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

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Summary

Background: YH4808, a K\(^+\)-competitive acid blocker, is under clinical development for the treatment of acid-related disorders, such as gastroesophageal reflux disease.

Aims: To determine the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of YH4808, compared to placebo and esomeprazole.

Methods: This double-blind, randomised, placebo- and active comparator (esomeprazole)-controlled study was conducted with 123 healthy male volunteers. We evaluated YH4808 (30-800 mg) properties, administered in single (N=55) and multiple (N=24) oral doses, and recorded the effects on 24-hour intragastric acidity. Results were compared to placebo (N=20) and esomeprazole 40 mg (N=24).

Results: Plasma YH4808 exposure increased dose-proportionally and declined in a multi-phasic manner. YH4808 \(\geq\)200 mg/d maintained intragastric acidity at pH >4 for longer times than esomeprazole during both day and night (%Time at pH >4: >70\% vs 58\% of a 24-hour period, respectively; and >50\% vs 33\% of a 9-hour night respectively). A twice-daily regimen of YH4808 more effectively controlled intragastric pH at night than a once-daily regimen. In evaluating the mean areas under the intragastric pH-time curves in 15-minute intervals for 2 hours after dosing, we found that YH4808 had a faster onset than esomeprazole. Moreover, unlike esomeprazole, YH4808 PK and PD were not significantly affected by the CYP2C19 genotype of the subjects. YH4808 was well-tolerated at all doses administered.

Conclusion: This study showed that YH4808 produced a rapid, sustained suppression of gastric secretion with good tolerability. The results at YH4808 \(\geq\)200 mg/d provide a rationale for further clinical investigations in populations with acid-related diseases.

1 INTRODUCTION

Proton pump inhibitors (PPIs) have been the treatment of choice for acid-related diseases, such as gastroesophageal reflux disease (GERD), erosive esophagitis and peptic ulcer disease.\(^1,2\) However, their clinical application has been limited, because PPI inhibition of acid secretion is rather slow; the maximum inhibition occurs only after 2-5 days of standard dosing. Furthermore, PPIs may not adequately control night-time gastric acidity, even when administered at bedtime.\(^2,3\) In addition, the effect of PPIs may vary significantly among patients, due to genetic polymorphism in drug-metabolising enzymes, particularly cytochrome P450 (CYP) 2C19, which...
metabolises PPIs (except for tenatoprazole).1,2 Moreover, according to recommendations, PPIs should be administered in the fasting state,4 because they must be converted to the active form in the acidic spaces of gastric parietal cells.2

Unlike PPIs, potassium-competitive acid blockers (P-CABs) reversibly inhibit the gastric H+/K+-ATPase. Because P-CABs are rapidly absorbed and do not require an acidic environment for activation or protonation, they can immediately bind to the H+/K+-ATPase, which leads to prompt, marked inhibition of gastric acid secretion.5 These advantageous characteristics of P-CABs have made them an attractive alternative to PPIs for treating acid-related diseases.5,6 Vono-prazan fumarate (TAKECAB), a P-CAB, was first approved in Japan in December, 2014, for the treatment of gastroduodenal ulcers and reflux esophagitis and as an adjunct to Helicobacter pylori (H. pylori) eradication.7

YH4808 is a novel P-CAB, currently under clinical drug development (Yuhan Co. Ltd., Seoul, Republic of Korea). In preclinical studies, YH4808 suppressed acid production more potently than esomeprazole, both in vitro and in vivo. For example, in a rat model of histamine-stimulated acid secretion treated with an intravenous injection of YH4808 or PPI, the half-maximum anti-secretory activity required a much lower dose (ED50) of YH4808 than of esomeprazole (0.1 mg/kg vs 0.9 mg/kg respectively).8 YH4808 showed a favourable safety profile in preclinical toxicity studies in mice, rats, and monkeys; moreover, no adverse effects were observed with doses up to 100 mg/kg/d in rats. In addition, the metabolism of YH4808 involved multiple cytochrome P450 enzymes, so the pharmacokinetics (PK) and pharmacodynamics (PD) of YH4808 would likely be less dependent on CYP2C19 genetic polymorphism than PPIs. Two major metabolites, M3 and M8, were detected readily in animal studies, and it was anticipated that they would also be significant metabolites in humans, although the major pharmacokinetic activity appeared to arise from the parent drug. An in vitro enzyme assay showed that M8 had negligible inhibitory effects on the H+/K+-ATPase, and M3 had an approximately 2-fold higher IC50 than the parent drug (5.1 nM vs 3.4 nM).

