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ORIGINAL RESEARCH

A Pharmacokinetic/Pharmacodynamic Study of Esomeprazole Comparing a Dual Delayed-Release Formulation (YYD601) to a Conventional Formulation Following Multiple Administrations in Healthy Adult Subjects

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Background: YYD601 is a new dual delayed-release formulation of esomeprazole, developed to enhance plasma exposure and prolong the duration of acid suppression.

Purpose: This study aimed to evaluate the safety, pharmacokinetic (PK), and pharmacodynamic (PD) profiles of YYD601 20 mg following single and multiple oral administrations in healthy, fasting adult Koreans, and to compare these outcomes to those of the conventional esomeprazole 20 mg capsule.

Methods: A randomized, open-label, two-period crossover study was conducted in 28 participants, who were divided into two treatment groups: one group received YYD601 20 mg, and the other received conventional esomeprazole 20 mg, once daily for five consecutive days. Blood samples for PK analysis were collected pre-dose and up to 24 hours post-dose. The primary PK parameters (AUC_{last} and AUC_{τ}) were evaluated. PD endpoints included integrated gastric acidity, percentage of time with intragastric pH > 4 over 24-hour and nighttime intervals, and percent change in serum gastrin levels after multiple dosing.

Results: A total of 22 participants completed the study. YYD601 displayed more prolonged plasma concentration-time profiles than the conventional formulation, although the extent of the systemic exposure (AUC values) showed no statistically significant difference between the two formulations. With regard to the 24-hour gastric acid inhibition, YYD601 was comparable to the conventional formulation. The YYD601 showed a greater tendency for acid inhibition at night, as indicated by the percentage change of time with nocturnal acid breakthrough and other PD parameters. Both treatments were well tolerated, with no serious adverse events reported.

Conclusion: Through extended systemic exposure of esomeprazole, YYD601 produces gastric acid suppression that is comparable to that of the conventional esomeprazole formulation, with a greater tendency to suppress acid at night. YYD601 20 mg was safe and well tolerated following single and multiple oral administrations, supporting its use as an effective alternative to conventional esomeprazole therapy.

Clinical Trial Registry: http://clinicaltrials.gov, NCT03985319 (Date of registration: May 29, 2019; Study period: between July 2019 and March 2020).

Keywords: esomeprazole, dual delayed-release formulation, pharmacokinetics, pharmacodynamics

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Introduction

Gastric acid is a key factor in the pathogenesis and persistence of esophageal mucosal injury in patients with gastro-esophageal reflux disease (GERD), a condition clinically characterized by symptoms such as heartburn and regurgitation.[1] Effective management of GERD relies on maintaining an intragastric pH above 4, as mucosal damage is closely associated with intraesophageal pH levels falling below this threshold.[2,3]

Proton-pump inhibitors (PPIs) have been shown to increase intragastric pH by inhibiting the secretion of hydrochloric acid via suppression of the H^+/K^+-adenosine triphosphatase (proton pump) in gastric parietal cells.[4] Compared to histamine-2 receptor antagonists (H2RAs), PPIs demonstrate superior efficacy and do not induce tachyphylaxis, establishing them as the first-line treatment for GERD and other acid-related disorders of the upper gastrointestinal tract.[5,6] Despite their efficacy, conventional once-daily PPI regimens are often insufficient for complete suppression of gastric acid secretion. This is primarily due to the fact that proton pumps are not continuously active, and conventional PPIs inhibit only approximately 70% of active pumps at steady state with once-daily dosing. Furthermore, most PPIs have relatively short plasma half-lives of 1–2 hours, resulting in a limited mean residence time within systemic circulation.[6,7] Consequently, various strategies, including modified-release (MR) PPI formulations, have been developed to prolong drug exposure and achieve sustained acid suppression.[7,8]

Among the available PPIs, esomeprazole, the S-isomer of omeprazole, at a 40 mg dose has demonstrated superior efficacy in alleviating GERD symptoms in several randomized, crossover trials compared to lansoprazole (30 mg), omeprazole (20 mg), pantoprazole (40 mg), and rabeprazole (20 mg).[9–11] Recently, a novel dual delayed-release (DDR) formulation of esomeprazole (YYD601) was developed by YooYoung Pharm. Co. Ltd. (Jincheon, Chungcheongbuk-do, Republic of Korea). This formulation utilizes a two-granule system, whereby 50% of the drug is released initially and the remaining 50% is released at a later time point. This dual release mechanism results in a second plasma concentration peak (C_{max}), thereby extending the duration of acid suppression compared to conventional esomeprazole formulations. The DDR mechanism of YYD601 is similar to that of dexlansoprazole MR (Dexilant™; TAK-390MR, Takeda Global Research & Development Center, Inc., Deerfield, IL, USA).[7]

In this study, the pharmacokinetics (PKs) and pharmacodynamics (PDs) of YYD601, a newly developed DDR esomeprazole formulation, were evaluated in healthy adult volunteers and compared with those of conventional esomeprazole.

Methods

Study Design and Subjects

This Phase I, randomized, open-label, two-way crossover, single- and multiple-dose PK and PD study was conducted in fasting, healthy volunteers. The study protocol was approved by the Institutional Review Board of Kyungpook National University Hospital (KNUH) (Approval No. 2019–07-015) and the Korea Ministry of Food and Drug Safety. The study adhered to ethical guidelines established by the Declaration of Helsinki and its subsequent revisions, the International Conference on Harmonization Good Clinical Practice (ICH-GCP), and applicable local laws and regulations. It was conducted at the KNUH Clinical Trial Center between July 2019 and March 2020 (ClinicalTrials.gov identifier: NCT03985319). All participants provided written informed consent after receiving detailed verbal and written explanations of the study procedures and potential risks.

Eligible participants were healthy adults aged 19 years or older, with a body weight of at least 50 kg and within 20% of their ideal body weight. Participants' eligibility was determined based on their medical history, physical examination, vital signs, clinical laboratory test results (blood chemistry, hematology, and urinalysis), and a 12-lead ECG.

