NOVEL, FAST & POTENT ACID BLOCKER, **K-CAB**® [1]

1. Treatment of Erosive Gastroesophageal Reflux Disease
2. Treatment of Non-Erosive Gastroesophageal Reflux Disease
3. Treatment of Gastric Ulcer
4. **Eradication of *H. pylori* concurrently given with appropriate antibiotic therapy treatment in patients** with peptic ulcer and/or chronic atrophic gastritis

H. pylori Helicobacter pylori

K-CAB
케이캡정
Tegoprazan 50mg

K-CAB® is a **fast and potent** acid blocker.[1]

01 Fast onset of action: reaching intragastric pH ≥ 4 within 1 hour & potent effect on day 1[1,2]

02 High stability in gastric acid. Film-coated tablet & bottle packaging.[3,4]

03 Less affected by the CYP2C19[3]

04 Nighttime acid control[5]

05 Without meal dependency & no relevant food effect[4]

06 Sustained control of intragastric acidity, optimal for successful *H. pylori* eradication[6]

K-CAB® has been approved for **various indications.**[3,4]

[Product information of K-CAB® tab.]

Indications

1. Treatment of Erosive Gastroesophageal Reflux Disease
2. Treatment of Non-Erosive Gastroesophageal Reflux Disease
3. Treatment of Gastric Ulcer
4. Eradication of *H. pylori* concurrently given with appropriate antibiotic therapy treatment in patients with peptic ulcer and/or chronic atrophic gastritis

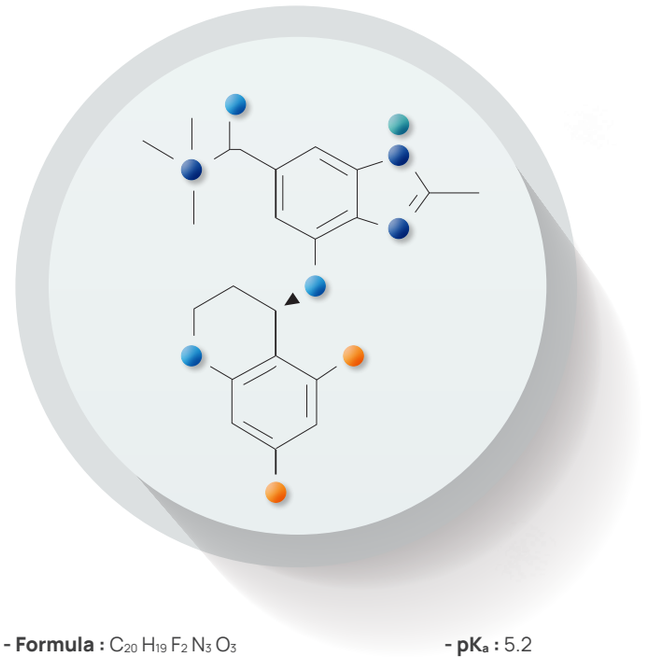
Dosage and administration

The drug should be administered to adults as follows.

1. **Treatment of ERD:** Oral administration of 50mg once daily for 4 weeks. Apply additional 4-week treatment for patients who do not show improvement of esophagitis or show persistent symptoms.
2. **Treatment of NERD:** Oral administration of 50mg once daily for 4 weeks.
3. **Treatment of GU:** Oral administration of 50mg once daily for 8 weeks.
4. ***H. pylori* eradication therapy** in combination with antibiotics in patients with peptic ulcer and/or chronic atrophic gastritis: Oral administration of tegoprazan 50 mg, clarithromycin 500 mg, and amoxicillin 1 g twice daily for 7days

K-CAB® can be taken without regard to food.

Tegoprazan



- **Formula :** $C_{20}H_{19}F_2N_3O_3$
- **MW :** 387.38 g/mol
- **Derivatives :** Benzimidazole Carboxamide
- **pK_a :** 5.2
- **T_{max} :** 0.75 hr (0.5-1.5)
- **$T_{1/2}$:** 4.1 hr

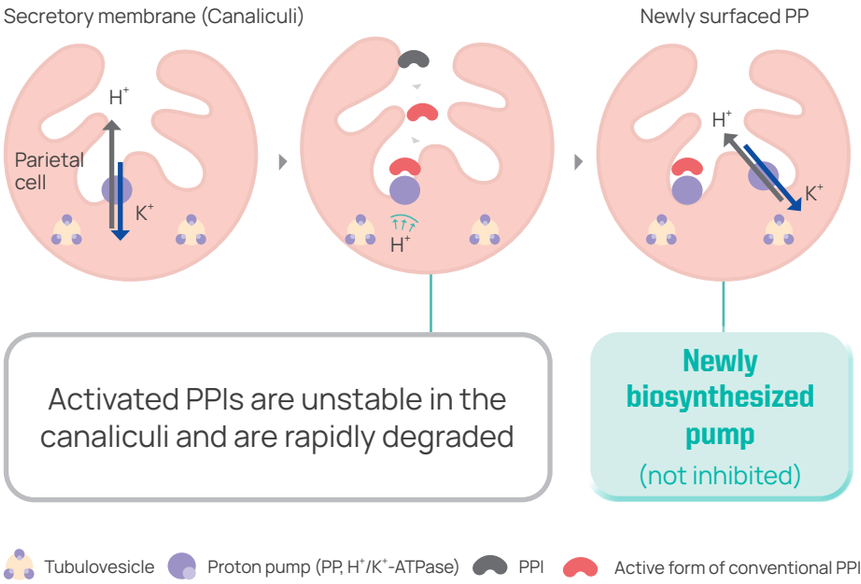
H. pylori=Helicobacter pylori

O N H F

K-CAB® is a novel potassium-competitive acid blocker (P-CAB).[3,4]

[Differences between Conventional PPI and P-CAB]

PPI[7,8]

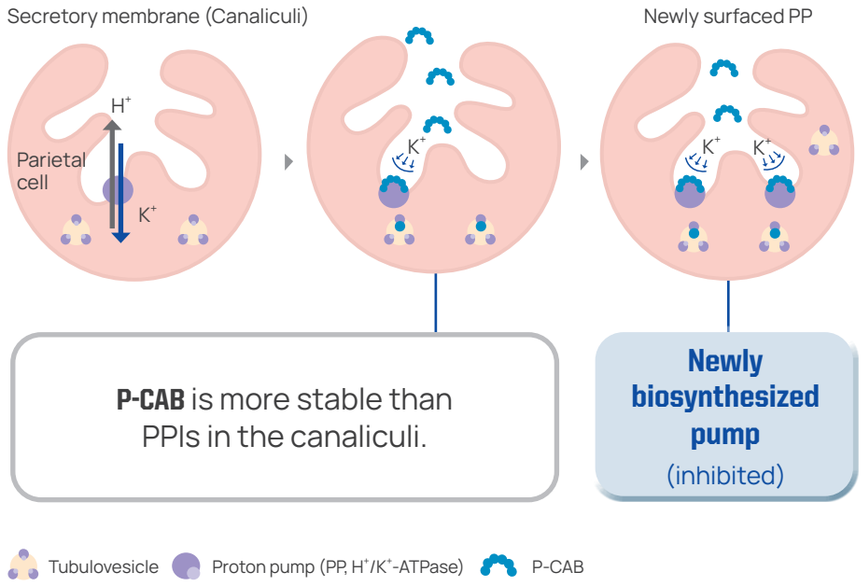


Activated PPIs are unstable in the canaliculi and are rapidly degraded

Newly biosynthesized pump (not inhibited)

Tubulovesicle | Proton pump (PP, H^+/K^+-ATPase) | PPI | Active form of conventional PPI

P-CAB[3,4,7,9]



P-CAB is more stable than PPIs in the canaliculi.

Newly biosynthesized pump (inhibited)

Tubulovesicle | Proton pump (PP, H^+/K^+-ATPase) | P-CAB

Proton pump inhibitors (PPIs)

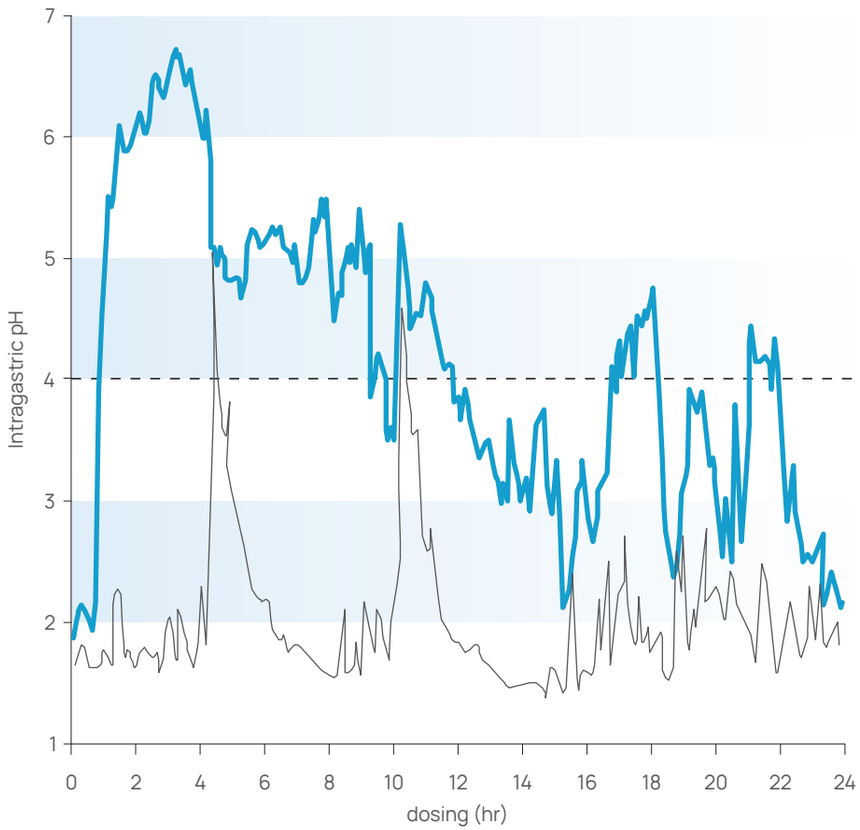
- are prodrugs, activated by gastric acid, so they need to be taken before meals.
- inhibit proton pump activation through irreversible binding only to active proton pumps.
- are instable in gastric acid and rapidly degraded in canaliculi, so they are not able to inhibit newly synthesized proton pumps.