On the basis of this knowledge, we performed the present first-in-human clinical study of YH4808. We aimed to investigate the PK, PD and tolerability profiles of YH4808 after single and multiple oral administrations in healthy volunteers. Furthermore, we compared the acid suppression effect of YH4808 to that of esomeprazole. We also explored the influence of CYP2C19 genetic polymorphism on the PK and PD profiles of YH4808.

2 | METHODS

2.1 | Subjects and study design

This study was a randomised, double-blind, placebo- and active comparator-controlled clinical study performed in two parts: a single ascending dose study, and a multiple ascending dose study. We recruited healthy male subjects, 20-45 years of age, with a body weight >50 kg, and within ±20% of ideal body weight. Subjects were enrolled when they showed no abnormality on the medical history, physical examination, vital signs, 12-lead electrocardiography (ECG), serology (HBsAg, anti-HCV and anti-HIV antibody), routine clinical laboratory tests (chemistry, haematology and urinalysis) and urinary drug screen. Smokers were excluded based on a urine cotinine test. In the single dose study, subjects who were both positive and negative for H. pylori were enrolled to explore the effects of YH4808 on intragastric pH profiles in the presence and absence of H. pylori infections. However, in the multiple-dose study, we included only H. pylori-negative subjects to avoid the effect of H. pylori infections on intragastric pH.9,10 In the 13C-urea breath test for detecting H. pylori infections, subjects were required to stay fasted for at least 4 hours before the test. Breath samples were taken before and 20 minutes after oral administration of a 13C-labelled urea capsule (Helifinder, Sejung Co. Ltd., Seoul, Republic of Korea) with water. The isotope ratio (13C/12C) in collected breath samples were analysed with gas mass spectrometry (Heliview, Medi-chems Co. Ltd., Chungcheongnam-do, Republic of Korea). All subjects were required to abstain from taking any medication, from 14 days before the study drug administration until after the last post-study visit. Alcohol, smoking, and food or beverages containing grapefruit or caffeine were not allowed during the entire study period.

The tested doses of YH4808 were 30, 50, 100, 200, 400, 600 and 800 mg in the single dose study, and 100, 200 and 400 mg once daily or 100 mg twice daily in the multiple-dose study. After an overnight fast, eligible subjects randomly received a single oral dose or multiple oral daily doses (7 days) of YH4808 at the assigned dose, esomeprazole 40 mg (Nexium®, AstraZeneca Korea, Seoul, Republic of Korea), or placebo at approximately 9:30. All dose groups (N=12) were randomly assigned to YH4808, esomeprazole, or placebo, at a ratio of 8:2:2, respectively, except for the YH4808 200 mg group in the multiple-dose study, where the ratio was 8:6:2 (N=16; Figure 1). In the YH4808 200 mg/d group, after a 7-day washout period at the end of once daily dosing, subjects received YH4808 100 mg twice daily, esomeprazole 40 mg once daily, or placebo (Figure 1B; cross-over design).

We performed 24-hours continuous, ambulatory intragastric pH monitoring on Day-1 (baseline), and Day 1 in the single dose study; on Day-1, Day 1, and Day 7 in the YH4808 100 mg and the 400 mg groups in the multiple-dose study. However, the YH4808 200 mg group in the multiple dose with crossover study design received intragastric pH monitoring only on Day-1 and Day 7 during each dosing period (Period I: 200 mg once daily and Period II: 100 mg twice daily; Figure 1B).

Intragastric monitoring was performed with a glass electrode, which was attached to a Digitrapper pH 400 recorder (Medtronic A/S, Skovlunde, Denmark). The electrode was inserted intranasally into the stomach and advanced a further 5 cm from the point that the monitored pH abruptly dropped to <pH 3. Before insertion, the electrode was calibrated with standard buffer solutions at pH 7.01 and pH 1.07. Intragastric pH recording began 30 minutes to 1 hour after the electrode was placed, and measurements were taken every
4 seconds for 24 hours. During pH monitoring, subjects remained in an upright position during the day (ie, 8:00-23:00) and lay supine during the night (ie, 23:00-8:00). Meals with identical content were provided at 4 and 9 hours after study drug administration. No other food or beverage was allowed, and vigorous physical activity was prohibited during pH monitoring. Intragastric pH data were analysed with GastroTrac software (Alpine Biomed ApS., Skovlunde, Denmark).