Exclusion criteria included any history of hypersensitivity to drugs, particularly esomeprazole or benzimidazoles, a history of active liver disease, or serum levels of aspartate aminotransferase, alanine aminotransferase, or total bilirubin greater than 1.5 times the upper limit of normal. Individuals with current or previous conditions that could affect the absorption, distribution, metabolism, or excretion of the study drug were also excluded. Participants unable to tolerate a pH monitoring device for 24-hour intragastric acidity measurement were excluded, as were those with a history of alcohol or drug abuse, those who had participated in another investigational drug study within the past six months,

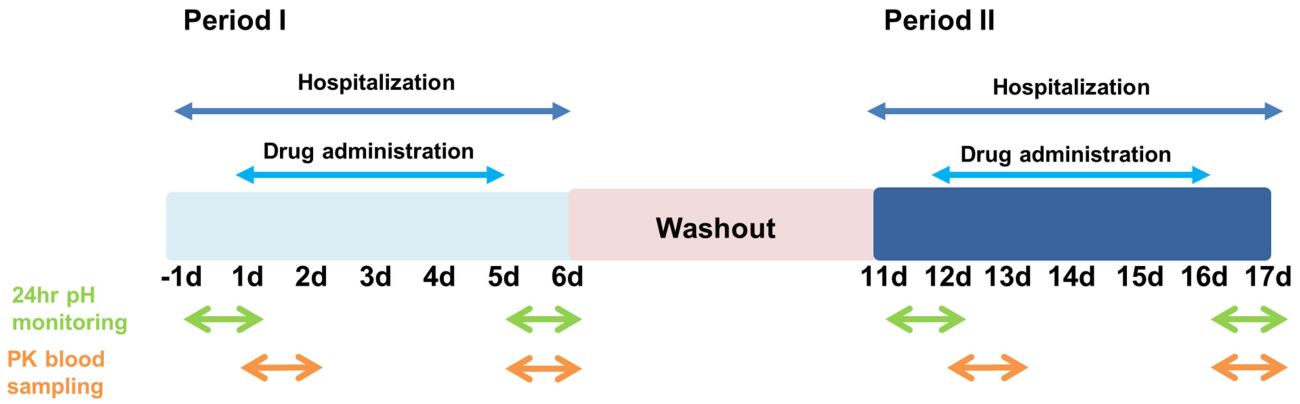

Figure 1 Schematic representation of the study design. Each group underwent two 5-day treatment periods in a crossover design following overnight fasting. A 7-day washout period was included between the final dose of Period I and the initiation of Period II.

donated blood within the previous two months, or used medications that might interfere with study outcomes within two weeks before the start of the study. Additional exclusion criteria included a positive ^{13}C urea breath test, a history of peptic ulcer, GERD, Barrett's esophagus, erosive esophagitis, or Zollinger-Ellison syndrome within three months prior to the first dose of the study drug.

A total of 28 eligible subjects were randomly assigned in a 1:1 ratio to one of two treatment sequence groups: Group 1 (TR) and Group 2 (RT). Each group received the study treatments in a predefined sequence over two periods. During each period, 14 subjects received one of the following treatments: (1) a 20 mg oral dose of conventional enteric-coated esomeprazole (Nexium®, AstraZeneca Korea, Seoul, Republic of Korea) once daily for five consecutive days as the reference treatment, or (2) a 20 mg oral dose of esomeprazole DDR formulation (YYD601, YooYoung Pharm. Co. Ltd., Jincheon, Chungcheongbuk-do, Republic of Korea) once daily for five consecutive days as the test treatment. Both treatments were administered under fasting conditions and supervised by the investigator in an open-label manner.

The study design is depicted in Figure 1. Subjects were admitted to the clinical trial center from day −2 to day 6 for each period. On day −1, baseline 24-hour intragastric pH monitoring was performed. On day 1, the study drug was administered with 150 mL of water following a 10-hour fasting period, and serial blood samples were collected for PK analysis. From day 2 to day 5, repeated doses of the assigned treatment were given under fasting conditions, as per the study protocol. On day 5, post-dose 24-hour intragastric pH monitoring was conducted, and blood samples were again collected for PK analysis. Standardized meals (lunch and dinner) were provided on each of the first five days of the period, 4 hours and 10 hours post-dose, respectively. Following the completion of all procedures on day 6, subjects were discharged from the study center. Subjects returned to the study center for Period II on day 10. A 7-day washout period was maintained between the last dose of one period and the first dose of the subsequent period.

Blood Sampling and Bioanalytical Methods

Venous blood samples (6 mL each) were collected into EDTA-K2 tubes at the following time points: pre-dose (0 h), and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 4.75, 5, 5.25, 5.5, 6, 8, 12, and 24 hours post-dose on days 1 (first single dose), 5 (last multiple dose), 12 (first single dose), and 16 (last multiple dose). Blood samples were centrifuged at 4°C and 3000 rpm for 10 minutes within 30 minutes of collection. Plasma was subsequently separated, aliquoted into three amber polypropylene tubes (1 mL/tube), and stored at −70°C or lower until analysis at an analytical laboratory (Dt & CRO Co., Yongin-si, Gyeonggi-do, Republic of Korea).

All plasma samples underwent protein precipitation using acetonitrile and were analyzed using ultra-fast liquid chromatography-tandem mass spectrometry (UFLC-MS/MS) on a SCIEX TQ5500 system (AB SCIEX, USA).[12–14] Chromatographic separation was performed on a Hypersil GOLD™ C_{18} column (100 × 2.1 mm i.d.; particle size 5 µm; Thermo Fisher, San Jose, CA, USA) with a mobile phase consisting of 10 mM ammonium formate and acetonitrile

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(40:60, v/v). Multiple reaction monitoring (MRM) transitions of mass-to-charge ratios 346.0 → 198.3 for esomeprazole and 349.1 → 198.1 for the internal standard (esomeprazole-d_3) were employed for detection.

The lower limit of quantification (LLOQ) was 5 ng/mL, with calibration curves demonstrating excellent linearity ($r \geq 0.9992$) over the concentration range of 5–5000 ng/mL. Intra- and inter-run precision, expressed as the coefficient of variation (CV%), ranged from 0.5% to 4.6% and 2.1% to 2.9%, respectively. The accuracy of the assay was between 98.8% and 104.5% for intra-run measurements, and between 101.3% and 102.4% for inter-run assessments.

