Comparison of the pharmacokinetics and pharmacodynamics of YH4808 in healthy subjects for defining an appropriate dosing regimen

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ABSTRACT

YH4808 is a novel potassium-competitive acid blocker developed for gastric acid-related disorders. Previous studies indicate its potential to improve symptoms of gastric acid-related disorders. The current study was aimed to find the optimal regimen of YH4808 for night time pH control. This study was performed in two parts. Each was a randomized, open-label, active-controlled, multiple-doses, two-treatment, two-period crossover study conducted in 20 healthy Korean volunteers. Subjects were randomly assigned to one of the four groups. The three groups received different dosage regimens of YH4808 (100 mg twice a day, 200 mg once a day, or 200 mg twice a day), and the fourth group received esomeprazole 40 mg twice a day. The pharmacokinetic parameters demonstrated that the systemic exposure of YH4808 increased in a dose-proportional manner. The difference in the proportion of time above pH 4 over 24 h from the baseline was the greatest in the group receiving YH4808 200 mg twice a day. The values of the area under the effect curve at night time (12 A.M.– 7 A.M.) were higher in all YH4808 groups than in the esomeprazole group. However, the differences among the YH4808 groups were not statistically significant (p > 0.05). YH4808 exhibited potential for better pH control during the night in comparison to esomeprazole. The optimal regimen for night time pH control among all the YH4808 regimens was 200 mg twice a day.

Trial Registration: ClinicalTrials.gov Identifier: NCT01761513

Keywords: YH4808; Esomeprazole; Pharmacokinetics; Pharmacodynamics

INTRODUCTION

Since the development of proton pump inhibitors (PPIs), they have been widely used as therapeutics for *Helicobacter pylori* (*H. pylori*) infections and acid-related disorders like gastroesophageal reflux disease (GERD) and peptic ulcer disease [1-3]. However, there are several limitations in their clinical application. The PPIs are weak base prodrugs; they concentrate in the acidic compartment of the secretory canaliculus of the parietal cells and
undergo an acid-catalyzed transformation. After activation by gastric acid, the inhibitor covalently bonds with specific cysteines on the luminal surface of the proton pump and inhibits gastric acid secretion [4]. Hence, its consumption is recommended before meals. In addition, it has a slow onset of action [5], and its maximum effect is achieved only when repeated administration is performed [6].

While PPIs have a unique mechanism of action based on their chemistry, potassium-competitive acid blockers (P-CABs) have a structural specificity for their target. P-CABs are lipophilic weak bases that are stable at low pH. This allows them to concentrate in acidic environments. Unlike PPIs, P-CABs act directly after protonation on the H⁺/K⁺-ATPase enzyme, and bind competitively to the K⁺-binding site of the H⁺/K⁺-ATPase. With these differences, P-CABs are expected to suppress gastric acid secretion faster and attain full effect even with a single dose [6].

YH4808 is one of the P-CABs developed by Yuhan Corporation (Seoul, Korea). In a previous study on subjects with *H. pylori* infection, the suppression of the 24-h gastric secretion was superior to that of esomeprazole when YH4808 was administered for 7 days under a repeated fasting state. Additionally, the tolerability and safety of YH4808 have been demonstrated following a single administration and repeated fasting administration [7].

In acid-related disorders, inhibition of gastric acid secretion is important for pH control. If the night time pH is not controlled in patients with GERD, sleep is disturbed by symptoms such as heartburn, which affect the quality of life. With this objective, the study aimed to identify the optimal regimen of YH4808 for night time pH control. This study intended to compare the pharmacokinetics (PK) of YH4808 among groups of various YH4808 regimens and compare the pharmacodynamics (PD) of YH4808 dosage groups with that of the active control, the esomeprazole group.

**METHODS**

**Ethics**
The protocol was approved by the institutional review board of the Severance Hospital, Yonsei University College of Medicine, Seoul, Korea (approval number: 4-2012-0610). It was performed following the relevant regulatory requirements, including those outlined in the Declaration of Helsinki and the Korean good clinical practice. All participants provided written informed consent before their enrollment into the study.