Potassium-competitive acid blocker (P-CAB)

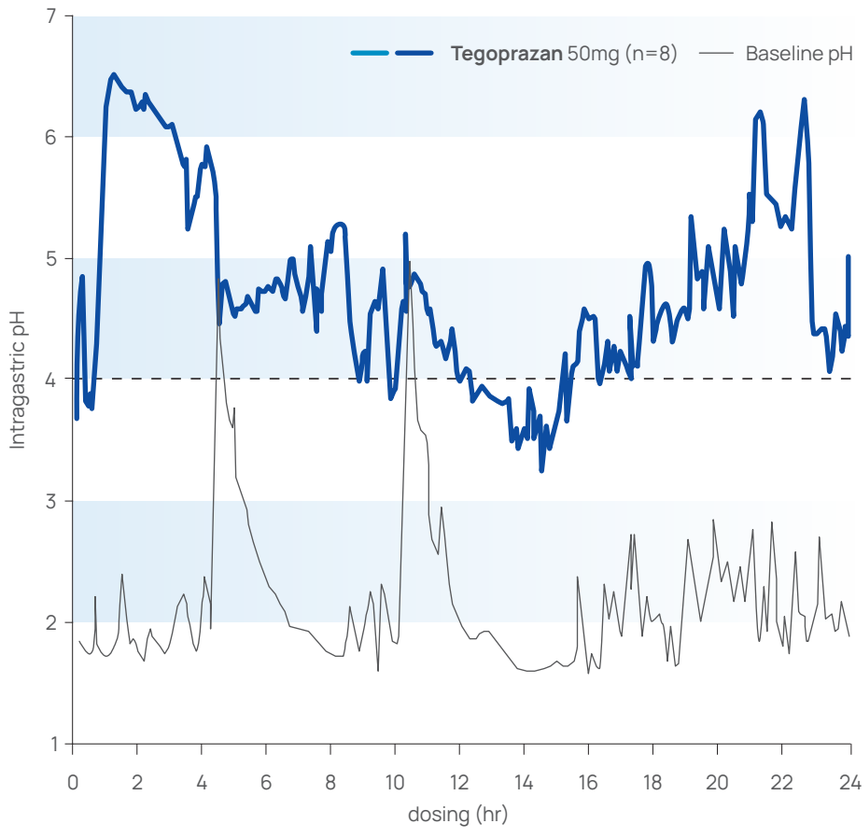
- inhibits the proton pump directly without activation by acid, so it can be taken without regard to food.
- inhibits both resting and activated proton pumps.
- reversibly binds to the proton pump to prevent potassium ions (K^+) from entering the parietal cells
- is highly stable in acidic environment, so it remains in the stomach for a long time and is able to inhibit newly synthesized proton pumps.

Within 1 hour,
single dose of K-CAB® can achieve intragastric **pH above 4.**[1,10]

Day 1. Fast onset (within 1 hour)



Day 7. Fast onset (within 1 hour)

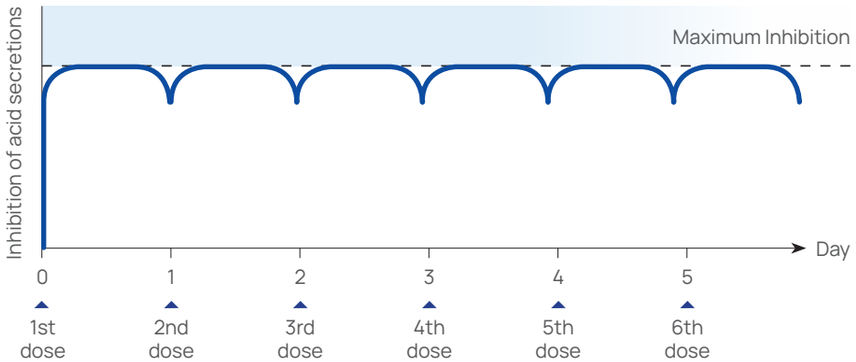


Study design phase I clinical trial of a randomized, open-label, active-controlled, multiple-dose study to evaluate the safety, tolerability, and pharmacodynamics of tegoprazan after oral administration in healthy male subjects.

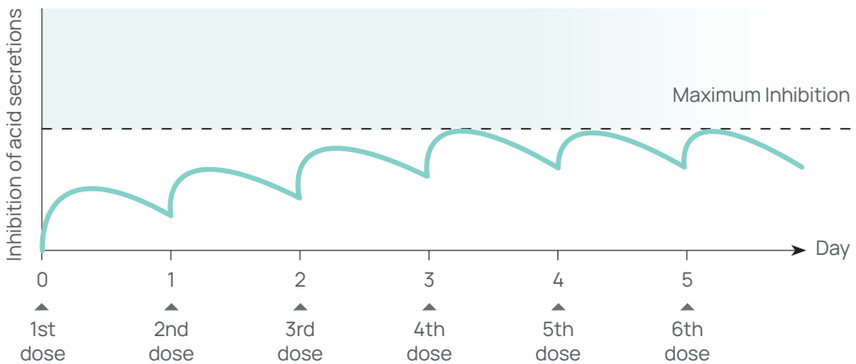
K-CAB® shows potent antisecretory effect from the **first day of administration.**[2]

Theoretical PD profile

• **P-CAB** shows maximum inhibitory effect from the first day of administration.[19]

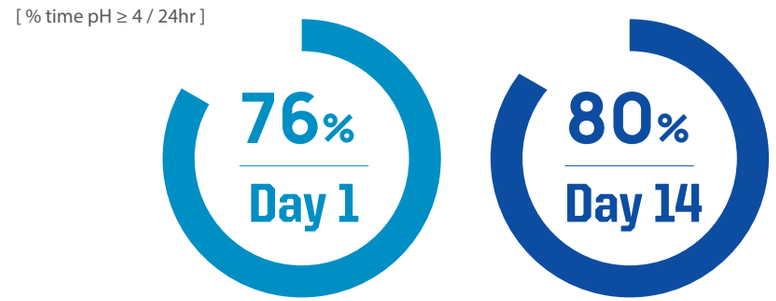


• It takes 4-5 days for **PPIs** to show maximal effects.[19]



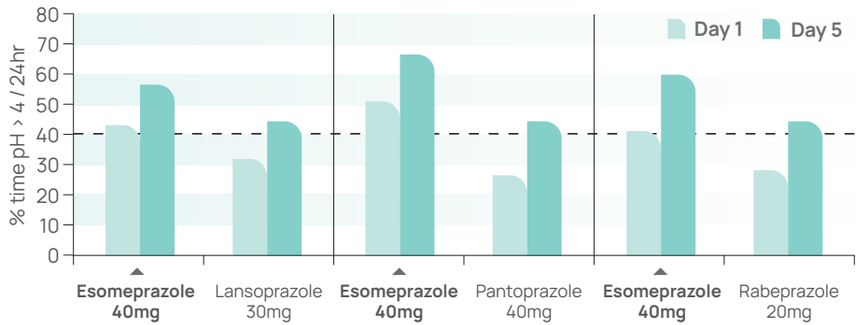
Clinical PD profile

• The inhibitory potency of K-CAB® on **day 1** was similar to that observed on **day 14**.[2]



Study design phase I clinical trial of a randomized, double-blinded, placebo-controlled, single and multiple-dose study to assess safety, tolerability, and pharmacodynamic characteristics after oral administration of Tegoprazan for 14 days to healthy male subjects.

• PPI shows different gastric acid inhibitory effects on day 1 and day 5 of administration.[20]



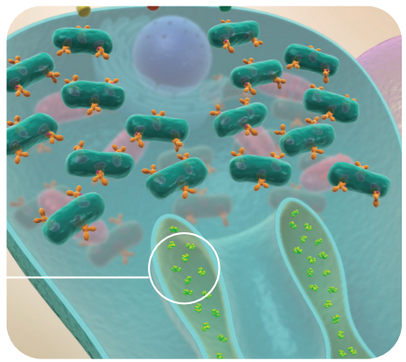
Study design three randomized crossover studies to compare the effect of PPIs in subjects with GERD. Subjects received esomeprazole 40mg, lansoprazole 30mg, omeprazole 20mg, pantoprazole 40mg and rabeprazole 20mg once daily for 5 days.

†**Omeprazole 20mg**: Only day 5 data available, omitted from the graph.