Pharmacokinetic Evaluations

A PK parameters for esomeprazole were calculated using a noncompartmental model, implemented through WinNonlin Pro 5.3 (Pharsight Corporation, Mountain View, CA, USA), based on plasma concentration–time data. The primary PK parameters for assessing the systemic exposure differences between two formulations of esomeprazole included the area under the plasma concentration–time curve to the last measurable concentration (AUC_{last}) following single dosing, and the AUC during steady-state conditions (AUC_{τ}) following multiple dosing. Secondary PK parameters included the maximum observed plasma concentration (C_{max}), the time to reach C_{max} (T_{max}), the area under the curve to infinity (AUC_{inf}), the steady-state maximum concentration during a dosing interval ($C_{max,ss}$), the time to reach C_{max} at steady state ($T_{max,ss}$), and the elimination half-life ($t_{1/2}$).

Pharmacodynamic Measurement

A 24-hour ambulatory intragastric pH monitoring was performed at baseline (day −1) prior to the first dose, and again on day 5 following the final dose of each treatment period. The pH probe was transnasally inserted into the stomach and connected to a pH recording system (ZepHr™, Sandhill Scientific Inc., Highlands Ranch, CO, USA). pH data were stored and processed using Zvu® v. 2.3.2086.1 software. Calibration of the pH probe was conducted before each recording session using standard pH buffers (pH 1.07 and pH 7.01), in accordance with the manufacturer's specifications. Recordings commenced at 8:00 a.m. and continued for a full 24-hour period.

The primary pharmacodynamic endpoint was the integrated gastric acidity, defined by pH values measured at one-second intervals at baseline (days −1 and 11) and after repeated administrations (days 5 and 16), as outlined in previous studies to evaluate the extent of acid suppression.[15] The secondary pharmacodynamic endpoints included the percentage of time with intragastric pH > 4 during the 24-hour monitoring, as well as the percent change in fasting serum gastrin levels, assessed at baseline and on days 1 and 5. PD values were also estimated for the nocturnal period (defined as 11:00 p.m. to 8:00 a.m)., including the percentage of time with nocturnal acid breakthrough (NAB) (%Time with NAB) and percentage of subjects who have had NAB at least once (%Subjects with NAB).

Safety of Subjects

Safety was evaluated through comprehensive monitoring of subjective symptoms, physical examinations, clinical laboratory tests, 12-lead ECG, and vital signs, including blood pressure, heart rate, and body temperature. Adverse events (AEs) occurring from the administration of the first dose onwards were classified as treatment-emergent adverse events (TEAEs) and recorded for all participants who received at least one dose of either YYD601 20 mg or 20 mg of the conventional formulation of esomeprazole.

Statistical Analyses

The sample size for the study was calculated on the basis of within-subject coefficient of variation values for AUC_{τ} of esomeprazole and percentage decrease from baseline in integrated gastric acidity from previous studies (20.91% and 14.13%, respectively). A total of 22 subjects was estimated to demonstrate a 20% difference in the log-transformed values between two different treatment groups with 90% power at the significance level of 5%. Therefore, assuming a 20% dropout rate, 28 volunteers in total were needed for enrollment in the study, with 14 subjects each group.

Demographic comparisons between the two sequence groups (T-R and R-T) were performed using independent t-tests and Mann–Whitney *U*-tests. Geometric mean ratios (GMRs) and 90% confidence intervals (CIs) for the pharmacokinetic parameters AUC_{last} and AUC_{τ} were calculated to assess the relative bioavailability of the two treatment groups (T/R).

For the primary pharmacodynamic endpoint, integrated gastric acidity (mmol·hr/L), a paired *t*-test was applied to compare baseline and post-administration values within each treatment group. Additionally, either a paired *t*-test or two-one-sided *t*-test was employed to compare the percent reductions in integrated gastric acidity from baseline between the two treatment groups over the 24-hour period and during the nocturnal period.

For the percentage of time with intragastric pH > 4 during the 24-hour and nocturnal periods, paired *t*-tests were used to assess within-group changes from baseline to post-administration, as well as between-group comparisons of the two formulations. Percent changes in fasting serum gastrin levels from baseline (day −1) to post-dosing (days 1 and 5) were analyzed using either a *t*-test or Mann–Whitney *U*-test, depending on the distribution of the data.

All statistical analyses were performed using SPSS version 18.0 (SPSS Korea, Seoul, Korea).

Results

Subjects

A total of 28 healthy Korean adult volunteers were enrolled in the study and randomized into two different sequence groups. Baseline demographic characteristics did not exhibit statistically significant differences between the groups. The demographics of 22 subjects who completed the study are presented in Table 1.

Three subjects voluntarily withdrew consent for personal reasons prior to admission for Period I. Additionally, two subjects withdrew due to catheter discomfort before the administration of the study medication in Period I, and one subject withdrew for personal reasons during Period I. Consequently, 22 subjects completed the study.

Pharmacokinetics

The PK analysis of esomeprazole included 22 subjects who completed the study (group 1, n = 11; group 2, n = 11). The primary PK parameters (AUC_{last} and AUC_{τ}) were evaluated. The mean plasma concentration–time profiles for esomeprazole after single-dose oral administration on day 1 (A) and following repeated-dose administration over 5 days (B) of YYD601 (20 mg) and the conventional 20-mg formulation of esomeprazole are illustrated in Figure 2. Compared to the conventional formulation, YYD601 (20 mg) exhibited delayed absorption with a prolonged T_{max} (Table 2).

The GMRs and 90% CIs of the primary PK parameters (AUC_{last} and AUC_{τ}) following single and multiple administrations of YYD601 (20 mg) and the conventional 20 mg esomeprazole formulation are presented in Table 3. Single-dose administration of YYD601 (20 mg) resulted in a 14.6% reduction in AUC_{last}, while multiple-dose administration resulted in an 8.6% reduction in AUC_{τ}, as indicated by the GMR (90% CI) values.