**Study participants**
Healthy Korean volunteers aged 20–55 years, with a body weight of 55 kg or more and a body mass index (BMI) of 18.5–25.0 kg/m² were eligible for this study. Those who tested negative for *H. pylori* in the ¹³C-urea breath test were enrolled. All participants were screened by documenting their medical histories, vital signs, and physical examination, 12-lead electrocardiography (ECG), and clinical laboratory test results. Subjects who were allergic to any of the ingredients of the investigational product (IP), those with gastrointestinal diseases, or those who had undergone a major surgery that may affect IP absorption were excluded from the study. During the study period, all the subjects were prohibited from taking any drugs, herbal products, or over-the-counter drugs that could affect the PK and PD evaluation. Further, the subjects were not allowed to smoke or consume alcohol, caffeine, any beverage, or food except the ones provided.
Study design
The study is registered at clinicaltrials.gov (identifier: NCT01761513). This study was performed in two parts: A and B. Each was a randomized, open-label, active-controlled, multiple-doses, two-treatment, two-period, crossover study with a 21-day washout interval between the treatment periods. Twenty healthy subjects were randomly assigned to four groups with five subjects per group. The study regimens are presented in Table 1.

In Part A, the subjects received 100 mg of YH4808 (Yuhan Corporation, Seoul, Korea) twice a day or 200 mg of YH4808 once a day at 8 p.m. for 14 days in each period according to the assigned group. In Part B, the subjects received 200 mg of YH4808 twice a day or 40 mg of esomeprazole (Astrazeneca Korea, Seoul, Korea) twice a day for 14 days in each period according to the assigned group. YH4808 and esomeprazole were orally administered 30 min after meals and 1 h before meals, respectively.

PK sampling and analytical methods
Peripheral venous blood was withdrawn at 0 (pre-dose) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after YH4808 administration on days 1, 7, and 14 of each period. In the group with once-a-day administration, additional samples were collected 24 hours after YH4808 administration on the same day. The samples were centrifuged for 10 min at 4°C at 1,910 × g, and the supernatants were stored at −70°C or below.

The plasma concentration of YH4808 was determined by high-performance liquid chromatography (LC-20AD, Shimadzu, Kyoto, Japan) coupled with mass spectrometry (API 4000 Triple Quad; AB Sciei, Washington, D.C., USA) based on validated analytical procedures adopted by the Korean Ministry of Food and Drug Safety. The calibration curves were linear in the range of 0.2–300 µg/L for YH4808 and the lower limit of quantification (LLOQ) was 0.2 µg/L.

PK analysis
The PK analysis was performed on the subjects who completed all PK blood sampling schedules. For each PK parameter, the maximum plasma concentration (C_{max}) and time to reach C_{max}(T_{max}) were calculated as measured values, the area under the time-concentration curve (AUC) was calculated by the linear trapezoidal rule, and other PK variables were calculated from the obtained data by performing a non-compartmental analysis using WinNonlin® version 6.3 (Pharsight, CA, USA).

Intragastric pH monitoring
The intragastric pH was continuously monitored for 24 hours on day -1 (baseline) and day 14 of each period. For this, ambulatory 24-h pH recording (Medtronic A/S, Skovlunde, Denmark) was used. The pH electrode was calibrated using standard solutions before use. Before insertion, the catheter was sufficiently moistened with a lubricating gel or water to

### Table 1. Study design

| Part | Group | Number of subjects | Period 1 | Period 2 |
|------|-------|--------------------|----------|----------|
| A    | 1     | 5                  | 100 BID  | 200 QD   |
|      | 2     | 5                  | 200 QD   | 100 BID  |
| B    | 3     | 5                  | 200 BID  | R40 BID  |
|      | 4     | 5                  | R40 BID  | 200 BID  |

100 BID, YH4808 100 mg twice a day for 14 days; 200 QD, YH4808 200 mg once a day for 14 days; 200 BID, YH4808 200 mg twice a day for 14 days; R40 BID, Esomeprazole 40 mg twice a day for 14 days.
reduce the feeling of a foreign body. The pH electrode was inserted through the nasal cavity, and the lower probe was positioned 5 cm below the lower part of the esophagus. The pH was measured once every 5 seconds, and the result was recorded automatically. The total pH monitoring time was 1,440 minutes (24 hours) in each measurement. The mean pH values, which represented the averages of the measurements for 1 min, were obtained using the moving average method. Moreover, to minimize the effect of posture on the intragastric pH, all subjects maintained a supine position from 12 A.M. to 7 A.M., and maintained an upright posture of 45 degrees or more from 7 A.M. to 12 A.M. The same meals were provided 30 min before dosing for the YH4808 groups and 1 hour after dosing for the esomeprazole group.