Tolerability was assessed throughout the study based on vital signs, clinical laboratory tests, 12-lead ECGs, physical examinations, and adverse events (AEs) reported by subjects or observed by the medical investigators. In the multiple-dose study, we also determined the serum gastrin levels at baseline and on Days 2, 4, 6 and 8, within a range of 0-1000 pg/mL, using a radioimmunoassay method performed with a commercial kit (DiaSorin Inc, Stillwater, MN, USA).

The Institutional Review Board of Seoul National University Hospital approved the study protocol on the 14 September, 2009, and all subjects gave written informed consent before any study procedure was performed. Before subject enrolment began, this study was registered in a public trial registry (ClinicalTrials.gov, registration no.: NCT01007019). This study was conducted in full accordance with the Declaration of Helsinki for biomedical research involving human subjects (59th World Medical Association General Assembly, Seoul, October 2008), and the Good Clinical Practice guidelines established by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Humans.

2.2 | Genotyping

A blood sample (4 mL) was collected from each subject on Day-1. DNA was isolated from each sample with the Gentra Puregene DNA Isolation Kit (Qiagen, Hilden, Germany). DNA was analysed by DNA Link. Co. Ltd. (Seoul, Republic of Korea) with the Targeted Human Drug-Metabolizing Enzymes and Transporters GeneChip (DMET Plus Array, Affymetrix, Santa Clara, CA, USA). The DMET Plus array included 1936 genetic variants (1931 Single-nucleotide polymorphisms (SNPs) and 5 Copy number variations (CNVs)) of 225 genes associated with drug-metabolising enzymes and transporters. On the basis of the known SNP variants for CYP2C19, ie, *2 (681G>A, rs4244285), *3 (636G>A, rs4986893), and *17 (–806C>T, rs12248560), we categorised subjects into three groups with different phenotypes: extensive metabolisers (EM, *1/*1 or *1/*17), intermediate metabolisers (IM, *1/*2, *1/*3, *17/*2, or *17/*3), and poor metabolisers (PM, *2/*2, *2/*3, or *3/*3).

2.3 | Determination of plasma concentrations of YH4808 and its metabolites

For the PK analysis, blood samples (8 mL) were drawn before the dose (ie, 0 hour) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours post-dose, on Days 1 and 7 (the multiple-dose study only); also, urine was collected for 24 hours post-dose, on Days 1 and 7.

Blood samples were centrifuged at 3000 rpm for 10 minutes at 4°C, and the plasma was aliquoted immediately into polypropylene tubes and stored at −70°C until analysis. Plasma concentrations of YH4808, its two metabolites (M3 and M8), and esomeprazole were determined with high performance liquid chromatography (HPLC, Agilent 1200 series, Agilent Technologies, Santa Clara, CA, USA), coupled with tandem mass spectrometry (MS/MS, API 3200 Quadrupole, Applied Biosystems/MDS SCIEX, Foster City, CA, USA), equipped with an electrospray ionisation source, which was operated...
parameters was determined with a linear regression analysis of the log-transformed $AUC_{inf}$ versus the log-transformed dose (power model). All statistical analyses were performed with SPSS Statistics 21.0 software (SPSS Korea, Seoul, Republic of Korea). $P<0.05$ were considered statistically significant.

3 | RESULTS

3.1 | Subjects

The present study enrolled 134 healthy male volunteers (91 and 43 for the single- and multiple-dose studies, respectively), aged 20-41 years (mean ± SD, 25.5±4.6 years), with body weights of 53.5-87.2 kg (67.5±7.1 kg). We found $H. pylori$ positivity in 32 of 91 participants (35.2%) in the single dose study, but no participants in the multiple-dose study.

Of 134 subjects, 123 completed this study (83 and 40 for the single- and multiple-dose studies respectively). Tolerability was assessed in all subjects that received at least a single dose of the study drug (N=126). The PK was assessed in all subjects that received any dose of YH4808 and completed the study as planned (N=79). Intragastric pH was analysed in all subjects that received any of the study drugs, completed the study as planned, and had complete intragastric recordings (ie, $>95\%$ of recording time for 24 hours). (N=120; three subjects in the single dose study were excluded due to incomplete recording.) Further detail information on subject participation is presented in Figure S1. The demographic characteristics of subjects included in the PK and PD analyses were comparable among treatment groups (Table S1).

3.2 | Intragastric pH

In subjects who were both negative and positive for $H. pylori$, the % Time of intragastric pH $>$4 increased significantly in a dose-dependent manner after a single administration of YH4808 (30-800 mg), compared to placebo (Figure S2). In particular, among $H. pylori$-negative subjects, ≥100 mg YH4808 showed effects similar or superior to the effects of 40 mg esomeprazole in terms of the %Time at pH $>$4.