Table 1 Demographics of the Study Subjects Who Completed the Study According to Sequence Groups

Characteristics	Total	Group 1	Group 2	*p* value*
No. of subjects	22	11	11	
Age, years				
Mean (SD)	29.0 (6.1)	30.6 (6.9)	27.4 (5.1)	0.2222†
Minimum-maximum	22–42	23–42	22–38	
Height, cm				
Mean (SD)	175.5 (6.1)	177.0 (7.2)	174.0 (4.7)	0.2740‡
Minimum-maximum	161.8–185.9	161.8–185.9	164.5–181.4	
Weight, kg				
Mean (SD)	72.9 (8.8)	74.7 (9.1)	71.0 (8.5)	0.3397‡
Minimum-maximum	57.6–91.6	59.3–91.6	57.6–82.3	
IBW, kg				
Mean (SD)	68.0 (5.5)	69.3 (6.5)	66.7 (4.3)	0.2780‡
Minimum-maximum	55.6–77.3	55.6–77.3	58.1–73.3	

Notes: Data are given as the mean (standard deviation). Group 1, TR; Group 2, RT; T, administration of YYD601 20 mg for 5 days; R, administration of esomeprazole 20 mg for 5 days. *Compared between two groups by Mann–Whitney *U*-test† or independent *t*-test‡.

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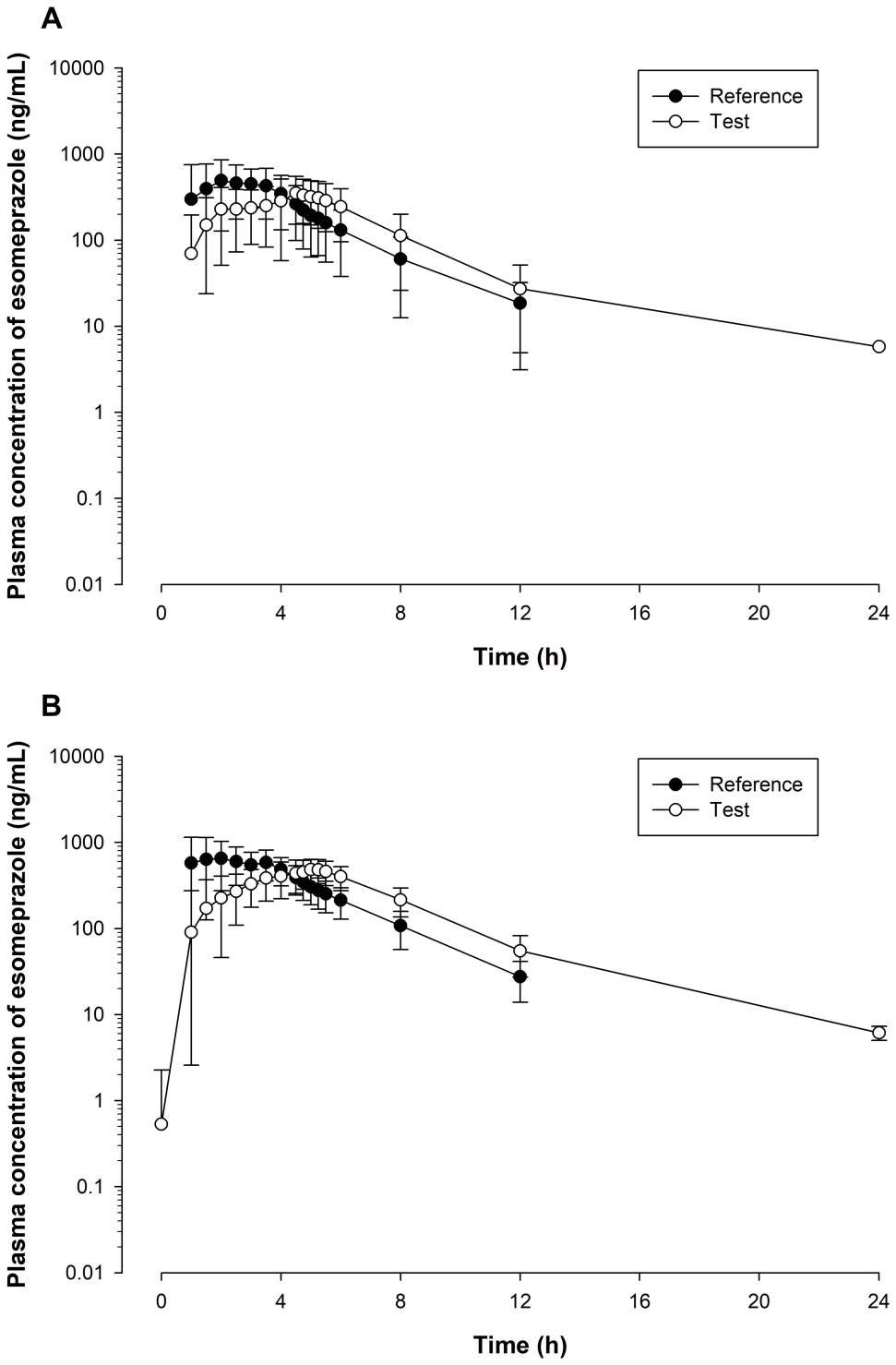

Figure 2 Mean plasma concentration–time profiles of esomeprazole: (**A**) after a single administration on Day 1 and (**B**) following multiple administrations on Day 5.
Notes: Vertical bars represent standard deviation (SD). Test: 20 mg YYD601 formulation; Reference: 20 mg esomeprazole conventional formulation.

Pharmacodynamics

The PD analysis included all 22 subjects who completed the study, with 100% of intragastric pH data collected for the total pH monitoring period. Tables 4 and 5 summarize the 24-hour and nighttime PD characteristics of esomeprazole for both formulations, respectively.

Table 2 Esomeprazole Pharmacokinetics Following Single and Multiple Oral Doses in Healthy Subjects

	Parameters	Test (n = 22)	Reference (n = 22)
Single-dose	AUC_{last} (h*ng/mL)	1930.6 ± 1081.8	2140.3 ± 1000.4
	AUC_{inf} (h*ng/mL)	1985.5 ± 1124.1	2182.1 ± 1022.1
	C_{max} (ng/mL)	446.1 ± 209.0	832.7 ± 257.1
	T_{max} (h) †	4.5 (3.0–6.0)	2.0 (1.0–3.5)
	$t_{1/2}$ (h)	1.6 ± 0.5	1.5 ± 0.4
Multiple-dose	AUC_{τ} (h*ng/mL)	3096.9 ± 887.3	3367.1 ± 879.8
	AUC_{inf} (h*ng/mL)	3102.0 ± 891.4	3368.3 ± 880.7
	$C_{max,ss}$ (ng/mL)	584.9 ± 152.9	1087.7 ± 256.8
	$T_{max,ss}$ (h) †	4.5 (3.0–8.0)	1.5 (1.0–3.5)
	$t_{1/2}$ (h)	2.1 ± 0.5	1.9 ± 0.3

Notes: Data are presented as mean ± SD except for T_{max} values as median (minimum-maximum)†. Test, YYD601 formulation 20mg; Reference, esomeprazole conventional formulation 20 mg.