K-CAB® can be **taken with or without food.**[4,11]

PPI

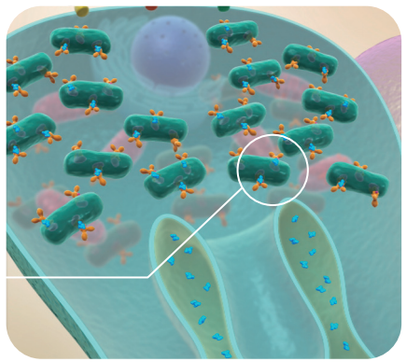
PPIs are activated by gastric acid, so they are affected by food intake.[12]



Tubulovesicle Proton pump (H^+/K^+-ATPase) PPI

P-CAB

P-CAB does not require activation by gastric acid.[7,9]



Tubulovesicle Proton pump (H^+/K^+-ATPase) **P-CAB**

The key pharmacodynamic parameters reflecting the effect of blocking gastric acid secretion of **K-CAB® were similar between fasting and fed conditions.**[4,11]

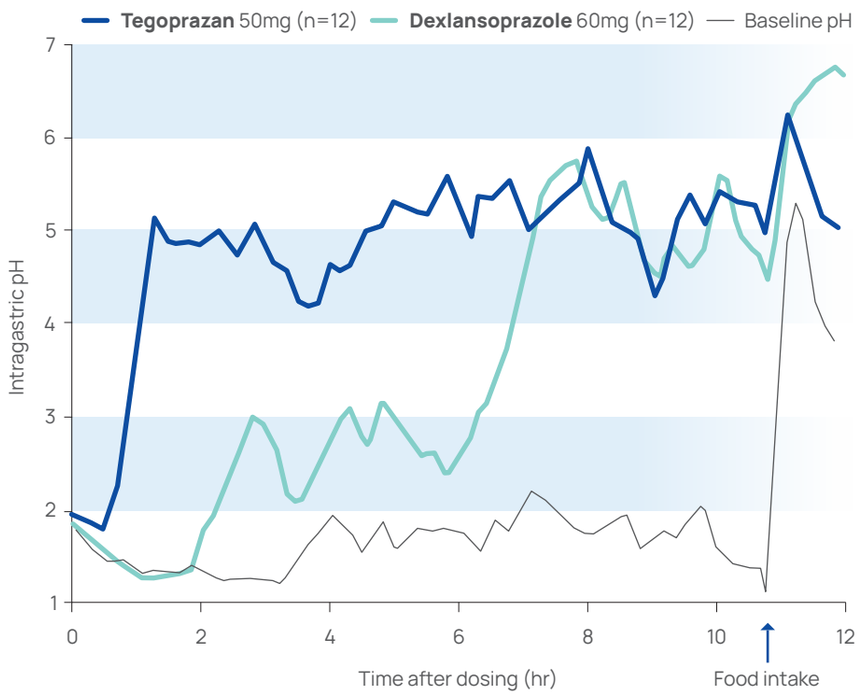
Study design phase I clinical trial to evaluate the food effect on pharmacokinetic and pharmacodynamic properties after administration of tegoprazan 200mg fasting and after meals to healthy adults.

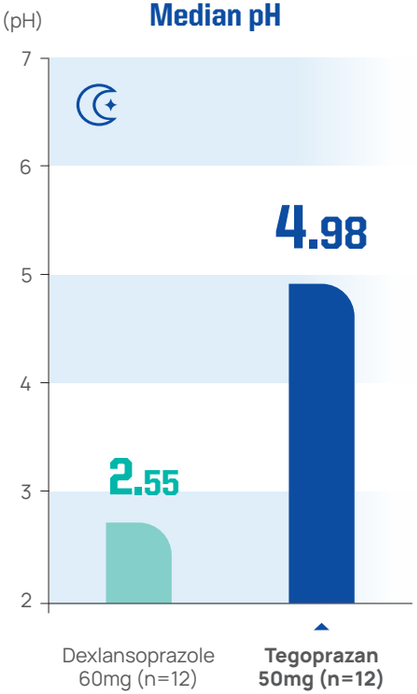
GERD: gastroesophageal reflux disease; **P-CAB**: potassium-competitive acid blocker; **PD**: pharmacodynamics; **PPI**: proton pump inhibitor

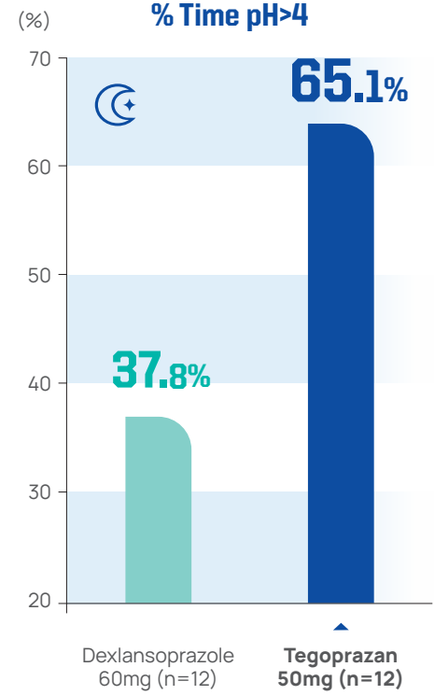
Pharmacodynamics (PD) parameter	Baseline (n=4)	Fasting condition (n=4)	Fed condition (n=4)
Median pH	1.19	**5.41**	**5.71**
% Time pH ≥ 4 / 24hr	11.8	**74.4**	**85.7**
Inhibition of Integrated Acidity (%)	N/A	93.4	99.3
Inhibition Time Gastric pH ≤ 4 (%)	N/A	71.1	83.2

K-CAB® can achieve intragastric pH above 4 within 1 hour **regardless of food intake at night.**[5]

Night time



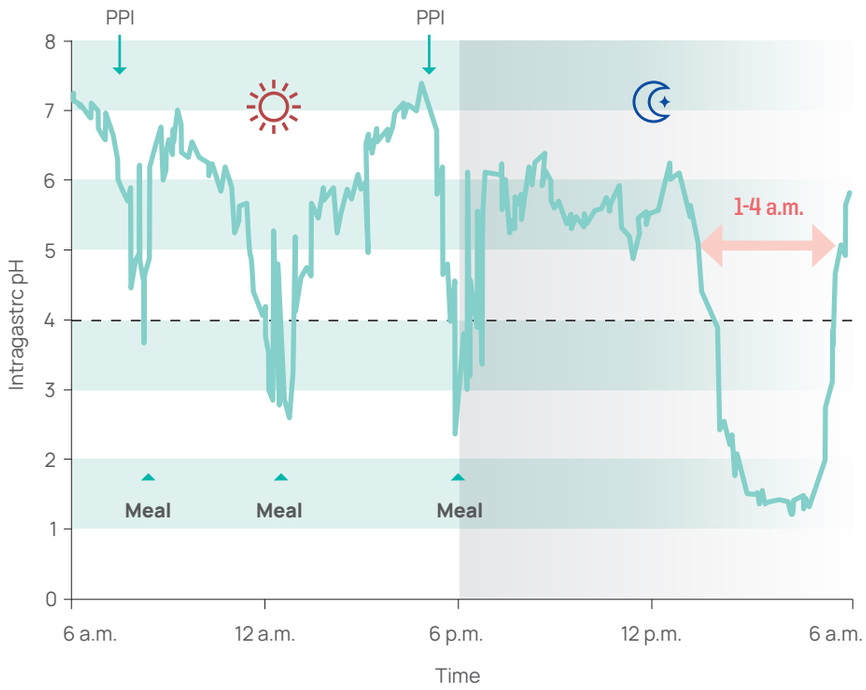




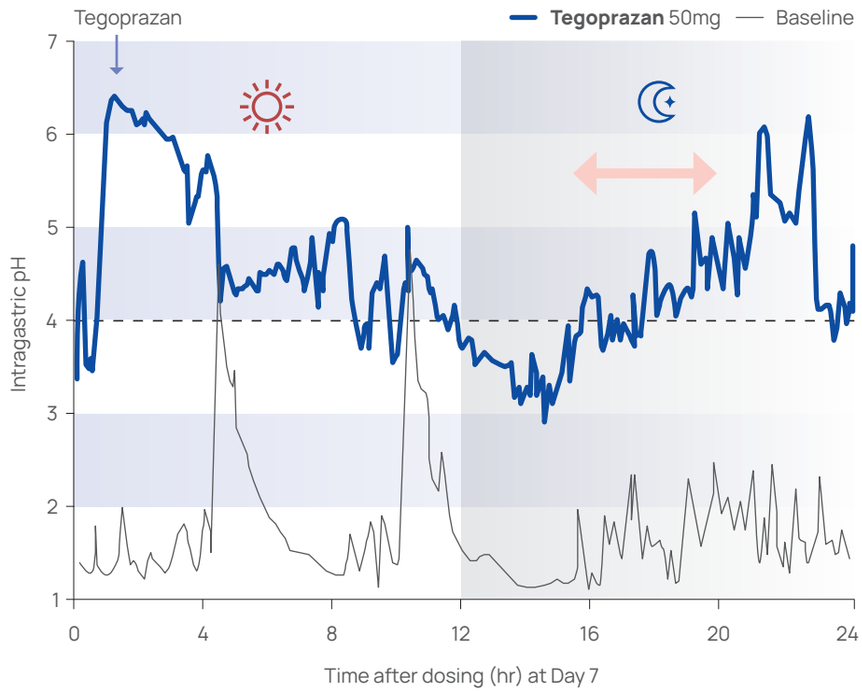
Study design A randomized, single-dose phase I clinical trial to compare the pharmacodynamic characteristics of Tegoprazan 50mg and Dexlansoprazole 60mg at night (9 p.m.) in healthy male subjects.

K-CAB® suppresses nocturnal gastric acid secretion.[5]

Conventional PPI[13]



K-CAB® (Tegoprazan)[5]



Nocturnal acid breakthrough† occurs despite treatment with twice daily PPI.