After YH4808 100-400 mg had been administered for 7 days, the %Time of intragastric pH $>$4 increased dose-dependently compared to placebo. However, YH4808 200 mg and 400 mg achieved similar values (Figure 2). At doses ≥200 mg/d, YH4808 maintained intragastric pH $>$4 for approximately 70% of a 24-hours time period, and the mean %Time at pH $>$4 increased both during day and night to values greater than those achieved with 40 mg/d esomeprazole (Table 1).

Despite the administrations of the same total daily dosage, YH4808 100 mg twice daily was more effective than 200 mg once daily; the twice daily regimen maintained intragastric pH $>$4 for a longer period of time (76.4% vs 70.2% of 24 hours), particularly at night (76.4% vs 54.1% of the night-time). The intragastric pH-time profiles (Figure 3) also showed that intragastric pH at night remained high for a longer time with the 100 mg twice daily regimen than with the 200 mg once daily regimen.
AUC from 45 to 60 minutes and 15-30 minutes compared to placebo, respectively. In contrast, esomeprazole did not show any significant increases in AUC within 2 hours. Moreover, on Day 7 of the multiple-dose study (Figure 4), the onset time was defined as first 15-minute interval showing a significant increase compared to placebo in AUEC15 min. With the first dose, YH4808 100 mg and 400 mg significantly elevated the AUEC15 min from 45 to 60 minutes and 15-30 minutes compared to placebo, respectively. In contrast, esomeprazole didn't show any significant increases in AUEC15 min within 2 hours. Moreover, on Day 7 of YH4808 ≥200 mg/d, the elevated AUEC15 min was sustained from 0 to 15 minutes after drug administration. On the other hand, following esomeprazole 40 mg/d for 7 days, the AUEC15 min started differing from placebo at the 60-75 minutes interval. This indicated that YH4808 achieved the pharmacological effect after dosing earlier than the time required for esomeprazole to achieve an effect.

The values of %Times at pH >4 over 24 hours were compared between Day 1 and Day 7, based on results from both the single- (only H. pylori-negative subjects) and multiple-dose studies. With a single dose of YH4808 100 mg, 200 mg, or 400 mg, the values of %Times at pH >4 over 24 hours were, respectively, 1.05, 0.91 and 0.83 of the values observed after the 7-day dosing. However, the corresponding ratio was 0.73 for 40 mg esomeprazole. This analysis suggested that YH4808 achieved >80% of its pharmacologic effect at steady state within a single day.

### 3.3 Pharmacokinetics

With a single oral administration of YH4808 at 30-800 mg, peak plasma concentrations were reached at 0.5-2.0 hours post-dose. The concentration then declined in a multi-phasic manner (Figure S3A), with a terminal half-life in the range of 17.6-24.1 hours (Table 2). Following multiple administrations for 7 days, trough plasma concentrations reached at steady state (data not shown). The systemic exposure to YH4808 varied highly among individuals; e.g. the CV% of the AUC0-t range was 31.0%-65.0% and 37.5%-45.9%, respectively, in the single- and multiple-dose studies, respectively.

The two metabolites, M3 and M8, behaved differently. The mean concentration-time profile of M3 was similar to that of YH4808 after a single oral administration of YH4808 at 200 mg, but M8 showed much higher concentrations than YH4808 and M3 over the entire post-dose period (Figure S3B). Plasma concentrations of M3 and M8 peaked at 0.75-2.0 hours, simultaneous with the T_max of YH4808. Furthermore, M8 had greater systemic exposure than YH4808, with a metabolic ratio range of 27.3-133.3 (Table 2).