Abbreviations: AUC_{last}, area under the plasma concentration-time curve from time zero to the last measurable time; $AUC_{inf,}$ area under the plasma concentration-time curve from time zero to infinity; $C_{max,}$ maximum plasma concentration; $T_{max,}$ time to reach C_{max}; $t_{1/2}$: terminal elimination half-life; AUC_{τ}, area under the plasma concentration-time curve during a dosing interval (τ) at steady state; $C_{max,\ ss}$: maximum plasma concentration at steady state; $T_{max,\ ss}$: time to reach $C_{max,\ ss}$.

Table 3 Geometric Mean and Geometric Mean Ratio (90% CIs) for the AUC_{last} and AUC_{τ} of Esomeprazole Following Single or Multiple Administration of YYD601 20 Mg and 20 Mg Esomeprazole in Healthy Male Subjects

Parameters	Geometric Mean		Geometric Mean Ratio (90% CI)
	Test	Reference	
AUC_{last} (h*ng/mL)	1617.41	1893.79	0.8541 (0.7231–1.0087)
AUC_{τ} (h*ng/mL)	2956.89	3234.49	0.9142 (0.8473–0.9863)

Notes: Test, administration of YYD601 20 mg for 5 days; Reference, administration of esomeprazole 20 mg for 5 days.

Abbreviation: AUC_{last}, area under the plasma concentration-time curve from time zero to the last measurable time; AUC_{τ}, area under the plasma concentration-time curve during a dosing interval (τ) at steady state.

Table 4 24-Hour Pharmacodynamics Parameters of Esomeprazole at the Baseline, on Day 5 Following Multiple Administration of YYD601 20 Mg and 20-Mg Conventional Formulation of Esomeprazole in Healthy Male Subjects

Pharmacodynamic Parameters		Test (n = 22)	Reference (n = 22)	*p* value**
Integrated gastric acidity (mmol·hr/L)	Day −1	515.5 ± 169.7	512.9 ± 190.4	
	Day 5	120.5 ± 108.2	110.6 ± 75.1	
	p value*	<0.0001	<0.0001	
	% decrease	76.5 ± 18.2	77.8 ± 14.8	0.7672
Mean % of time with gastric pH > 4	Day −1	12.4 ± 10.5	8.4 ± 7.7	
	Day 5	61.0 ± 14.4	63.5 ± 12.1	
	p value*	<0.0001	<0.0001	
	Change from baseline	48.7 ± 15.3	55.1 ± 12.2	0.0560

(*Continued*)

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Table 4 (Continued).

Pharmacodynamic Parameters		Test (n = 22)	Reference (n = 22)	*p* value**
Mean gastric pH	Day −1	2.3 ± 0.4	2.2 ± 0.4	
	Day 5	4.6 ± 0.7	4.7 ± 0.6	
	p value*	<0.0001	<0.0001	
	Change from baseline	2.3 ± 0.6	2.5 ±0.6	0.1364

Notes: Data are presented as mean ± SD. Test, administration of YYD601 20 mg; Reference, administration of esomeprazole conventional formulation 20 mg; % decrease, percentage decrease from baseline after 5-day multiple administration. *Compared between the two groups (before and after 5-day administration) by paired *t*-test. **Compared between the two groups (test and reference) by paired *t*-test.

Table 5 Night-Time Pharmacodynamics Parameters of Esomeprazole at Baseline, and on Day 5 Following Multiple Administration of YYD601 20 Mg and 20-Mg Conventional Formulation of Esomeprazole in Healthy Male Subjects

Pharmacodynamic Parameters		Test (n = 22)	Reference (n = 22)	*p* value
Integrated gastric acidity (mmol·hr/L)	Day −1	310.4 ± 109.4	286.3 ± 100.6	
	Day 5	77.0 ± 72.3	90.5 ± 64.9	
	p value*	<0.0001	<0.0001	
	% decrease	73.9 ± 24.2	67.2 ± 21.6	0.2289**
Mean % of time with gastric pH > 4	Day −1	3.5 ± 7.9	3.1 ± 6.9	
	Day 5	42.9 ± 24.6	35.4 ± 21.5	
	p value*	<0.0001	<0.0001	
	Change from baseline	39.4 ± 25.6	32.3 ± 23.2	0.0708**
Mean gastric pH	Day −1	1.7 ± 0.5	1.7 ± 0.5	
	Day 5	3.9 ± 1.1	3.6 ± 1.1	
	p value*	<0.0001	<0.0001	
	Change from baseline	2.2 ± 1.2	1.9 ± 1.2	0.1324**
%Time with NAB (%)	Day −1	91.6 ± 13.0	94.9 ± 13.2	
	Day 5	38.1 ± 26.9	43.7 ± 26.4	
	p value*	<0.0001	<0.0001	
	% change	58.3 ± 30.7	52.3 ± 29.8	0.3122**
%Subjects with NAB (%)	Day −1	100	100	
	Day 5	81.8	90.9	0.4795†

Notes: Data are presented as mean ± SD. T, administration of YYD601 20 mg; R, administration of esomeprazole conventional formulation 20 mg; % decrease, percentage decrease from baseline after 5-day multiple administration; NAB, nocturnal acid breakthrough; %Time with NAB, percentage of time with NAB; %Subjects with NAB, percentage of subjects who have experienced NAB at least once. The night-time was defined as the period between 11 pm and 8 am.*Compared between the two groups (before and after 5-day administration) by paired *t*-test. **Compared between the two groups (test and reference) by paired *t*-test. †Compared between the two groups (test and reference) by McNemar test.

Following the oral administration of either YYD601 or the conventional formulation, integrated gastric acidity significantly decreased in both groups compared to baseline values. On day 5, no statistically significant differences were observed in integrated gastric acidity between the two formulations ($p = 0.7672$). Figure 3 shows the mean integrated gastric acidity values at baseline and after the fifth dose of each formulation.