PD analysis
The PD evaluation was performed on the subjects who completed pH monitoring. Each subject was evaluated by calculating the pH change pattern over time and the difference in the pH from the baseline value over time. Further, the arithmetic means, and the ratio of maintaining pH above 4 over a 24-h period in each subject were evaluated. The areas under the effect curves (AUECs) for pH*time from 5 to 12 hours, and from 0 to 24 hours on day 14 were analyzed to evaluate the effect of the IPs.

Safety assessment
Adverse events (AEs) were monitored throughout the study. Safety evaluation was performed via physical examination, monitoring of vital signs, 12-lead ECG, and laboratory testing including hematology, serum chemistry, and urinalysis.

Statistical analysis
All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA) and WinNonlin® version 6.3 (Pharsight). Baseline demographic characteristics were summarized using descriptive statistics. The PK and PD data were analyzed using descriptive statistics and compared among the treatment groups. Demographic characteristics were analyzed using the Kruskal-Wallis test for the comparison of groups. Differences in AUECs among groups were analyzed by the one-way ANOVA test. The safety data are presented using descriptive statistics.

RESULTS

Study subjects
The 20 healthy male subjects enrolled in the study completed the scheduled procedures. The summary of the demographic characteristics of each group is presented in Table 2. There were no significant differences in the demographic characteristics among the groups.

Table 2. Demographic characteristics of the subjects

| Demographic variables | 1 (n = 5) | 2 (n = 5) | 3 (n = 5) | 4 (n = 5) | Total (n = 20) | p-value* |
|-----------------------|----------|----------|----------|----------|---------------|----------|
| Age (yr)              | 25.0 ± 1.2 | 27.8 ± 6.6 | 32.6 ± 5.9 | 26.6 ± 3.6 | 28.0 ± 5.3 | 0.149    |
| Weight (kg)           | 68.5 ± 9.7 | 69.5 ± 6.5 | 64.2 ± 8.5 | 66.7 ± 10.5 | 67.2 ± 8.5 | 0.613    |
| Height (cm)           | 173.3 ± 6.5 | 172.4 ± 3.8 | 170.9 ± 7.4 | 175.0 ± 7.0 | 172.9 ± 6.0 | 0.843    |
| BMI (kg/m²)           | 22.7 ± 1.8 | 23.3 ± 1.7 | 21.9 ± 1.9 | 21.6 ± 2.0 | 22.4 ± 1.8 | 0.315    |

Values are presented as arithmetic mean ± standard deviation in each group.
BMI, body mass index.
*p-values were calculated using the Kruskal-Wallis test.
The plot of the mean plasma concentration vs. time is presented in Fig. 1. As shown in the figure, plasma concentration decreased rapidly after reaching $C_{\text{max}}$, but the slope gradually decreased. The PK parameters of YH4808 for each group are summarized in Table 3. In all treatment groups, the median $T_{\text{max}}$ on days 1 and 14 were 3.5–4.0 hours and 4.0–5.0 hours, respectively.

On day 1, the values of the dose-normalized $C_{\text{max}}$ and AUC$_{\tau}$ did not differ between the 100 BID and 200 BID groups ($p > 0.05$). The AUC$_{\tau}$ of the 200 BID group was approximately double that of the 100 BID group indicating a dose-proportional increment in the exposure of YH4808. There was no difference in the $C_{\text{max}}$ between the 200 QD group and the 200 BID group ($p > 0.05$). Moreover, the dose-normalized $C_{\text{max}}$ was not different among all groups ($p > 0.05$). On day 14, the value of the dose-normalized AUC$_{\tau,\text{ss}}$ did not differ between the 100 BID and the 200 QD groups that were administered the same dose ($p > 0.05$). Drug exposure continued to increase...
In proportion to the dose at the AUC\(\tau\),ss values of the 100 BID and the 200 BID groups. Further, the drug accumulation between the 100 BID and the 200 BID groups with the same dosing interval did not differ.