†**Nocturnal acid breakthrough** (NAB): intragastric pH < 4 for more than an hour during the overnight period (22:00 - 06:00)
GERD: gastroesophageal reflux disease; **PPI**: proton pump inhibitor

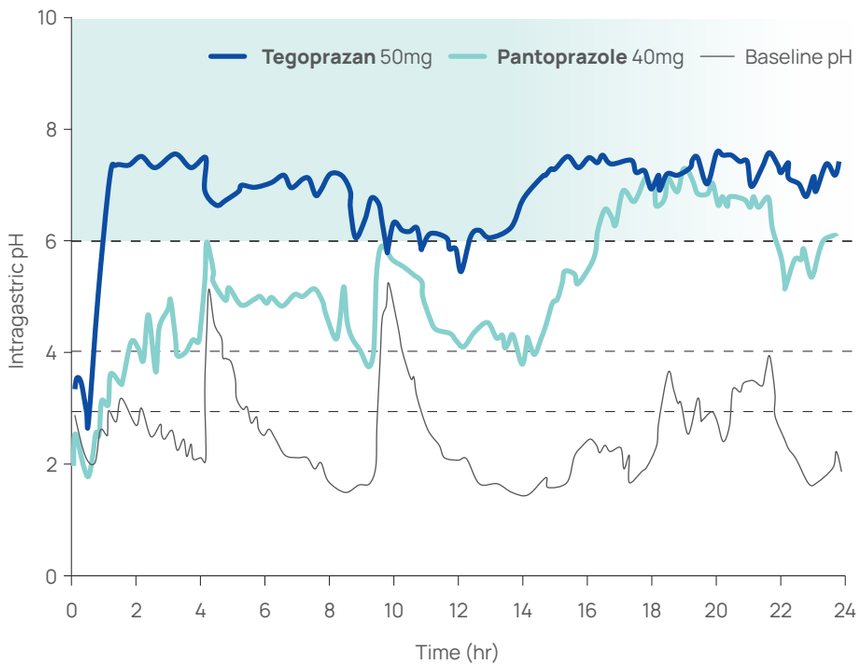
K-CAB® almost exhibits sustained control of intragastric acidity for 24 hours.

K-CAB® 50mg once daily can maintain intragastric pH above 4 most of the time at night.

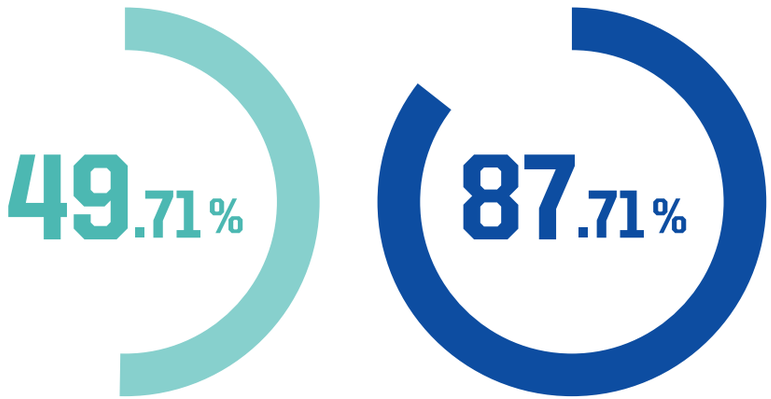
K-CAB® exhibits rapid onset of action and sustained co

- **K-CAB®** achieved intragastric **pH above 6 from the first day** by twice daily administration for *H. pylori* eradication.

Intragastric pH on day 1



Mean % time pH > 6



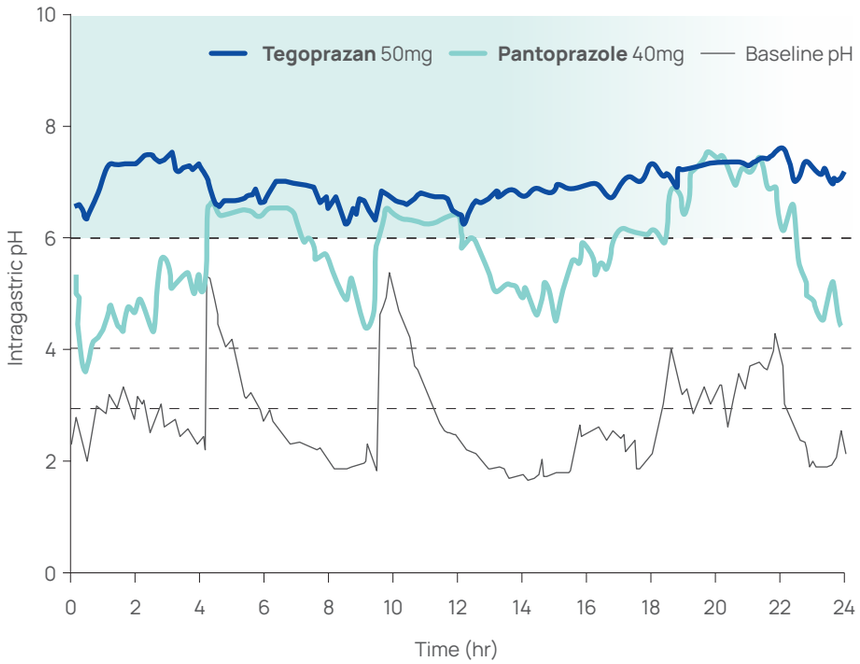
Pantoprazole
40mg BID

Tegoprazan
50mg BID

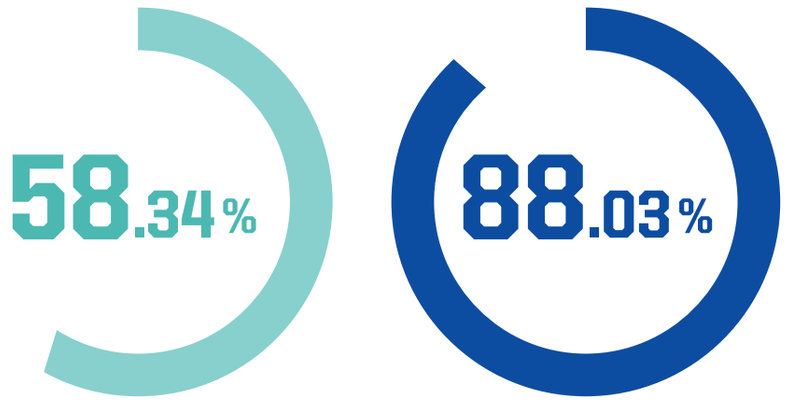
control of intragastric acidity for optimal *H. pylori* eradication.[6]

- **K-CAB®** continually showed higher inhibitory effect of gastric acid secretion than pantoprazole on the 7th day of administration.

Intragastric pH on day 7



Mean % time pH > 6



Pantoprazole
40mg BID

Tegoprazan
50mg BID

Study design phase I clinical trial of open-label, randomized, active-controlled, multiple-dose study to evaluate the pharmacodynamic characteristics and safety of multiple oral doses of Tegoprazan and amoxicillin/clarithromycin in *H. pylori* positive healthy adults.
Drugs : tegoprazan 50mg, amoxicillin 1g, clarithromycin 500mg BID, 7 days.

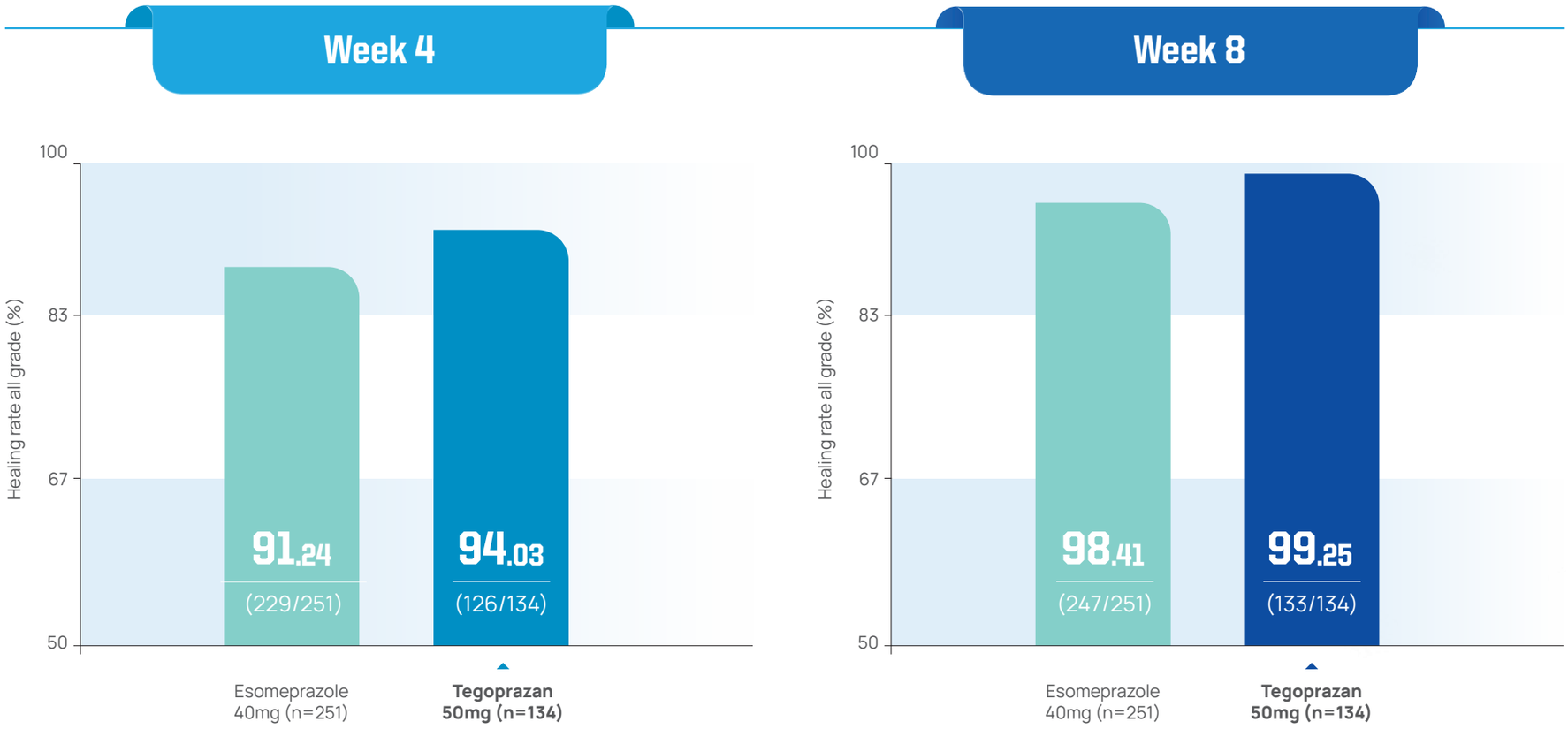
BID: twice a day; ***H. pylori*:** Helicobacter pylori

K-CAB® is **rarely affected by CYP2C19.**[3,4]

- **K-CAB®** is mainly metabolized by CYP3A4.
- **K-CAB®** does not have potential as a CYP3A4 inhibitor or inducer.