Figure 4 depicts the intragastric pH (mean pH per hour) over a 24-hour period at baseline and following the 5-day multiple administration of either YYD601 or the conventional formulation, with meal times indicated. For the first four

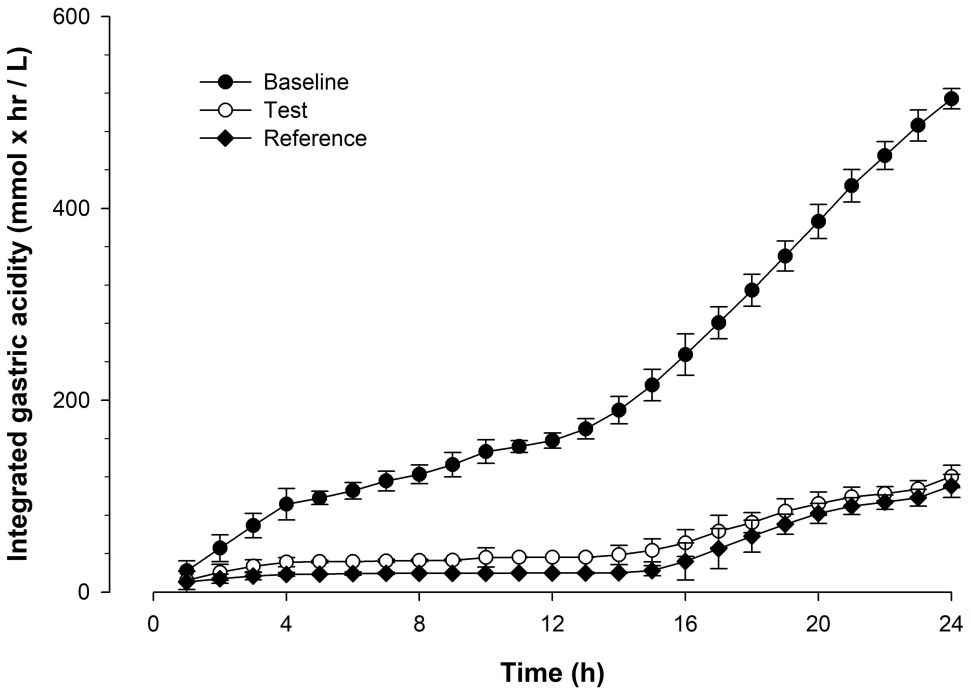

Figure 3 Cumulative integrated gastric acidity on Day −1 (baseline) and Day 5 following oral administration of 20 mg YYD601 (test) and 20 mg esomeprazole conventional formulation (reference) over 5 days.

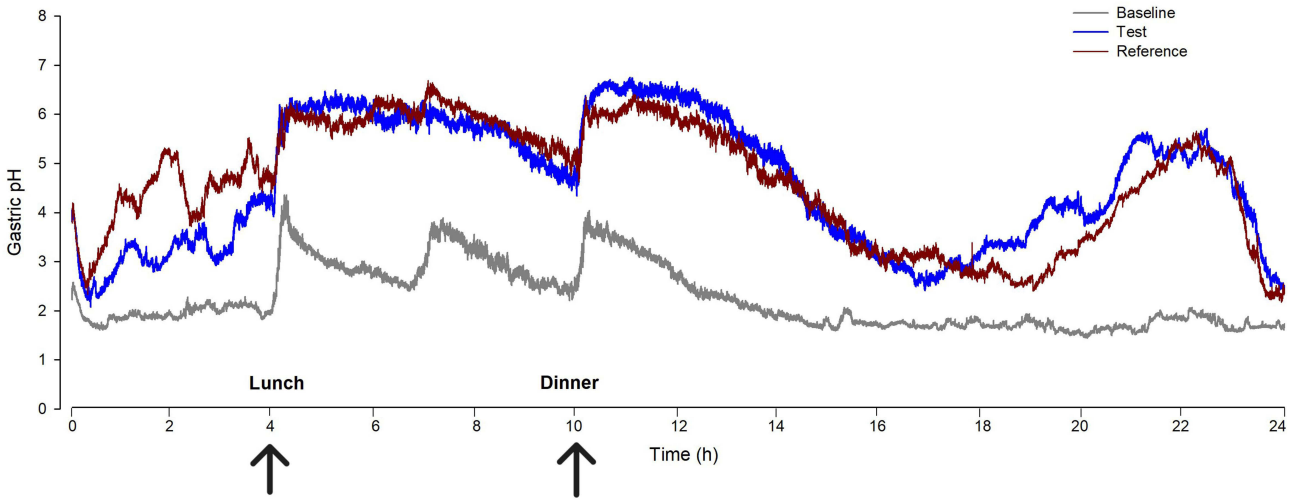

Figure 4 Mean intragastric pH-time profiles on Day −1 (baseline) and Day 5 after oral administration of 20 mg YYD601 (test) and 20 mg esomeprazole conventional formulation (reference) once daily for 5 consecutive days under fasting conditions. The x-axis represents the 24-hour scale, from 0 h (8:00 AM on Day 5) to 24 h (8:00 AM on Day 6). Arrows indicate meal times (12:00 PM and 6:00 PM).

hours post-administration (prior to lunch) on day 5, the intragastric pH values of YYD601 were lower than those of the conventional formulation, but later demonstrated comparable or higher values.

On day 5, both the conventional formulation and YYD601 resulted in a significant increase in the percentage of time with intragastric pH > 4 over a 24-hour period compared to baseline ($p < 0.0001$ for both; Table 3). Individual data showing the percentage of time with intragastric pH > 4 at baseline and on day 5 are presented in Figure 5: (A) for 24 hours, and (B) during nighttime.