**Intragastric pH**

The proportion of time above pH 4 over a 24-h period on day-1 and day-14 is presented in Fig. 2. In all treatment groups, the proportion of the time above pH 4 was significantly higher than that of the baseline. There was no statistically significant difference in the baseline

### Table 3. Pharmacokinetic parameters of YH4808 after single and multiple oral administrations

| Day   | PK parameters | Treatment                      |
|-------|---------------|--------------------------------|
|       |               | 100 BID (n = 10) | 200 QD (n = 10) | 200 BID (n = 10) |
| Day 1 | \(T_{\text{max}}\) (h) | 4.00 (1.50–8.00) | 4.00 (2.00–6.00) | 3.50 (2.00–6.00) |
|       | \(C_{\text{max}}\) (\(\mu\)g/L) | 43.80 ± 23.93 | 114.38 ± 54.20 | 107.62 ± 69.67 |
|       | \(C_{\text{max}}/D\) (\(\mu\)g/L/mg) | 0.44 ± 0.24 | 0.57 ± 0.30 | 0.54 ± 0.35 |
|       | AUC,ss (\(\mu\)g·h/L) | 159.86 ± 64.92 | 472.35 ± 210.50 | 332.64 ± 178.46 |
|       | AUC,ss/D (\(\mu\)g·h/L/mg) | 1.60 ± 0.65 | 2.36 ± 1.05 | 1.66 ± 0.89 |
| Day 14| \(T_{\text{max},\text{ss}}\) (h) | 4.00 (1.50–8.00) | 5.00 (2.00–8.00) | 4.00 (2.00–11.97) |
|       | \(C_{\text{max},\text{ss}}\) (\(\mu\)g/L) | 71.94 ± 21.03 | 121.44 ± 66.68 | 103.18 ± 54.84 |
|       | \(C_{\text{max},\text{ss}}/D\) (\(\mu\)g/L/mg) | 0.72 ± 0.21 | 0.61 ± 0.33 | 0.52 ± 0.27 |
|       | AUC,ss (\(\mu\)g·h/L) | 301.58 ± 81.34 | 658.04 ± 256.81 | 518.35 ± 217.60 |
|       | AUC,ss/D (\(\mu\)g·h/L/mg) | 3.02 ± 0.81 | 3.29 ± 1.28 | 2.59 ± 1.09 |
|       | C\text{trough,ss} (\(\mu\)g/L) | 13.24 ± 5.61 | 11.79 ± 4.36 | 26.25 ± 13.95 |
|       | Fluuctuation | 2.46 ± 0.57 | 4.04 ± 1.40 | 3.83 ± 1.68 |
|       | R | 2.03 ± 0.68 | 1.48 ± 0.40 | 1.83 ± 0.84 |

Data are presented as mean ± standard deviation except for \(T_{\text{max}}\) shown as median (main-max). PK, pharmacokinetic; \(T_{\text{max}}\), the time to reach maximum plasma concentration; \(C_{\text{max}}\), the maximum plasma concentration; \(D\), dose; AUC, the area under the time-concentration curve within a dosing interval; \(T_{\text{max,ss}}\), the time to reach maximum plasma concentration at the steady-state; \(C_{\text{max},ss}\), the maximum plasma concentration at the steady-state; AUC,ss, the area under the time-concentration curve within a dosing interval; C\text{trough,ss}, trough plasma concentration at the steady-state; CL\text{ss,}\(F\), total clearance of the drug from the plasma at the steady-state; F, bioavailability of drug; Fluctuation, \((C_{\text{max},\text{ss}}-C_{\text{trough,ss}})/C_{\text{avg},\text{ss}}\); R, accumulation index.

Further, the drug accumulation between the 100 BID and the 200 BID groups with the same dosing interval did not differ.

**Intragastric pH**

The proportion of time above pH 4 over a 24-h period on day-1 and day-14 is presented in Fig. 2. In all treatment groups, the proportion of the time above pH 4 was significantly higher than that of the baseline. There was no statistically significant difference in the baseline

### Figure 2. The proportion of the time above pH 4 over a 24-h period (mean ± standard deviation) measured on day-1 and day-14.