K-CAB® is **non-inferior** compared to esomeprazole in patients with erosive gastroesophageal reflux disease(ERD).[14-16]

[Integrated cumulative healing rate of ERD]

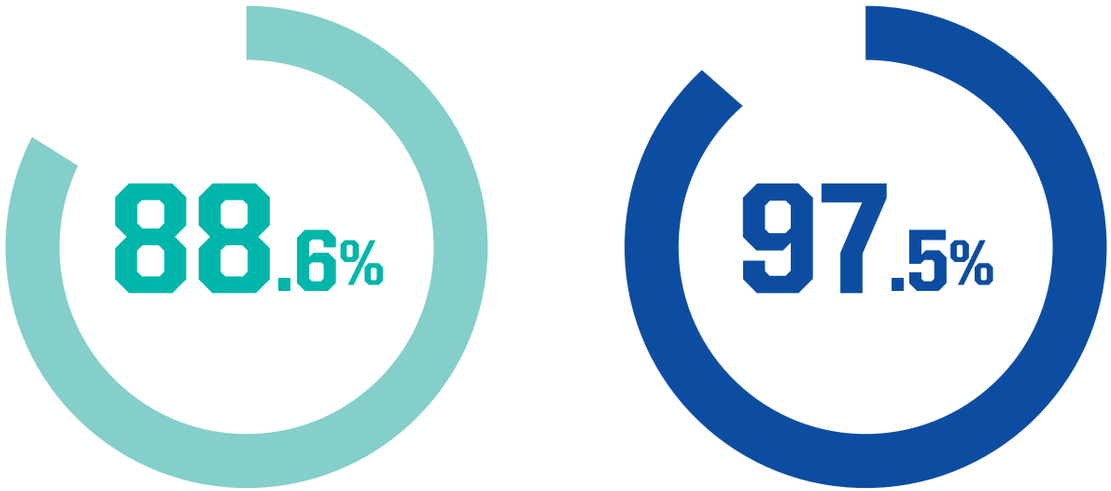


- Non-inferiority margin -10%
- Difference vs. esomeprazole : 8W 0.84 [95% CI (-1.28, 2.97), p<0.0001], 4W 2.79 [95% CI (-2.53, 8.12), p<0.0001]

Study design the efficacy assessments by analyzing cure rates according to LA classification, identifying the severity of erosion in endoscopic findings from phase II and III clinical trials of erosive reflux disease(CJ_APA_201, CJ_APA_301, CJ_APA_304).

K-CAB® achieved **greater healing rate** compared to esomeprazole in patients with moderate to severe esophagitis.[14-16]

The healing rate of moderate to severe esophagitis† at 4 weeks



Esomeprazole
40mg (n=79)

Tegoprazan
50mg (n=40)

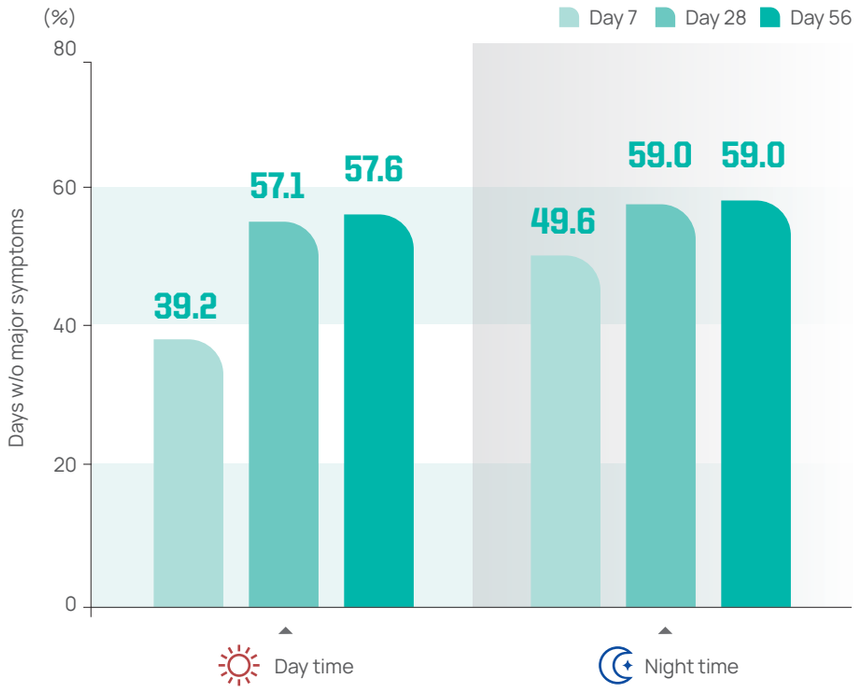
- †moderate to severe esophagitis : Los Angeles classification grade B,C,D
- Difference: about 8%(95% CI, [0.38, 17.41])

Study design the efficacy assessments by analyzing cure rates according to LA classification, identifying the severity of erosion in endoscopic findings in phase Ⅱ and Ⅲ clinical trials of erosive reflux disease(CJ_APA_201, CJ_APA_301, CJ_APA_304).

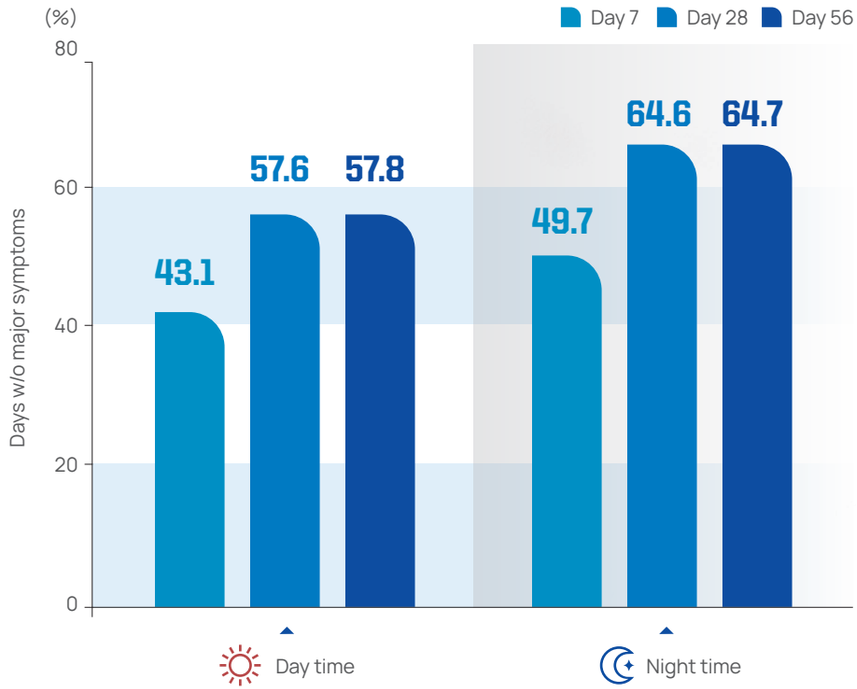
K-CAB® improves **heartburn and acid reflux symptoms** in patients with reflux esophagitis.[14-16]

[% of the day without major symptom (heartburn & regurgitation) during daytime and nighttime]

Esomeprazole 40mg



Tegoprazan 50mg



Study design a randomized, double-blinded, dose-exploratory phase II clinical trial to evaluate the safety and efficacy of Tegoprazan in patients with erosive esophagitis. An exploratory comparison of the safety and efficacy of the two drugs after oral administration of tegoprazan 50mg, 100mg or 200mg, esomeprazole 40mg, once daily. Evaluation of efficacy upon Full Analysis Set(FAS).