### Table 1 Pharmacodynamics parameters (mean ± SD) obtained in the multiple-dose study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>%Time at pH &gt;4 for 24 hours</th>
<th>Day-time</th>
<th>Night-time</th>
<th>Mean pH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Placebo</td>
<td>4</td>
<td>9.3±2.3</td>
<td>15.3±3.9</td>
<td>0.0±0.0</td>
<td>1.9±0.2</td>
</tr>
<tr>
<td>Esomeprazole 40 mg</td>
<td>4</td>
<td>44.3±20.7</td>
<td>60.0±20.0</td>
<td>18.6±22.2</td>
<td>3.6±0.9</td>
</tr>
<tr>
<td>YH4808 100 mg</td>
<td>8</td>
<td>44.0±10.2</td>
<td>66.0±11.9</td>
<td>10.3±16.2</td>
<td>3.6±0.6</td>
</tr>
<tr>
<td>YH4808 400 mg</td>
<td>8</td>
<td>56.6±12.1</td>
<td>72.5±7.6</td>
<td>28.5±22.2</td>
<td>4.3±0.5</td>
</tr>
<tr>
<td><strong>Day 7</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>6</td>
<td>12.7±5.6</td>
<td>18.5±10.5</td>
<td>3.7±4.7</td>
<td>2.1±0.2</td>
</tr>
<tr>
<td>Esomeprazole 40 mg once</td>
<td>10</td>
<td>58.3±9.3</td>
<td>73.3±9.1</td>
<td>32.7±15.6</td>
<td>4.3±0.4</td>
</tr>
<tr>
<td>daily</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>YH4808 100 mg once daily</td>
<td>8</td>
<td>43.1±11.3</td>
<td>51.8±14.0</td>
<td>29.1±18.8</td>
<td>3.7±0.5</td>
</tr>
<tr>
<td>YH4808 200 mg once daily</td>
<td>8</td>
<td>70.2±14.7</td>
<td>79.7±13.9</td>
<td>54.1±16.8</td>
<td>4.9±0.6</td>
</tr>
<tr>
<td>YH4808 100 mg twice daily</td>
<td>8</td>
<td>76.4±15.4*</td>
<td>76.7±16.2</td>
<td>76.4±22.4*</td>
<td>5.2±0.8*</td>
</tr>
<tr>
<td>YH4808 400 mg once daily</td>
<td>8</td>
<td>72.0±15.6</td>
<td>84.5±9.2</td>
<td>50.4±29.3</td>
<td>5.2±0.9*</td>
</tr>
</tbody>
</table>

*P<0.05, compared to esomeprazole (one-sided test, multiple simultaneous comparison with a Dunnett analysis).
TABLE 2 Pharmacokinetic parameters of YH4808 after a single and multiple oral administrations

<table>
<thead>
<tr>
<th>Dose group</th>
<th>N</th>
<th>Tₘₐₓ (Tₘₐₓ,7d) (hours)</th>
<th>Cₘₐₓ (Cₘₐₓ,7d) (µg/L)</th>
<th>AUC₀₋₁₂ (AUC₀₋₁₂,7d) (µg h/L)</th>
<th>AUCₘₐₓ (AUCₘₐₓ,7d) (µg h/L)</th>
<th>CL/F (L/h)</th>
<th>t₁/₂ (h)</th>
<th>Accumulation index</th>
<th>MR of M₃</th>
<th>MR of M₈</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single ascending dose study</strong></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>30 mg</td>
<td>7</td>
<td>0.5 (0.5-1.0)</td>
<td>33.2±18.5</td>
<td>41.9±16.3</td>
<td>49.6±19.1</td>
<td>732.9±408.7</td>
<td>17.8±13.2</td>
<td>-</td>
<td>2.30±0.67</td>
<td>82.0±33.5</td>
</tr>
<tr>
<td>50 mg</td>
<td>8</td>
<td>0.75 (0.5-1.5)</td>
<td>47.8±40.1</td>
<td>73.4±49.1</td>
<td>81.0±51.2</td>
<td>805.8±376.2</td>
<td>17.6±7.3</td>
<td>-</td>
<td>2.63±0.37</td>
<td>133.3±63.7</td>
</tr>
<tr>
<td>100 mg</td>
<td>8</td>
<td>0.75 (0.5-1.0)</td>
<td>110.9±56.5</td>
<td>222.5±102.1</td>
<td>241.8±110.4</td>
<td>489.6±197.8</td>
<td>22.8±3.4</td>
<td>-</td>
<td>1.99±0.61</td>
<td>52.6±29.1</td>
</tr>
<tr>
<td>200 mg</td>
<td>8</td>
<td>0.75 (0.48-2.0)</td>
<td>241.8±186.2</td>
<td>427.2±274.7</td>
<td>466.3±292.9</td>
<td>558.4±240.0</td>
<td>24.1±4.9</td>
<td>-</td>
<td>1.49±0.61</td>
<td>42.3±30.7</td>
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<tr>
<td>400 mg</td>
<td>8</td>
<td>1.0 (0.73-1.5)</td>
<td>437.2±208.7</td>
<td>1077.7±645.1</td>
<td>1195.1±702.9</td>
<td>429.1±225.7</td>
<td>233±4.3</td>
<td>-</td>
<td>1.60±0.52</td>
<td>40.5±26.7</td>
</tr>
<tr>
<td>600 mg</td>
<td>8</td>
<td>1.0 (0.75-1.5)</td>
<td>642.3±383.2</td>
<td>1508.1±833.0</td>
<td>1670.1±940.1</td>
<td>513.8±375.0</td>
<td>20.9±4.9</td>
<td>-</td>
<td>1.28±0.40</td>
<td>27.3±15.6</td>
</tr>
<tr>
<td>800 mg</td>
<td>8</td>
<td>1.0 (0.52-1.5)</td>
<td>780.6±411.0</td>
<td>1756.3±886.7</td>
<td>1967.4±997.8</td>
<td>732.9±408.7</td>
<td>23.6±5.3</td>
<td>-</td>
<td>1.35±0.34</td>
<td>28.2±13.6</td>
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<td><strong>Multiple ascending dose study</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>100 mg once daily</td>
<td>8</td>
<td>0.63 (0.5-1.53)</td>
<td>142.4±120.3</td>
<td>227.8±126.0</td>
<td>452.4±253.0</td>
<td>579.0±319.6</td>
<td>50.4±45.6</td>
<td>1.09±0.24</td>
<td>1.84±0.56</td>
<td>86.3±70.8</td>
</tr>
<tr>
<td>200 mg once daily</td>
<td>8</td>
<td>0.75 (0.5-3.0)</td>
<td>115.2±97.9</td>
<td>397.7±180.4</td>
<td>932.9±419.8</td>
<td>589.1±234.7</td>
<td>44±3.9</td>
<td>0.94±0.7</td>
<td>1.16±0.36</td>
<td>45.7±26.2</td>
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<tr>
<td>100 mg twice daily</td>
<td>8</td>
<td>0.5 (0.5-1.0)</td>
<td>82.5±60.9</td>
<td>234.5±123.3*</td>
<td>863.6±265.1</td>
<td>517.4±210.3</td>
<td>34.9±11.0</td>
<td>0.98±0.33</td>
<td>1.31±0.48</td>
<td>46.8±26.4</td>
</tr>
<tr>
<td>400 mg once daily</td>
<td>8</td>
<td>0.75 (0.5-1.0)</td>
<td>210.3±166.8</td>
<td>618.0±276.9</td>
<td>1184.7±402.6</td>
<td>776.5±349.9</td>
<td>31.9±6.7</td>
<td>0.63±0.16</td>
<td>1.62±0.43</td>
<td>65.9±40.5</td>
</tr>
</tbody>
</table>