100 BID, YH4808 100 mg twice a day for 14 days; 200 BID, YH4808 200 mg twice a day for 14 days; 200 QD, YH4808 200 mg once a day for 14 days; R40 BID,esomeprazole 40 mg twice a day for 14 days.
among the treatment groups ($p > 0.05$) and the change from the baseline was the greatest in the YH4808 200 mg BID group at 78.0% of the total and 75.1% of the upright position groups. However, the difference was not statistically significant when compared with the esomeprazole 40 mg BID group ($p > 0.05$).

A comparison of the 24-h intragastric pH vs. time profiles of esomeprazole and the YH4808 groups is shown in Fig. 3. After repeated administration for 14 days, the intra-gastric pH in the 100 BID group remained relatively stable at 4 or higher throughout the day; the night time intragastric pH was also similar to that of the R40 BID group. In the 200 BID group, the changes in the 24-h intragastric pH were generally similar to those observed in the R40 BID group.

The AUEC values following the oral administration of YH4808 and esomeprazole for 14 days are summarized in Table 4. The values of the AUEC (5–12 hours after dosing; 12 AM to 7 AM) and the ΔAUEC (5–12 hours after dosing) were greater in all YH4808 groups than in the esomeprazole group. However, there was no significant difference among the groups ($p > 0.05$).

Figure 3. Mean 24-h intragastric pH vs. time profiles at baseline (lower) and on day 14 (upper).
Intra-gastric pH is measured from 7 P.M. to 7 P.M., the next day; Dosing times (8 A.M., 8 P.M.) of 100 BID (A) and 200 BID group (B) are presented by red arrows; Dosing time (8 P.M.) of the 200 QD group (C) is presented by a red arrow. The meal times of the esomeprazole group (9 P.M., 9 A.M., and 2:30 P.M.) are presented by gray arrows; the meal times of the YH4808 groups (7:30 P.M., 7:30 A.M., and 1 P.M.) are presented by orange, green, and blue arrows, respectively. 100 BID, YH4808 100 mg twice daily for 14 days; 200 QD, YH4808 200 mg once daily for 14 days; 200 BID, YH4808 200 mg twice daily for 14 days; R40 BID, esomeprazole 40 mg twice daily for 14 days.
Safety

There were no serious AEs observed during the study. There were seven cases of adverse drug reactions (Table 5): one case in the 100 BID group, one case in the 200 QD group, and five cases in the R40 BID group. The differences in the frequency of adverse drug reactions between the treatment groups were not statistically significant. The most reported adverse drug reaction was dyspepsia. All AEs were mild or moderate and recovered without any complications. Further, the changes in the vital signs, or in the results of the physical examinations, 12-lead ECG, or clinical laboratory tests were not clinically significant.

DISCUSSION

In acid-related disorders such as GERD, many patients suffer from night time symptoms, which reduce their quality of life. PPIs are widely prescribed for the treatment of such disorders. However, PPIs also have limitations and are less effective in some cases. Therefore, the PK and PD studies were performed on YH4808 to identify its optimal regimen for night time pH control, and it exhibited potential for replacing the conventional drugs.

There were no differences in the dose-normalized C_{max,ss} and AUC_{τ,ss} among the YH4808 groups in the PK profile (p > 0.05). Thus, it was estimated that the systemic exposure of YH4808 increased in a dose-proportional manner, as observed in the previous study [7]. When YH4808 was administered in a fasting state, the T_{max} was about one hour [7]. However, it was delayed by about four hours in this study. Food is known to increase gastric emptying time and affect the T_{max} of the drug [8]. Therefore, the T_{max} of YH4808 increased because...
it was administered after the meals. In the current regimens, there were no other special features observed with respect to fluctuation and accumulation.

In the intragastric pH analysis, the time above pH 4 over 24 hours on day 14 in the YH4808 groups was higher when twice-daily dosing was administered. Moreover, this time above pH 4 over 24 hours on day 14 was not different from that of the esomeprazole group \((p > 0.05)\). The difference in 0–24 h AUEC from baseline was greater only when YH4808 was administered at 200 mg twice a day compared to the esomeprazole group; those values of the remaining YH4808 groups were not greater than that of the esomeprazole group. But, the difference in 0–24 h AUEC from baseline and the time above pH 4 were no statistically significant difference among the groups \((p > 0.05)\). The 5–12 h AUEC, which represents the night time pH control, was slightly higher in all YH4808 groups than in the esomeprazole group. However, the difference among the groups was not statistically significant \((p > 0.05)\). Because this study was an exploratory study, the number of participants per groups was small \((n = 5)\), and there might be no statistical difference. In addition, since this study was performed in two parts, there was a limitation in statistical comparison among the treatment groups. The observation of a pH control by YH4808 compared to that achieved with the PPIs needs confirmation through follow-up studies.