K-CAB® showed **superior efficacy** compared to placebo in non-erosive gastroesophageal reflux disease(NERD) patients.[17]

[Efficacy comparison of PPIs vs. Tegoprazan in NERD patients]

PPIs vs. P-CAB

Drug	Omeprazole[21]		Esomeprazole[22]		**Tegoprazan[17]**	
Endpoint at week 4 (= Efficacy)	%, patients with complete **heartburn relief**		%, patients with complete **heartburn relief**		%, patients with complete **symptom relief (heartburn & regurgitation)**	
Dose	**20mg**	placebo	**20mg**	placebo	**50mg**	placebo
Efficacy (%)	**25.8***	12.0	**33.1***	13.7	**42.5***	24.2

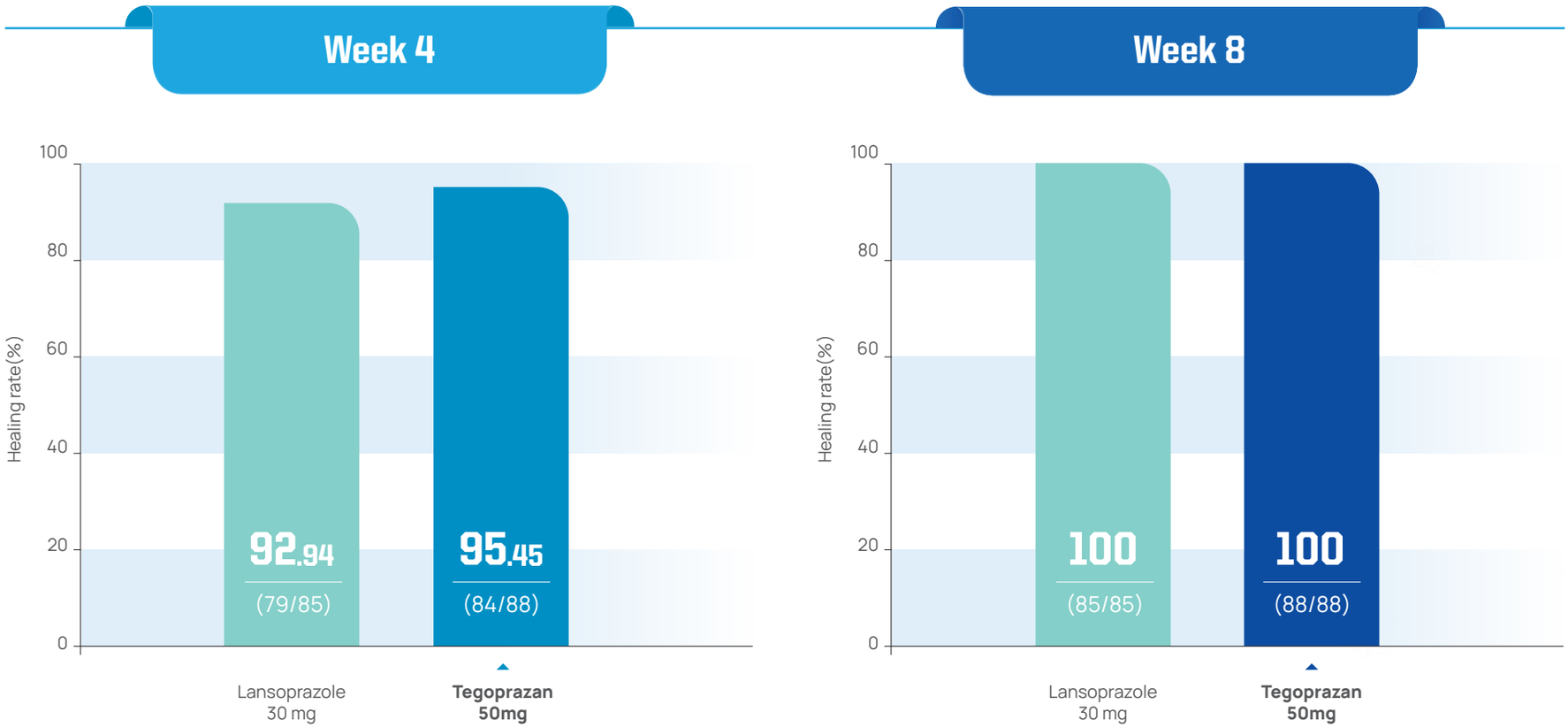
• For Tegoprazan, “complete symptom relief” means “percentage of patients with symptom-free of heartburn & regurgitation in the last 7 days at week 4”.

*$p < 0.05$

The above is not a head to head direct comparison study, but the result of studies on each drug.

K-CAB® is **non-inferior** compared to lansoprazole in gastric ulcer(GU) patients.[18]

[Cumulative Healing Rates of Gastric Ulcers]



• Non-inferiority margin -10%

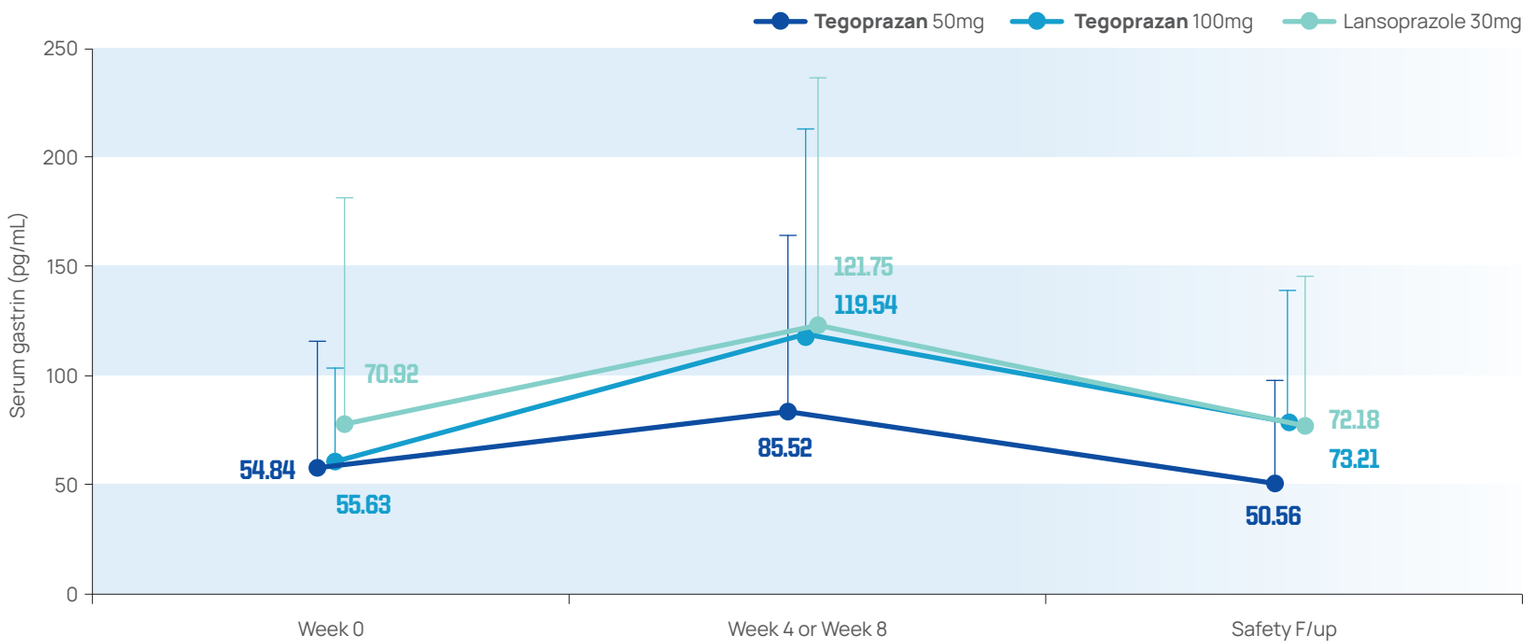
Study design a double-blinded, randomized, active-controlled phase III study to evaluate the safety and efficacy of Tegoprazan in patients with gastric ulcers (Therapeutic confirmatory clinical trial).
Drugs: Tegoprazan 50mg or 100mg, Lansoprazole 30mg, once daily, up to 8 weeks (4 weeks + 4 weeks)

P-CAB: potassium-competitive acid; **PPI:** proton pump inhibitor

K-CAB® **did not significantly increase** serum gastrin levels.[18]

[Low potential risk for hypergastrinemia]

K-CAB® (Tegoprazan)



Study design a double-blinded, randomized, active-controlled phase III study to evaluate the safety and efficacy of Tegoprazan in patients with gastric ulcers (Therapeutic confirmatory clinical trial).
Drugs: Tegoprazan 50mg or 100mg, Lansoprazole 30mg, once daily, up to 8 weeks (4 weeks + 4 weeks)

K-CAB® Tab. 50mg (Tegoprazan) Prescribing Information

Indication

1. Treatment of Erosive Gastroesophageal Reflux Disease

2. Treatment of Non-Erosive Gastroesophageal Reflux Disease

3. Treatment of Gastric Ulcer

4. Eradication of *H. pylori* concurrently given with appropriate antibiotic therapy treatment in patients with peptic ulcer and/or chronic atrophic gastritis

Dosage and Administration Adult

1. Treatment of Erosive Gastroesophageal Reflux Disease
- 50mg once daily for 4 weeks.
- For patients who do not heal or have persistent symptoms after 4 weeks, an additional 4-week treatment may be considered.

2. Treatment of Non-Erosive Gastroesophageal Reflux Disease - 50mg once daily for 4 weeks.

3. Treatment of Gastric Ulcer - 50mg once daily for 8 weeks.

4. Eradication of *H. pylori* concurrently given with appropriate antibiotic therapy treatment in patients with peptic ulcer and/or chronic atrophic gastritis
- Patients with *H. pylori* infection should be treated with eradication therapy.
  Tegoprazan 50mg, clarithromycin 500mg, and amoxicillin 1g are orally administered twice daily for 7 days.

K-CAB® can be taken without regard to food.

Precautions in Use

1. Contraindications 1) (Patients with) Hypersensitivity to the tegoprazan, any of the product components or substituted benzimidazoles 2) Patients who take atazanavir, nelfinavir or rilpivirine-containing products (see '5. Drug Interactions'). 3) Pregnant women or nursing mothers (see '6. Pregnant Women and Nursing Mothers)

2. Warnings and Precautions 1) Hepatic impairment : There is no data on patients with hepatic impairment. 2) Renal impairment (There is no data on patients with renal impairment.) 3) Elderly people (See '8. Geriatric use')

3. Adverse Reactions 1) A total of 5 clinical studies were conducted with erosive gastroesophageal reflux disease and non-erosive gastroesophageal reflux disease and gastric ulcer patients. 360 patients were treated with tegoprazan 50mg. Adverse events and adverse drug reactions (marked with *) reported during the clinical trials are as following.

