [Table 89, see "4.(iii).B.(4).2).(a) Treatment for RE" of the Review Report (1)]; and the short treatment period is desirable.

Regarding efficacy of the maintenance therapy for RE, non-inferiority of both vonoprazan 10 mg group and the vonoprazan 20 mg group to the LPZ 15 mg group was verified in terms of the RE recurrence rate at Week 24 of the maintenance period, which is the primary endpoint in Study CCT-003. In the subgroups such as those of patients with severe baseline RE under LA classification (Grade C/D) and patients with *H. pylori* negative and esophageal hiatal hernia who were deemed to have enhanced gastric acid secretion or have a high risk of acid reflux, the recurrence rate of RE in the vonoprazan 20 mg group tended to be lower than that in the vonoprazan 10 mg group [Table 71, see "4.(iii).B.(1).1).(b).ii) Recurrence rate of RE by patient characteristic" of the Review Report (1)], suggesting clinical usefulness of vonoprazan at the dose of 20 mg. On the other hand, no considerable differences have been observed in the safety between the vonoprazan 10 mg group and 20 mg group, but the serum gastrin level tended to be slightly higher in the vonoprazan 20 mg group than in the 10 mg group. In consideration of the above findings and a desirable state in which unnecessary drug exposure is avoided wherever possible, PMDA has concluded that it is acceptable to set the recommended dosage and administration of vonoprazan in the maintenance therapy for RE as follows: the dose of 10 mg is administered once daily, and if response to the initial dose is inadequate, the dose may be increased to 20 mg once daily.

In terms of the prevention of recurrent gastric or duodenal ulcer associated with the LDA treatment and with the NSAID treatment, no considerable differences were observed in the efficacy or safety between the vonoprazan 10 mg group and the vonoprazan 20 mg group in the relevant phase III studies and their extension studies. PMDA has thus concluded that it is appropriate to set the dosage at 10 mg, the lower dose level in the above studies.

The above conclusion of PMDA was supported by the expert advisors. PMDA therefore requested the applicant to modify the "Dosage and Administration" of vonoprazan as shown below. To the request, the applicant responded appropriately, and PMDA accepted the response.

[Dosage and administration]

- Treatment of gastric ulcer and duodenal ulcer:
  The usual adult dosage is 20 mg of vonoprazan administered orally once daily. The usual treatment period should be up to 8 weeks for gastric ulcer and up to 6 weeks for duodenal ulcer.

- Treatment of reflux esophagitis:
  The usual adult dosage is 20 mg of vonoprazan administered orally once daily. The usual treatment period should be up to 4 weeks, but it may be extended up to 8 weeks if response to the initial course of the treatment is inadequate.

  For the maintenance therapy to prevent recurrence or relapse of reflux esophagitis, the dosage is 10 mg administered orally once daily. However, when response to the initial dose is inadequate, the dose may be increased to 20 mg once daily.

- Prevention of recurrent gastric or duodenal ulcer assosicated with low-dose aspirin administration:
  The usual adult dosage is 10 mg of vonoprazan administered orally once daily.

- Prevention of recurrent gastric or duodenal ulcer associated with non-steroidal anti-inflammatory drug administration:
  The usual adult dosage is 10 mg of vonoprazan administered orally once daily.

- Adjunct therapy to *Helicobacter pylori* eradication:
  For adults, the following 3-drug regimen should be administered orally at the same time twice daily for 7 days: 20 mg of vonoprazan, 750 mg (potency) of amoxicillin hydrate, and 200 mg (potency) of clarithromycin. The dose of clarithromycin may be increased as clinically warranted, but it should not exceed 400 mg (potency)/dose twice daily.

  In adult patients in whom *Helicobacter pylori* eradication with a 3-drug regimen comprising a proton pump inhibitor, amoxicillin hydrate, and clarithromycin was unsuccessful, the following 3 drugs should be administered orally twice daily for 7 days as an alternative treatment: 20 mg of vonoprazan, 750 mg (potency) of amoxicillin hydrate, and 250 mg of metronidazole.