Considering that PPIs reach their maximum effect only when administered repeatedly, YH4808 is expected to provide better night time pH control when administered for a duration that is shorter than that investigated in the current study. Additionally, in a previous study, P-CAB improved the treatment of gastric acid-related conditions like GERD and low-dose aspirin (LDA)- or nonsteroidal anti-inflammatory drug (NSAID)-induced peptic ulcers and was also effective in patients with PPI-resistant esophagitis \([9,10]\). Further, it was demonstrated that a novel triple regimen that adopted YH4808 was as effective as the conventional standard triple treatment regimen of esomeprazole, amoxicillin, and clarithromycin for the eradication of \(H. pylori\). Additionally, YH4808 increased the gastric pH relatively rapidly and maintained it almost as effectively as esomeprazole \([11]\). Unfortunately, the advantage of fast onset could not be confirmed due to the limitations of our study design that necessitated the administration of YH4808 after a meal when the pH had already increased.

In conclusion, the administration of YH4808 200 mg twice a day was observed to be the most suitable therapeutic regimen for controlling gastric pH for 24 hours and during the night. There were no differences in safety compared with the lower dose groups. Although there were no statistically significant differences, the pH control of the YH4808 groups could be better to that of the esomeprazole group. Therefore, YH4808 is expected to replace PPIs in controlling the night time symptoms of acid-related disorders.

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**REFERENCES**

1. Kim SG, Jung HK, Lee HL, Jang JY, Lee H, Kim CG, et al. Guidelines for the diagnosis and treatment of Helicobacter pylori infection in Korea, 2013 revised edition. J Gastroenterol Hepatol 2014;29:1371-1386.
2. Satoh K, Yoshino J, Akamatsu T, Itoh T, Kato M, Kamada T, et al. Evidence-based clinical practice guidelines for peptic ulcer disease 2015. J Gastroenterol 2016;51:177-194.

3. Iwakiri K, Kinoshita Y, Habu Y, Oshima T, Manabe N, Fujiwara Y, et al. Evidence-based clinical practice guidelines for gastroesophageal reflux disease 2015. J Gastroenterol 2016;51:751-767.

4. Huang JQ, Hunt RH. Pharmacological and pharmacodynamic essentials of H(2)-receptor antagonists and proton pump inhibitors for the practising physician. Best Pract Res Clin Gastroenterol 2001;15:355-370.

5. Andersson K, Carlsson E. Potassium-competitive acid blockade: a new therapeutic strategy in acid-related diseases. Pharmacol Ther 2005;108:294-307.

6. Scarpignato C, Hunt RH. Editorial: towards extended acid suppression—the search continues. Aliment Pharmacol Ther 2015;42:1027-1029.

7. Yi S, Lee H, Jang SB, Byun HM, Yoon SH, Cho JY, et al. A novel K+ competitive acid blocker, YH4808, sustains inhibition of gastric acid secretion with a faster onset than esomeprazole: randomised clinical study in healthy volunteers. Aliment Pharmacol Ther 2017;46:337-346.

8. Rowland M, Tozer TN. Clinical pharmacokinetics and pharmacodynamics: concepts and applications, 4th ed. Philadelphia (PA): Wolters Kluwer, Health/Lippincott William & Wilkins; 2011, 201

9. Hoshino S, Kawami N, Takenouchi N, Umezawa M, Hanada Y, Hoshikawa Y, et al. Efficacy of vonoprazan for proton pump inhibitor-resistant reflux esophagitis. Digestion 2017;95:156-161.

10. Mori H, Suzuki H. Role of acid suppression in acid-related diseases: proton pump inhibitor and potassium-competitive acid blocker. J Neurogastroenterol Motil 2019;25:6-14.

11. Park H, Kim CO, Kim M, Lim Y, Lee WY, Yoon S, et al. Pharmacodynamic evaluation of YH4808 for Helicobacter pylori eradication in healthy subjects. Transl Clin Pharmacol 2020;28:136-146.