All data represent the mean±SD except for Tₘₐₓ or Tₘₐₓ,7d which represent the median. Metabolic ratio, metabolite AUC/YH4808 AUC.

* AUC₀₋₁₂ h,₇d.
For both the parent drug and its metabolites, negligible amounts were excreted in the urine. The unchanged parent drug was excreted at amounts too low to quantify precisely; the amounts of M3 and M8 excreted were less than 3% of the dose administered.

A power model analysis of logarithmic transformations of AUC_{0-4} for administered doses showed that the systemic exposure to YH4808 increased in a dose-proportional manner in the range of 30-800 mg after a single oral administration. The slopes of the regression lines were 1.15 (95% CI: 1.02-1.28) for AUC_{0-4} and 1.00 (0.85-1.15) for C_{max}.

### 3.4 Relationship between pharmacokinetics, pharmacodynamics, and CYP2C19 genotypes

An E_{max} model adequately described the PK-PD relationship between the YH4808 AUC_{0-1} and the %Time at pH >4 for 24 hours (Figure 5A) in H. pylori-negative subjects. Furthermore, the PK-PD relationship of YH4808 was not altered by the different CYP2C19 genotypes. That is, among the different CYP2C19 genotypes, the differences in AUC were not sufficiently remarkable to alter the PD responses in terms of the %Time at pH >4, even though the dose-normalised AUC_{0-4} after a single dose was higher in the CYP2C19 PM group than in the CYP2C19 EM group (Figure 5A). In contrast, both the PK and the PK-PD relationship of esomeprazole 40 mg were different among the different CYP2C19 genotypes (Figure 5B and Table 3). For example, after a single dose of esomeprazole, subjects with the CYP2C19 EM genotype had a significantly lower AUC_{0-4} and %Time at pH >4 than subjects with the CYP2C19 IM or PM genotype.