Common adverse events reported (≥1%) in tegoprazan 50mg treatment group are presented in Table 1.

Table 1. Adverse events (%) reported in ≥1% patients from clinical trials

Body System	Adverse Events
Gastrointestinal	Nausea, diarrhea, dyspepsia
Infections and Infestations	Nasopharyngitis, viral upper respiratory tract infection
General disorders and administration site conditions	Chest discomfort

Less common adverse events reported in <1% patients after administration of K-CAB® 50mg from clinical studies are listed below by body system;

- *Gastrointestinal Disorders:* abdominal pain upper*, abdominal discomfort*, constipation*, abdominal pain*, abdominal distension*, vomiting, eructation, abdominal pain lower, gastric ulcer*, anal haemorrhage*, erosive duodenitis*, flatulence*, gastric polyps*, gastroesophageal reflux disease*, intestinal metaplasia, haematemesis, hemorrhoids, melaena* - *Infections and Infestations:* folliculitis*, gastroenteritis bacterial, latent tuberculosis - *Laboratory Investigations:* alanine aminotransferase increased*, aspartate aminotransferase increased*, gamma-glutamyltransferase increased*, blood bilirubin increased*, blood creatine phosphokinase increased*, blood urine present*, Red blood cells urine positive, blood gastrin increased*, blood triglycerides increased* - *General Disorders and Administration Site Conditions:* fatigue* - *Injury, Poisoning and Procedural Complications:* ligament sprain, concussion, excoriation, foot fracture, joint injury, muscle strain - *Musculoskeletal and Connective Tissue Disorders:* myalgia*, arthralgia*, tendonitis* - *Nervous System Disorders:* headache*, dizziness - *Skin and Subcutaneous Tissue Disorders:* angioedema, dermatitis, seborrhoeic dermatitis* - *Respiratory, Thoracic and Mediastinal Disorders:* cough*, oropharyngeal pain, throat irritation, nasopharyngitis* - *Reproductive System and Breast Disorders:* vaginal discharge, vulvovaginal pruritus, breast calcifications*, adenomyosis , ovarian cyst - *Hepatobiliary Disorders:* bile duct stone, hepatic cyst - *Renal and Urinary Disorders:* hypertonic bladder*, nocturia, renal cyst - *Neoplasms Benign, Malignant and Unspecified:* breast cancer, gastrointestinal tract adenoma*, adenocarcinoma gastric, uterine leiomyoma - *Cardiac Disorders:* ventricular extrasystoles* - *Blood and Lymphatic System Disorders:* lymphadenitis*, anaemia* - *Psychiatric Disorders:* insomnia* - *Surgical and Medical Procedures:* dental implantation - *Ear and Labyrinth Disorders:* ear pain* - *Metabolism and nutrition disorders:* diabetes mellitus - *Vascular disorder:* hypertension - *Endocrine disorders:* thyroid cyst*

2) A clinical study was conducted in patients with peptic ulcer and/or chronic atrophic gastritis who were positive for *H. pylori*. 172 patients were treated with tegoprazan 50mg, in combination with amoxicillin 1g and clarithromycin 500mg. Adverse events and adverse drug reactions (marked with *) reported during the clinical trial is as following; Common adverse events reported (≥1%) in tegoprazan 50mg in combination with amoxicillin 1g and clarithromycin 500mg treatment group are presented in Table 2.

Table 2. Adverse events (%) reported in ≥1% patients from clinical trials

Body System	Adverse Events
Gastrointestinal	Nausea*, diarrhea*, dyspepsia*, abdominal pain upper*, abdominal pain*, abdominal distention*
Laboratory Investigations	CPK increased*
Infections and Infestations	Cystitis*
General Disorders and Administration Site Conditions	Asthenia*
Nervous System Disorders	Headache*, dizziness*, dysgeusia*
Skin and Subcutaneous Tissue Disorders	Urticaria*, pruritus*, erythema*

Less common adverse events reported in <1% patients after administration of K-CAB® 50mg in combination with amoxicillin 1g and clarithromycin 500mg from clinical study is listed below by body system;

- *Gastrointestinal Disorders:* Vomiting, anal incontinence* - *Infections and Infestations:* Folliculitis*, tonsillitis* - *Skin and Subcutaneous Tissue Disorders:* Rash*, drug eruption*, toxic skin eruption* -*Cardiac Disorders:* Palpitation* - *Laboratory Investigations:* AST increased, LDH increased* - *Nervous System Disorders:* Migraine* - *Respiratory, Thoracic and Mediastinal Disorders:* Oropharyngeal pain, dysphonia - *Vascular Disorders:* Hot flush*, flushing*

4. General Precautions 1) In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with K-CAB®may alleviate symptoms and delay diagnosis. 2) **Cyanocobalamin (Vitamin B_{12}) Deficiency** : Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B_{12}) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed. 3) **Bone Fracture**: Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose(defined as multiple daily doses) and long-term PPI therapy (a year or longer). Patients should use the appropriate dose and shortest duration of K-CAB® therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines 4) Hypomagnesemia has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPIs. For patients expected to be on prolonged treatment or who take K-CAB® with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), healthcare professionals may consider monitoring magnesium levels prior to initiation of treatment and periodically. Serious adverse events include tetany, arrhythmias, and seizures. 5) Decreased gastric acidity due to PPIs, increases counts of bacteria normally present in the gastrointestinal tract. Treatment with gastric acid suppressants may possibly increase the risk of gastrointestinal infections such as *Salmonella, Campylobacter* and *Clostridium difficile*. Published observational studies suggest that PPI therapy may be associated with an increased risk of *Clostridium difficile*-associated diarrhea (CDAD), especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. CDAD has been reported with use of nearly all antibacterial agents. Patients should use the lowest dose and shortest duration of K-CAB® therapy appropriate to the condition being treated. 6) No studies on the effects on the ability to drive and use machines have been performed for K-CAB®, and the loss of this ability cannot be predicted from its pharmacological action. Nevertheless, when considering the patient's ability to drive and use machines, the clinical condition of the patient and the adverse reactions of the drug should be considered.

5. Drug Interactions 1) Drugs Dependent on Gastric pH for Absorption Due to its effects on gastric acid secretion, tegoprazan can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. Like with other drugs that decrease the intragastric acidity, the absorption of drugs such as ketoconazole, itraconazole, ampicillin ester, atazanavir, iron salts, erlotinib, gefitinib and mycophenolate mofetil (MMF) can decrease during treatment with tegoprazan. While absorption of drugs such as digoxin can increase during treatment with K-CAB®. Because tegoprazan inhibits gastric acid secretion, co-administration of atazanavir, nelfinavir and rilpivirin with tegoprazan is expected to decrease plasma concentration of atazanavir, nelfinavir or rilpivirin which is dependent on gastric pH for absorption, results in a loss of the therapeutic effect. Therefore, concomitant use of atazanavir, nelfinavir and rilpivirine with K-CAB® is contraindicated. 2) Tegoprazan is mainly metabolized by CYP3A4. Concomitant use of clarithromycin, a CYP3A4 inhibitor, with tegoprazan has increased $AUC_τ$ of tegoprazan and clarithromycin by 2.5 times and 1.25 times, respectively. 3) Tegoprazan has been shown to have no clinically significant effects on the pharmacokinetics of amoxicillin.

6. Pregnant women and Nursing mothers 1) Pregnant women There is no safety data for exposure to tegoprazan in pregnant women. In an embryo-fetal development study, short supernumerary cervical ribs were observed with a higher incidence in rats. Therefore K-CAB® is contraindicated during pregnancy. **2) Nursing mothers** As it is not known whether tegoprazan is excreted into human milk, discontinue nursing while taking K-CAB®. Excretion of tegoprazan into milk has been reported in rats.

7. Pediatric use Clinical safety and efficacy or tegoprazan in pediatric and adolescent patients have not been established.

8. Geriatric use In general, it should be administered to the elderly patients with caution, keeping in mind the greater frequency of decreased physiological functions, such as liver or kidney.

9. Renal Impairment Safety and efficacy of tegoprazan have not been established in patients with renal impairment.

10. Hepatic Impairment Safety and efficacy of tegoprazan have not been established in patients with hepatic impairment.

11. Overdosage There have been no reports of significant overdose with tegoprazan. In clinical trials, there have been cases where up to 400mg of this drug has been administered to healthy adults. In the event of an overdose with K-CAB®, the patients should be monitored for poisoning symptoms and treatment should be supportive if necessary.

12. How to store 1) Keep K-CAB® out of the sight and reach of children.2) Be careful to replace it in another container as it is not desirable in terms of quality or causing accident.

13. Information for Healthcare Professionals

13.1 Pharmacology Tegoprazan is a potassium-competitive acid blocker(P-CAB) that reversibly blocks gastric acid secretion by competitively binding with potassium to the proton pumps(H^+/K^+-ATPase) present in gastric wall cells. Tegoprazan binds in a concentration-dependent manner and blocks gastric acid secretion. Binding has reversibility. Tegoprazan inhibits the proton pump directly without activation by acid.