Table 5 shows that during the nighttime hours (23:00–8:00) the YYD601 formulation tended to have lower %Time with NAB and %Subjects with NAB after the fifth dose than the conventional formulation. In comparison to the baseline

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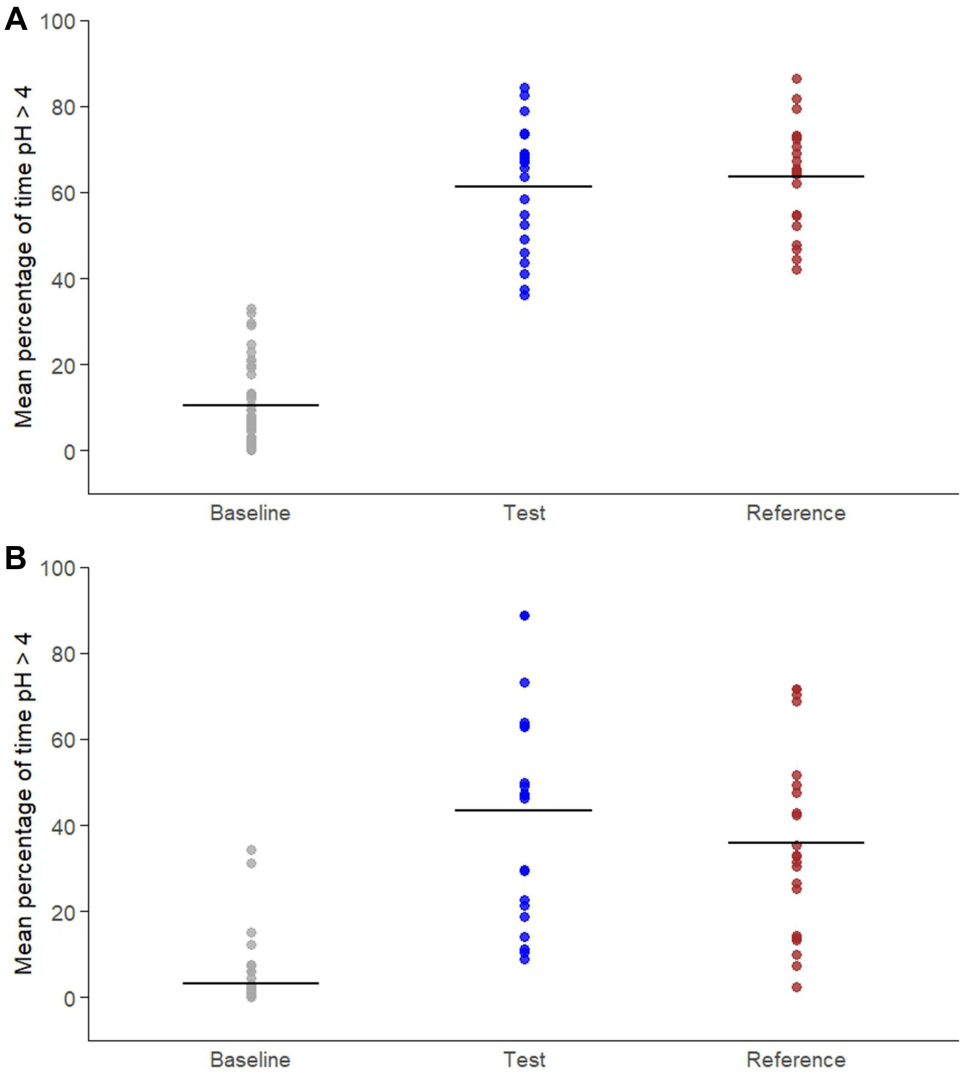

Figure 5 Individual subject data showing the percentage of time with intragastric pH > 4 on Day −1 (baseline) and Day 5 following multiple oral administrations of 20 mg YYD601 (test) and 20 mg esomeprazole conventional formulation (reference): (**A**) over the 24-hour period, and (**B**) during nighttime.

values, the mean percentage changes in %Time with NAB following the fifth dose were 58.3% for YYD601 and 52.3% for the conventional formulation.

Additionally, following multiple administrations of esomeprazole (YYD601 or the conventional formulation), mean serum gastrin concentrations significantly increased compared to baseline. For YYD601, serum gastrin increased from 19.2 pg/mL to 47.1 pg/mL ($p = 0.0012$), while for the conventional formulation, the increase was from 26.0 pg/mL to 68.9 pg/mL ($p = 0.0010$).

Safety

The safety analysis included 23 subjects who received at least one dose of the study medication. The subject who withdrew during Period I was included in the safety assessment but excluded from the PK/PD analyses.

A total of three TEAEs were reported by three subjects (13.0%), all of which were classified as adverse drug reactions (ADRs). One ADR (an increase in eosinophil percentage) was observed in the YYD601 group, while two ADRs (a decrease in white blood cell count and an increase in alanine aminotransferase) were reported for the conventional formulation group. All ADRs were mild in severity, and no serious AEs were reported.

Discussion

Esomeprazole, a widely used PPI for the treatment of acid reflux-related diseases, has a relatively short plasma half-life, which may limit its efficacy in maintaining prolonged gastric acid suppression.[16] YYD601, a DDR formulation of esomeprazole, was developed to extend plasma concentrations and prolong the duration of gastric acid suppression compared to conventional formulations.[17] This formulation comprises two distinct types of granules that release the active ingredient in a biphasic manner.

In this open-label, randomized, multiple-dose trial involving healthy participants, we assessed the PK and PD of esomeprazole in YYD601 compared to the conventional formulation. The results demonstrated that YYD601 formulation displayed longer plasma-concentration-time profiles than the conventional formulation, with no statistically significant difference between the two formulations in terms of the extent of systemic exposure (AUC values). Over a 24-hour period, YYD601 showed a comparable effect on gastric acid inhibition, with an even greater tendency to inhibit acid at night. Furthermore, the administration of YYD601 was safe and well tolerated, with only mild AEs reported throughout the study.

Lee et al previously reported that a 40 mg dose of YYD601 administered once daily for five days showed similar PD outcomes to the conventional formulation, including the mean percentage of time with intragastric pH >4 over 24 hours and during nighttime, mean intragastric pH, and percent reduction in integrated gastric acidity.[17] Moreover, simulation data from Lee et al suggested that YYD601 exhibits dose-proportional increases in the AUC and acid suppression with ascending doses, administered once or multiple times. Based on these findings, the 20 mg dose of YYD601 was expected to demonstrate acid-suppressive effects equivalent or superior to the conventional 20 mg formulation of esomeprazole.[17] Therefore, YYD601 20 mg was selected for the present study, as this dose aligns with the daily recommended dose of conventional esomeprazole for the maintenance of healing in patients with erosive esophagitis or symptomatic gastro-esophageal reflux disease.[18]

As shown in Table 2, the median T_{max} values for esomeprazole following repeated doses of YYD601 20 mg and the conventional 20 mg formulation in this study were 4.5 hours and 1.5 hours, respectively, consistent with previous findings by Lee et al, who reported a delayed T_{max} for YYD601 compared to the conventional formulation.[17] The GMR (90% CI) for AUC_{last} was 0.8541 (0.7231–1.0087), reflecting a slight decrease. However, the GMR (90% CI) for AUC_{τ} fell within the bioequivalence range of 0.80–1.25, indicating no significant difference in esomeprazole exposure between the test and reference formulations after multiple administrations.