### 3.5 Tolerability

YH4808 exhibited acceptable tolerability in healthy volunteers following a single dose of 30 mg to 800 mg and after multiple doses of 100 mg to 400 mg for 7 days. Of 80 subjects treated with YH4808, 24 (30.0%) reported 40 AEs, comparable to the AE rate in the placebo group (ie, 10 AEs reported by 6 of 20 subjects [30.0%]) and in the esomeprazole group (ie, 19 AEs reported by 8 of 26 subjects [30.7%]). All AEs were resolved without sequelae, and no serious AE was observed. The incidence of treatment-related AEs did not rise as the YH4808 dose increased. The most common treatment-related AEs experienced by at least two subjects were, in the YH4808 treatment: diarrhoea (4 cases), abdominal pain (2 cases), and headache (2 cases); in the esomeprazole treatment: headache (4 cases), dizziness (3 cases), and abdominal pain (2 cases); and in the placebo treatment, no AE was experienced by more than 1 subject.

Following repeated administrations of YH4808, serum gastrin increased in a dose-dependent manner, compared to the placebo group or the baseline level. However, most of the observed changes in serum gastrin remained within the normal range (0-110 pg/mL; Figure S4). There was no clinically significant finding in the clinical laboratory tests, 12-lead ECGs, vital signs or physical examinations during the study.

### 4 DISCUSSION

The present study was the first clinical study of YH4808 to assess PK, PD, and tolerability in healthy male subjects at both single and multiple-dose administrations. YH4808 exhibited a dose-proportional PK profile, and its pharmacological effect at ≥200 mg/d was comparable to that of esomeprazole at 40 mg/d; ie, YH4808 maintained intragastric pH >4 for about 70% of a day. YH4808 was well-tolerated, both at a single dose of 30-800 mg and at multiple doses of 100-400 mg for 7 days in healthy subjects.

In this study, we found some potential advantages that YH4808 might have over PPIs, the current standard therapy. First, in direct comparisons between YH4808 and esomeprazole treatments, YH4808 ≥200 mg/d sustained intragastric pH >4 for longer times.
than esomeprazole 40 mg during both day and night. In addition, splitting the YH4808 dose into a twice-daily regimen was significantly more effective than the once-daily regimen for controlling acid secretion at night. Although previous studies showed that a twice-daily PPI dose regimen also improved acid suppression over the once-daily PPI regimen,13,14 patients with GERD and healthy subjects continued secreting gastric acid at night; this lack of suppression might lead to an insufficient therapeutic response to PPIs.13-15 Consequently, further study will be needed in a patient population to compare therapeutic responses between groups given twice-daily doses of YH4808 or PPIs, based on the control of acid secretion at night. The second advantage of YH4808 was that its PK and PD were less susceptible to specific genetic polymorphism that affect drug metabolising enzymes and transporters,13,14,17,18 human CYP enzymes. Indeed, in an exploratory analysis for multiplex experiments with human liver microsomes and various recombinant human CYP enzymes. These characteristics appeared to contribute to the positive results observed in a non-inferiority trial between vonoprazan at 20 mg/day and lansoprazole at 30 mg/day in patients with erosive esophagitis.19 Although those two treatments were equally effective at 8 weeks, at 2 weeks, a higher proportion of patients healed in the vonoprazan group than in the lansoprazole group. Moreover, in a subgroup of patients with the CYP2C19 EM genotype, the proportion of patients healed tended to be higher in the vonoprazan group.17,18 These characteristics appeared to contribute to the positive results observed in a non-inferiority trial between vonoprazan at 20 mg/d and lansoprazole at 30 mg/day in patients with erosive esophagitis. In this study, our results of ambulatory intragastric pH monitoring appeared reliable. Our observations of the mean intragastric pH

### TABLE 3 Effect of CYP2C19 genotypes on pharmacokinetics (AUC) and pharmacodynamics (%Time at pH >4)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>YH4808</th>
<th>Esomeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CYP2C19</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Day 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N9</td>
<td>40</td>
<td>6</td>
</tr>
<tr>
<td>AUC0-t/Dose</td>
<td>1.81±0.91</td>
<td>28.2±13.3</td>
</tr>
<tr>
<td>N0</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>%Time at pH &gt;4</td>
<td>55.7±18.4</td>
<td>19.1±9.6</td>
</tr>
<tr>
<td>Day 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>AUC0-t/Dose</td>
<td>1.66±0.99</td>
<td>87.6±17.8</td>
</tr>
<tr>
<td>N</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>%Time at pH &gt;4</td>
<td>71.1±19.5</td>
<td>63.0±6.3</td>
</tr>
</tbody>
</table>

CYP2C19 genotypes are indicated by the extent of drug metabolism: EM, extensive metaboliser; IM, intermediate metaboliser; PM, poor metaboliser.

1*Data on Day 1 from both the single and multiple-dose studies is all included.