13.2 Pharmacokinetics 1) Absorption T_{max} of tegoprazan following single oral dose to healthy adults was ranged from 0.5 to 1.5 hours across the doses tested 50~400mg. After single administration, the mean peak plasma concentration (C_{max}) and mean exposure level (AUC) tended to increase dose portionally within the administration dose range. After 7 days of repeated administration, the mean peak plasma concentration of each dose group was similar or decreased in comparison with that of single administration. Food effects on bioavailability were evaluated after administration of 200mg of oral tegoprazan fasting and after meals to healthy adults. Although there was a tendency to delay the T_{max} and decrease the C_{max} after food intake, There was no significant difference on the AUC_{last} and pharmacodynamic parameter(the maintenance time of intragastric acidity above pH 4). **2) Distribution** The proportion of in vitro non-protein-binding drug was 8.7 ~ 9.0% human in the concentration range of 1 ~ 10 μM. **3) Metabolism and Excretion** Tegoprazan is mainly metabolized by CYP3A4. The main metabolite is metabolite M1(dealkylated metabolite). After intravenous administration of tegoprazan to rats and dogs, amount of unchanged tegoprazan excreted in urine was less than 1%. After oral administration of [14C]-tegoprazan to rats, recovery of radioactivity at 168 hours (of dosing) were 93% and 97% in the female and male, respectively. 22% to 24% of the total radioactivity was excreted in urine, and 65% to 69% was eliminated in feces in both female and male rats. After oral administration to rats with biliary intubation, tegoprazan was excreted 41.4% in bile acid, 25.7% in urine and 28.4% in feces. And the total recovery of radioactivity was 97.7%. Less than 1% of unchanged tegoprazan was found 1% in bile acid and urine, 15% was in feces. 6% of metabolite M1 was found in feces. Following the administration of tegoprazan to healthy male subjects, the plasma elimination half-life of unchanged tegoprazan and metabolite M1 were 4.1 hours and 22.8 hours, respectively. Urinary excretion rate of the unchanged tegoprazan was approximately 4.1% and the clearance was 1.1L/hr. Urinary excretion rate of the major metabolie M1 was about 2.3% and the clearance was 0.5L/hr. **4) Drug Interaction (1) Effects of other drugs on tegoprazan** ① Tegoprazan is metabolized in liver by CYP3A4. In vitro studies have shown that ketoconazole, a CYP3A4 inhibitor, significantly inhibited the metabolism of tegoprazan, and while inhibitors of CYP1A2, CYP2C9, CYP2C19, CYP2D6 did not significantly reduced the metabolism of tegoprazan. Concomitant use of tegoprazan with CYP3A4 inhibitors may elevate exposure of tegoprazan. ② Tegoprazan is a substrate of P-gp. *In vitro* studies have shown that the efflux ratio of tegoprazan was decreased by verapamil, a P-gp inhibitor. Co-administration of tegoprazan and P-gp inhibitors may result in increase of exposure by increasing gastrointestinal absorption of tegoprazan. ③ In healthy adult subjects, co-administration of tegoprazan with clarithromycin (substrates and inhibitors of CYP3A4 and P-gp) resulted in increase of $C_{ss,max}$ and $AUC_τ$ of tegoprazan by 1.65 times and 2.5 times, respectively. $AUC_τ$ of clarithromycin increased slightly by 1.25 times and there was no significant increase of $C_{ss,max}$. Neither adverse events nor adverse drug reaction clinically significant were observed. **(2) Effects of tegoprazan on other drugs** ① *In vitro* studies have shown that tegoprazan showed competitive inhibition against CYP2C8 and CYP3A4. But, the IC50 values were approximately 25-fold greater than the peak plasma concentration of the recommended human dose. ② For OATP1B1, there was a difference in the inhibitory activity of tegoprazan depending on substrates and it is expected that the plasma concentrations of some drugs which are substrate for OATP1B1 may be increased slightly considering the C_{max} at the clinical doses.

13.3 Clinical studies 1) Erosive Gastroesophageal Reflux Disease A randomized, double-blind, active-controlled, comparative phase III study was conducted in 302patients with erosive gastroesophageal reflux disease to evaluate K-CAB® 50mg, 100mg or esomeprazole 40mg for up to 8 weeks. The cumulative healing rate at week 8 was 98.91%(91patients/92patients), 98.90%(90patients/91 patients), and 98.86%(87 patients/88 patients), respectively, in the K-CAB® 50mg, 100mg and esomeprazole 40mg treatment groups, demonstrating non-inferiority. (Table 3).

Table 3. Cumulative healing rate of Erosive Gastroesophageal Reflux Disease at week 8

	K-CAB®		Esomeprazole
	50mg	100mg	40mg
PPS	N=92	N=91	N=88
ERD Healing Rate [%(N)]	98.91 (91)	98.90 (90)	98.86 (87)
Difference with 95% confidence interval	0.05 [-3.02, 3.11]	0.04 [-3.04, 3.12]	
p-value*	<0.001	<0.001	

* Non-inferiority margin -10%, significance level 0.025(one-sided test), PPS: Per Protocol Set

2) Non-Erosive Gastroesophageal Reflux Disease A randomized, double-blind, placebo-controlled, phase III study was conducted in 324patients with non-erosive gastroesophageal reflux disease to evaluate K-CAB® 50mg, 100mg or placebo for 4 weeks. The rate of patients with complete resolution of main symptoms, heartburn and reflux of gastric acid, at week 4 was 42.45%(45 patients/106 patients), 48.48%(48 patients/99 patients), 24.24%(24 patients/99 patients), respectively in treatment group of K-CAB® 50mg, 100mg and placebo, demonstrating superiority (Table 4).

Table 4. Percentages of patients with complete resolution of main symptoms at week 4 in non-erosive gastroesophageal reflux disease

	K-CAB®		Placebo
	50mg	100mg	
FAS	N=106	N=99	N=99
Symptom resolution [N(%)]	45 (42.45)	48 (48.48)	24 (24.24)
p-value*	0.0058	0.0004	

* Chi-square test, significance level 0.05(two-sided test), FAS; Full Analysis Set

3) Gastric Ulcer A randomized, double-blind, active-controlled, comparative phase III study was conducted in 306 patients with gastric ulcer to evaluate K-CAB® 50mg, 100mg or lansoprazole 30 mg for up to 8 weeks. The cumulative healing rate at week 8 was 100.00%(88 patients/88 patients), 97.85%(91 patients/93 patients), and 100.00%(85 patients/85 patients), respectively, in the K-CAB® 50mg, 100mg and 30mg lansoprazole treatment groups, demonstrating non-inferiority. (Table 5).

Table 5. Cumulative healing rate of Gastric Ulcer at week 8

	K-CAB®		lansoprazole
	50mg	100mg	30mg
PPS	N=88	N=93	N=85
GU Healing Rate [% (N)]	100.00 (88)	97.85 (91)	100.00 (85)
Difference with 95% confidence interval	0.00	-2.15 [-7.66, 2.43]	
p-value*		<0.0001	

* Non-inferiority margin -8.54%, significance level 0.025(one-sided test), PPS: Per Protocol Set

4) Eradication of *H. pylori* concurrently given with appropriate antibiotic therapy treatment in patients with peptic ulcer and/or chronic atrophic gastritis A randomized, double-blind, active-controlled, comparative phase III study was conducted in 350patients with peptic ulcer and/or chronic atrophic gastritis who are positive for *H. pylori* to evaluate K-CAB® 50mg or lansoprazole 30mg in combination with amoxicillin 1g and clarithromycin 500mg twice daily for 7 days. The *H. pylori* eradication rate was 69.33% (104patients/150patients) and 67.33% (101 patients/150 patients), respectively, in the K-CAB® 50mg and lansoprazole 30mg with antibiotic combination therapy treatment groups, demonstrating non-inferiority. (Table 6).

Table 6. *H. pylori* eradication rate

	K-CAB®	lansoprazole
	50mg with amoxicillin 1g and clarithromycin 500mg	30mg with amoxicillin 1g and clarithromycin 500mg
PPS	N=150	N=150
H. pylori Eradication Rate [% (N)]	69.33(104)	67.33 (101)
Difference with 95% confidence interval	2.00 [-8.53,12.53]	
p-value*	0.0127	

* Non-inferiority margin -10%, significance level 0.025(one-sided test), PPS: Per Protocol Set

13.4 Nonclinical Toxicology 1) Mutagenesis Tegoprazan was negative in the bacterial reverse mutation test using *Salmonella* and *E. coli*. Tegoprazan was positive in the CHL cell chromosome aberration assay, but negative in the *in vivo* micronucleus test using rat bone marrow cells not to induce micronucleus. **2) Carcinogenesis** In a 2 year carcinogenicity study in rats, gastrointestinal neuroendocrine tumor was observed in the male 15 mg/kg/day (about 4.8 times AUC of the recommended human dose) group and the female 6 mg/kg/day (about 6.8 times AUC of the recommended human dose). **3) Impairment of Fertility** No effects on fertility and early embryonic development were observed up to a high dose of 500mg/kg/day. As a result of the embryo-fetal development studies, short supernumerary cervical ribs were observed with a higher incidence in rats. The NOAEL for maternal rats was determined to be 500mg/kg/day, which was 369 times the AUC of the human recommended dose, and the NOEL for embryos and fetuses was determined to be 20mg/kg/day, which was 15.6 times the AUC of the human recommended dose. There were no effects on fetal development despite abortions and weight loss symptoms in the maximum dose(10mg/kg/day) group of rabbit. The NOAEL for maternal rabbits was determined to be 5mg/kg/day, which was 2 times the AUC of the human recommended dose, and the NOAEL for embryos and fetuses was determined to be 10mg/kg/day, which was 4.8 times the AUC of the human recommended dose. In a pre- and post-natal development study and maternal function study in rats, tegoprazan and metabolite M1 were shown to be excreted in breast milk. And the NOAEL was determined to be 20mg/kg/day, which was 8 times the AUC of the human recommended dose on the basis of the decreased survival rate of the first filial rats at 60mg/kg/day, the maximal dose.

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