(5) Draft risk management plan

The outlines (draft) of the use-results survey plan and specified drug use-results survey plan submitted by the applicant were found to have no major problems. PMDA, however, considers that it is necessary to collect the information on the dosing status of clopidogrel as well as the presence or absence of cardiovascular and cerebrovascular events in patients receiving LDA.

The above conclusion of PMDA was supported by the expert advisors.

Based on the above discussion, PMDA instructed the applicant to examine the draft risk management plan. The applicant submitted the safety specifications and efficacy specifications listed in Table 95, additional pharmacovigilance activities and risk minimization activities shown in Table 96, as well as outlines (draft) of the use-results survey plan and specified drug use-results survey plan shown in Table 97 to Table 101. PMDA accepted them.

Table 95. Safety and efficacy specifications in the risk management plan (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
Not applicable	• Neuroendocrine tumor due to increased serum gastrin levels • Hepatic impairment • Fracture • Gastrointestinal infection due to *Clostridium difficile* (CD) • Pneumonia	Not applicable
Efficacy specifications		
• Efficacy in routine clinical use • Efficacy in long-term treatment		

Table 96. Summary of additional pharmacovigilance activities and risk minimization activities in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Use-results survey (treatment for gastric ulcer, duodenal ulcer, and RE) • Use-results survey (adjunct to *H. pylori* eradication) • Specified drug use-results survey (maintenance therapy for RE, long-term use) • Specified drug use-results survey (prevention of recurrent gastric or duodenal ulcer during LDA treatment, long-term use) • Specified drug use-results survey (prevention of recurrent gastric or duodenal ulcer during NSAID treatment, long-term use)	• Providing information through early post-marketing phase vigilance

Table 97. Outline of use-results survey (treatment for gastric ulcer, duodenal ulcer, and RE) (draft)

Objective	To investigate the safety and efficacy of vonoprazan in patients with gastric ulcer, duodenal ulcer, and RE in routine medical use
Survey method	Central registry system
Patients surveyed	Patients with gastric ulcer, duodenal ulcer, or RE
Target sample size	3000 patients (≥500 patients each with gastric ulcer or duodenal ulcer, ≥1000 patients with RE)
Survey period	2 years and 2 months (registration period, 2 years)
Observation period	8 weeks for gastric ulcer, 6 weeks for duodenal ulcer, 8 weeks for RE
Main survey items	• Patient characteristics (gender, age, disease to be treated, medical history, complications, presence or absence of *H. pylori* infection, etc.) • Administration status of vonoprazan (daily dose, duration, reason for discontinuing treatment) • Administration status of concomitant drugs (presence or absence of concomitant drugs, drug name, treatment objective) • Efficacy (endoscopy, subjective symptoms) • Liver function test values • Adverse events (date of onset, seriousness, vonoprazan treatment completed or discontinued, outcome, causal relationship to vonoprazan, etc.) (detailed information on the hepatic impairment and gastrointestinal infection due to CD will be collected at the time of onset)

Table 98. Outline of use-results survey plan (adjunct to *H. pylori* eradication) (draft)

Objective	To investigate the safety and efficacy of vonoprazan in patients who are undergoing *H. pylori* eradication with the 3-drug combination therapy including vonoprazan in routine medical use
Survey method	Central registry system
Patients surveyed	The following patients who are undergoing *H. pylori* eradication with the 3-drug combination therapy including vonoprazan • Patients who are undergoing *H. pylori* eradication by the primary eradication regimen for the first time • Patients who have failed in *H. pylori* eradication with amoxicillin hydrate, clarithromycin, and PPIs including vonoprazan and undergoing the secondary eradication regimen
Target sample size	500 patients
Survey period	1 year and 8 months (registration period, 1 year and 6 months)
Observation period	From the start of the treatment to eradication assessment (eradication should be assessed between 4 weeks to ≤2 months after the end of the eradication regimen)
Main survey items	• Patient characteristics (gender, age, primary disease to be treated with *H. pylori* eradication, previous *H. pylori* eradication regimens, time of diagnosis of *H. pylori* infection and diagnosis method, medical history, complication, etc.) • Administration status of vonoprazan and antimicrobial drugs (drug name, daily dose, duration of 3-drug eradication therapy, reason for discontinuing 3-drug eradication therapy) • Administration status of concomitant drugs other than antimicrobial agents (presence or absence of concomitant drugs, drug name, treatment objective) • Efficacy (*H. pylori* eradication assessment [examination method, date of examination, assessment results]) • Liver function test values • Adverse events (date of onset, seriousness, 3-drug eradication therapy completed or discontinued, outcome, causal relationship to the 3-drug eradication therapy, etc.) (detailed information on the hepatic impairment and gastrointestinal infection due to CD will be collected at the time of onset)