2*Data on Day 1 from only Helicobacter pylori-negative subjects in both the single and multiple-dose studies is included.

3P<.05, vs EM (multiple simultaneous comparison with the Dunnett analysis).
and the %Time at pH >4 after single and multiple doses of esomeprazole 40 mg (active comparator) were similar to previously reported values. In the single dose study, we included H. pylori-positive subjects (33.7% of subjects) to explore the effects of YH4808 on intragastric pH profiles in the presence and absence of an H. pylori infection. Moreover, it was deemed acceptable to include these patients in the assessments of tolerability and PK up to highest dose level, because the presence of H. pylori would be unlikely to have significant effects on either the tolerability or the single-dose PK. Even H. pylori-positive subjects showed dose-dependent increases in the %Time at pH >4 after a single dose of YH4808, similar to H. pylori-negative subjects. Subsequently, we chose YH4808 doses of 100, 200 and 400 mg/d for the multiple-dose study, based on the results from the single dose study. In the multiple-dose study, we assessed intragastric pH independent of H. pylori infections by excluding H. pylori-positive subjects. Moreover, the PD data in H. pylori-positive subjects were excluded from further analyses of the PK-PD relationship.

The observed metabolism of YH4808 to both M3 and M8 was both acute and excessive, which was consistent with findings in previous animal studies. A large proportion of the drug administered was likely to be metabolised via the first-pass effect, which would lead to low YH4808 bioavailability. This assumption was based on the results from nonclinical studies, which showed that the absolute oral bioavailabilities in rat and dog were 9.2% and 4.5%, respectively. Moreover, a mass balance study, where a radio-labelled drug was administered to rats either intravenously or orally, showed that 98% of the radioactivity was recovered mainly in the metabolites. However, a clinical PK study with both oral and intravenous administrations of radio-labelled drug will be required to confirm the absolute oral bioavailability in humans.

The PK-PD relationship of YH4808, assessed as the %Time at pH >4 vs the drug AUC, was captured with a simple \( E_{\text{max}} \) model, which represents a classical dose-response profile: %Time at pH >4 over 24 hours = \( \frac{(E_{\text{max}} \times \text{AUC})}{(E_{50} + \text{AUC})} \). Kirchheiner et al. analyzed the relative potency of five PPIs in terms of the mean pH over 24 hours and the dose per day for each PPI, with the following \( E_{\text{max}} \) model: Mean pH = Baseline mean pH + \( (E_{\text{max}} \times \text{Dose})/(ED_{50} + \text{Dose}) \). They reported an \( E_{\text{max}} \) = 3.46, and a baseline mean pH = 3.06, which indicated that at least 11.1-89.2 mg/d of PPIs would be required to achieve a mean pH of 4 over 24 hours. To explore the potency of YH4808 compared to the PPIs from the literature, we obtained corresponding values based on our current data from H. pylori-negative subjects: an \( ED_{50} \) (95% CI), 78.1 (44.7-111.4) mg/d; a mean pH of baseline, 1.99; and an \( E_{\text{max}} \) = 3.39. With those values, the minimum required dose derived was 114 mg/d to achieve a mean pH of 4 over 24 hours. This analysis indicated that YH4808 had a similar \( E_{\text{max}} \) value to that of PPIs, but a higher \( ED_{50} \) than PPIs. These results may be attributed to the low bioavailability of YH4808.

In the present study, the observed elevation of serum gastrin following multiple dosing of YH4808 could be explained as a physiological feedback response to the suppression of gastric acid secretion. As this observation was similar to that reported in previous clinical studies on PPIs or P-CAB in healthy volunteers, we presumed that this effect was a drug-related change but would not lead to clinically significant adverse effects. However, additional long-term safety assessment should be performed in patients with acid-related diseases in future.

Previous studies reported that intragastric pH profiles were not different between patients with GERD and healthy subjects, between younger and older subjects, or between females and males. Although we can speculate that the intragastric pH profiles in future studies in patients will not differ substantially from the profiles in healthy subjects observed in this study, the present findings may be limited in extrapolations of therapeutic efficacy in patients with GERD.

In conclusion, results from the present study suggested that YH4808, a new potassium-competitive acid blocker, inhibited gastric acid secretion remarkably, sustainably, and rapidly, with favourable tolerability. Its efficacy at doses greater than 200 mg/d was comparable to that of esomeprazole at 40 mg/d. YH4808 showed potential for the treatment of acid-related diseases. Further clinical investigations of YH4808 in patients with acid-related diseases will be required to establish therapeutic outcomes.

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