When compared to baseline, the integrated gastric acidity in both treatment groups was significantly reduced following administration of either YYD601 or the conventional formulation. After the fifth dose, the mean ± standard deviation (SD) percent reduction from baseline in integrated gastric acidity was 76.5% ± 18.2% for YYD601 and 77.8% ± 14.8% for the conventional formulation. The GMRs for the percent decrease in integrated gastric acidity over the 24-hour period following the fifth dose of YYD601 versus the conventional formulation were 0.9651 (90% CI; 0.8575, 1.0862), indicating that YYD601 20 mg exhibited a gastric acid suppression profile comparable to that of the conventional 20-mg formulation after once-daily oral administration. Similar findings were reported by Kim et al, who evaluated the pharmacokinetics and pharmacodynamics of esomeprazole 20 mg in both its conventional and novel DDR formulations.[19] After the seventh dose, the percent reduction in integrated gastric acidity from baseline (82.05% ± 17.14% for the conventional formulation and 75.70% ± 17.74% for the DDR formulation) was consistent with the current study's findings, with a GMR of 1.0895 (90% CI, 1.0053, 1.1808). Additionally, the mean percentage of time with intragastric pH above 4 in this study (61.0% ± 14.4% for YYD601 and 63.5% ± 12.1% for the conventional formulation) was comparable to the results of Kim et al (63.0% ± 20.4% and 56.5% ± 20.4%, respectively).[19]

NAB, first described by Peghini et al in 1998, refers to the occurrence of intragastric pH falling below 4 for at least 60 consecutive minutes during the overnight period in patients receiving twice-daily PPI therapy.[20] It has been reported that over 70% of patients on twice-daily PPI therapy experience NAB. The clinical relevance of NAB was highlighted by Tutuian et al, who suggested that the addition of bedtime H2-receptor antagonists (H2RAs) to twice-daily PPI therapy may be effective in managing NAB, particularly in patients with complicated GERD, Barrett's esophagus, or esophageal motility disorders.[21] DDR formulations, such as YYD601 and dexlansoprazole MR, were developed to improve

medication adherence and optimize control of NAB with a once-daily dosing regimen, extending systemic exposure and prolonging the acid suppression effect compared to conventional single-release formulations.[7,17,19] The mean %Time with NAB following the fifth dose during the night (23:00–08:00) was 38.1% for YYD601 and 43.7% for the conventional formulation in our study. These findings are consistent with the study results by Kim et al, who reported those values after 7-day repeated oral administration of a new DDR formulation.[19] Compared to the conventional formulation, the YYD601 formulation tended to have a lower %Time with NAB and a lower %Subjects with NAB following the fifth dose in our study.

In the present study, baseline mean intragastric pH values during the night (23:00–08:00) were in the range of pH 1–2, but following the fifth dose (day 5) of either YYD601 or the conventional formulation, the values significantly increased, reaching pH 2.5–6 (Figure 4). During the night (23:00–08:00), the mean (SD) percent reduction from baseline in integrated gastric acidity after the fifth dose was 73.9% ± 24.2% for YYD601 and 67.2% ± 21.6% for the conventional formulation, with a GMR (YYD601/conventional formulation) of 1.0545 (90% CI; 0.8374, 1.3277), comparable to the results from a previous study using another DDR formulation (73.8% ± 37.3% and 69.1% ± 29.1%, respectively).[19] Furthermore, YYD601 demonstrated a greater tendency toward higher mean intragastric pH values and a longer duration with pH above 4 during the nighttime period compared to the conventional formulation. These findings suggest that YYD601 may provide more effective nighttime gastric acid suppression, which is critical for managing nocturnal symptoms.

Several studies have examined the relationship between *Helicobacter pylori* (*H. pylori*) infection and GERD, identifying significant links between *H. pylori* infection, its eradication, and alterations in esophageal motility, lower esophageal sphincter pressure, and esophageal acid exposure.[22,23] To eliminate potential confounding factors associated with *H. pylori* infection, participants testing positive in the[13] C urea breath test were excluded from the present study.[24] As a result, it is important to acknowledge that the acid-inhibitory effects and clinical efficacy of YYD601 in a larger cohort of patients with acid-related disorders may differ from the outcomes observed in this study, which was limited to a relatively small group of healthy volunteers.

Conclusions

This study assessed the PK and PD profiles of YYD601 in comparison to a conventional esomeprazole formulation following repeated dosing in healthy adult male subjects. The results show that YYD601, when administered at the recommended once-daily dose, achieves comparable gastric acid suppression to the conventional esomeprazole formulation, primarily through prolonged esomeprazole exposure, with a greater tendency to suppress acid at night. The novel DDR formulation technology used in YYD601 was found to result in longer esomeprazole exposure compared to the conventional formulation. Moreover, YYD601 was generally well tolerated by the healthy participants in this study.

Abbreviations

GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; H2RA, histamine-2 receptor antagonist; MR, modified-release; DR, delayed-release; DDR, dual delayed-release; PK, pharmacokinetic; PD, pharmacodynamics; KNUH, Kyungpook National University Hospital; AUC, area under the plasma concentration-time curve; AUC_{last}, AUC to the last measurable time; AUC_{τ}, AUC after repeated dosing at steady state; C_{max}, maximum plasma concentration; AUC_{inf}, AUC to infinity; $C_{max,ss}$, C_{max} during a dosing interval (τ) at steady state; $t_{1/2}$, elimination half-life; AE, adverse event; TEAE, treatment-emergent AE; GMR, geometric mean ratio; CIs, confidence intervals; ADR, adverse drug reaction; SD, standard deviation; NAB, nocturnal acid breakthrough; *H. pylori, Helicobacter pylori*.

Data Sharing Statement

We, the authors, intend to share individual de-identified participant data. However, there must be a limit on our data sharing, because this study was sponsored by a pharmaceutical company. Young-Ran Yoon should be contacted for the sharing of the data.

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Disclosure

The authors report no conflicts of interest regarding the content of this article.

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