Table 99. Outline of specified drug use-results survey on long-term use (maintenance therapy for RE) (draft)

Objective	To investigate the safety and efficacy of vonoprazan in a long-term administration as a maintenance therapy for RE in routine medical use
Survey method	Central registry system
Patients surveyed	Patients who receive vonoprazan as the maintenance therapy for RE for a long period
Target sample size	1000 patients (300 patients who have received vonoprazan for 12 months)
Survey period	2 years and 6 months (registration period, 1 year and 6 months)
Observation period	12 months
Main survey items	• Patient background (gender, age, medical history, complication, presence or absence of *H. pylori* infection, etc.) • Administration status of vonoprazan (daily dose, treatment period, reason for discontinuing treatment) • Administration status of concomitant drugs (presence or absence of concomitant drugs, drug name, treatment objective) • Efficacy (endoscopy, subjective symptoms) • Liver function test values • Serum gastrin levels • Adverse events (date of onset, seriousness, vonoprazan treatment completed or discontinued, outcome, causal relationship to vonoprazan, etc.) (detailed information on the hepatic impairment, fracture, gastrointestinal infection due to CD, and neuroendocrine tumor will be collected at the time of onset)

Table 100. Outline of specified drug use-results survey on long-term use (prevention of recurrent LDA ulcer) (draft)

Objective	To investigate the safety and efficacy of long-term treatment with vonoprazan in patients on LDA in routine medical use
Survey method	Central registry system
Patients surveyed	Patients who have continued receiving LDA to prevent thrombogenesis/embolization, have a medical history of gastric or duodenal ulcer, and have to receive vonoprazan for a long period to prevent its recurrence. Excluding patients who have gastric ulcer, duodenal ulcer, or active upper gastrointestinal haemorrhage at the baseline of vonoprazan treatment.
Target sample size	1000 patients (300 patients who have received vonoprazan for 12 months)
Survey period	3 years (registration period, 2 years)
Observation period	12 months
Main survey items	• Patient characteristics (gender, age, disease to be treated with LDA, medical history, complications, presence or absence of *H. pylori* infection, etc.) • Administration status of vonoprazan (daily dose, treatment period, reason for treatment discontinuation) • Administration status of LDA (drug name, daily dose, treatment period) • Dosing status of concomitant drugs (including clopidogrel) other than LDA (presence or absence of concomitant drugs, drug name, treatment objective) • Efficacy (presence or absence in development of gastric or duodenal ulcer and gastric or duodenal haemorrhagic lesion after the start of the vonoprazan treatment, etc.) • Liver function test values • Serum gastrin levels • Adverse events (date of onset, seriousness, completed/discontinued vonoprazan treatment, outcome, causal relationship to vonoprazan, etc.) (detailed information on the hepatic impairment, fracture, gastrointestinal infection due to CD, and neuroendocrine tumor, as well as cardiovascular and cerebrovascular events will be collected at the time of onset)

Table 101. Outline of specified drug use-results survey on long-term use (prevention of recurrent NSAID ulcer) (draft)

Objective	To investigate the safety and efficacy of long-term treatment with vonoprazan to patients on NSAID in routine medical use
Survey method	Central registry system
Patients surveyed	Patients who continue receiving NSAID (except for LDA) to control pain associated with rheumatoid arthritis, osteoarthritis, etc., have a medical history of gastric or duodenal ulcer, and have to receive vonoprazan for a long period to prevent its recurrence. Excluding patients who have gastric ulcer, duodenal ulcer, or active upper gastrointestinal haemorrhage at the baseline of vonoprazan treatment.
Target sample size	1000 patients (300 patients who have received vonoprazan for 12 months)
Survey period	3 years (registration period, 2 years)
Observation period	12 months
Main survey items	• Patient characteristics (gender, age, disease to be treated with NSAID, medical history, complication, presence or absence of *H. pylori* infection, etc.) • Administration status of vonoprazan (daily dose, treatment period, reason for treatment discontinuation) • Administration status of NSAID (drug name, daily dose, treatment period) • Administration status of concomitant drugs other than NSAID (presence or absence of concomitant use, drug name, treatment objective) • Efficacy (presence or absence in development of gastric or duodenal ulcer and gastric or duodenal haemorrhagic lesion after the start of the vonoprazan treatment, etc.) • Liver function test values • Serum gastrin levels • Adverse events (date of onset, seriousness, vonoprazan treatment completed or discontinued, outcome, causal relationship to vonoprazan, etc.) (detailed information on the hepatic impairment, fracture, gastrointestinal infection due to CD, and neuroendocrine tumor will be collected at the time of onset)

III. Overall Evaluation

As a result of the above review, PMDA concludes that the product may be approved after modifying the indication and the dosage and administration as shown below, with the following conditions. Since the product contains a new active ingredient, the re-examination period is 8 years. The drug substance is classified as a powerful drug, and the product is not classified as a poisonous drug or a powerful drug. The product is not classified as a biological product or a specified biological product.

[Indications]

- Treatment of gastric ulcer, duodenal ulcer, or reflux esophagitis; prevention of recurrent gastric or duodenal ulcer associated with low-dose aspirin administration, and prevention of recurrent gastric or duodenal ulcer associated with non-steroidal anti-inflammatory drug administration

- Adjunct therapy to *Helicobacter pylori* eradication in the following: Gastric or duodenal ulcer, gastric mucosa-associated lymphatic tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, the stomach after endoscopic resection of early stage gastric cancer, or *Helicobacter pylori* gastritis

[Dosage and administration]

- Treatment of gastric ulcer and duodenal ulcer:
  The usual adult dosage is 20 mg of vonoprazan administered orally once daily. The usual treatment period should be up to 8 weeks for gastric ulcer and up to 6 weeks for duodenal ulcer.

- Treatment of reflux esophagitis:
  The usual adult dosage is 20 mg of vonoprazan administered orally once daily. The usual treatment period should be up to 4 weeks, but it may be extended up to 8 weeks if response to the initial course of the treatment is inadequate.

  For the maintenance therapy to prevent recurrence or relapse of reflux esophagitis, the dosage is 10 mg administered orally once daily. However, when response to the initial dose is inadequate, the dosage may be increased to 20 mg once daily.

- Prevention of recurrent gastric or duodenal ulcer assosicated with low-dose aspirin administration:
  The usual adult dosage is 10 mg of vonoprazan administered orally once daily.

- Prevention of recurrent gastric or duodenal ulcer associated with non-steroidal anti-inflammatory drug administration:
  The usual adult dosage is 10 mg of vonoprazan administered orally once daily.

- Adjunct therapy to *Helicobacter pylori* eradication:
  For adults, the following 3-drug regimen should be administered orally at the same time twice daily for 7 days: 20 mg of vonoprazan, 750 mg (potency) of amoxicillin hydrate, and 200 mg (potency) of clarithromycin. The dose of clarithromycin may be increased as clinically warranted, but it should not exceed 400 mg (potency)/dose twice daily.

  In adult patients in whom *Helicobacter pylori* eradication with a 3-drug regimen comprising a proton pump inhibitor, amoxicillin hydrate, and clarithromycin was unsuccessful, the following 3 drugs should be administered orally twice daily for 7 days as an alternative

treatment: 20 mg of vonoprazan, 750 mg (potency) of amoxicillin hydrate, and 250 mg of metronidazole.

[Conditions for approval] The applicant is required to develop a risk management plan, and implement it appropriately.