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ARTICLE

A population PK–PD model of YH4808, a novel P-CAB, and intragastric pH that incorporated negative feedback by increased intragastric pH onto the systemic exposure to YH4808

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Abstract

YH4808 is a novel potassium-competitive acid blocker that is under clinical development to treat patients with gastroesophageal reflux disease and peptic ulcer diseases. In this study, the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of YH4808 were modeled in healthy male volunteers who received a single oral dose of YH4808 at 30, 50, 100, 200, 400, 600, and 800 mg or matching placebo and multiple once-daily oral doses of YH4808 at 100, 200, and 400 mg or matching placebo for 7 days. A population PK–PD model adequately described the time–concentration-effect profiles of YH4808. The maximum increasing effect of YH4808 on intragastric pH was 4.38, which was higher than the observed maximum increase in intragastric pH after omeprazole at 40 mg (2.2 in pH). The maximum inhibitory effect by the increased intragastric pH on the exposure to repeated YH4808 was 58% from baseline. Monte–Carlo simulation experiments based on the final model showed that YH4808 at 200 mg will produce a higher percentage of time at pH > 4 over 24 h on day 1 than observed value of esomeprazole at 40 mg once-daily, an active comparator (84.7% time vs. 58.3% time, respectively). Because YH4808 at ≥200 mg resulted in a higher percentage of time at intragastric pH > 4 than seen after once-daily esomeprazole at 40 mg and YH4808 showed acceptable tolerability at a single-dose of 30–800 mg, we suggest to test the 200 mg once daily dosage regimen in further clinical trials of YH4808.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

YH4808, a novel potassium-competitive acid blocker, showed a reduced systemic exposure after multiple oral administrations, particularly at higher doses (i.e., 200 and 400 mg). Because the solubility of YH4808 is pH-dependent, the reduced

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solubility of YH4808 caused by the elevated intragastric pH after treatment was suggested as the main cause of the reduced systemic exposure.

WHAT QUESTION DID THIS STUDY ADDRESS?

We developed a population pharmacokinetic-pharmacodynamic (PK–PD) model that described the impact of increased intragastric pH on the exposure to YH4808 in healthy male volunteers. We also simulated the PK and intragastric pH profiles for different dosage regimens.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The population PK–PD model of YH4808 adequately described the impact of increased intragastric pH on the exposure to YH4808 in healthy male volunteers. The simulation experiment and supporting evidences from the phase I clinical trial of YH4808 indicated that YH4808 at 200 mg once daily might be the most suitable therapeutic regimen for elevating intragastric pH over 24 h.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The negative feedback by increased intragastric pH onto the reduced exposure to YH4808 incorporated in the population PK–PD model of YH4808 can be used as an example for characterizing the PK profile that is affected by its pharmacological response. In addition, our simulation experiments helped determine an optimal dosage regimen that can be tested in further clinical trials of YH4808.

INTRODUCTION

Potassium-competitive acid blockers (P-CABs) increase the intragastric pH by reversibly binding to the H+/K+-ATPase on the luminal surface of the gastric wall.[1–4] Because no acidic environment is required to activate P-CABs, unlike proton pump inhibitors (PPIs), P-CABs can block the secretion of gastric acid even in a neutral environment.[5] In addition, P-CABs inhibit the secretion of gastric acid faster than PPI and raise intragastric pH for a longer period of time.[3,6,7]

YH4808 is a novel P-CAB that is under clinical development to treat patients with gastroesophageal reflux disease and peptic ulcer diseases.[8–10] In a first-in-human phase I clinical trial, the percentage of time at intragastric pH > 4 significantly increased from only ~5% after placebo to ~75% after YH4808 at 800 mg.[8] The effect of YH4808 on increasing intragastric pH was higher than that of esomeprazole, a PPI. For example, the percentage of time at intragastric pH > 4 by YH4808 at ≥200 mg once daily was greater than that by esomeprazole at 40 mg in both 24-h and night-time periods (>70% vs. 58%, >50% vs. 33%, respectively).[8] In healthy male volunteers, YH4808 was extensively metabolized into two active metabolites, M3 and M8.[11] However, an in vitro enzyme assay showed that M3 has a twofold higher maximal inhibitory concentration than the parent drug and M8 has only a minor inhibitory effects on the H+/K+-ATPase, indicating that the increase in intragastric pH mainly arises from the parent drug of YH4808.[8]

In a phase I clinical trial, the systemic exposure to YH4808 was dose-proportional over the dose range of 30–800 mg and declined in a multiphasic manner. However, it tended to reduce after multiple oral administrations, particularly at higher doses (i.e., 200 and 400 mg). Because the solubility of YH4808 is pH-dependent (i.e., 2.137 and 0.042 mg/ml at pH 2.0 and 6.0, respectively), the reduced solubility of YH4808 caused by the elevated intragastric pH after treatment was suggested as the main cause of the reduced systemic exposure. This hypothesis was supported by physiologically-based pharmacokinetic (PBPK) modeling and simulation experiments.[12] For example, the maximum plasma concentration (C_{max}) and area under the curve from dosing to 8 h after YH4808 administration (AUC_{0-8h}) at 400 mg was reduced by 12.7–28.9 and 7.9–18.6%, respectively, in 100 virtual male subjects when intragastric pH was increased from 1.5 to 7.

The objectives of this study were (1) to develop a population pharmacokinetic-pharmacodynamic (PK–PD) model that adequately describes exposure–response relationship of YH4808, (2) to evaluate the impact of increased intragastric pH on the exposure to YH4808 particularly after repeated administration, and (3) to investigate the PK–PD profiles of YH4808 in different dosage regimens for further clinical studies using simulation. To this end, we characterized not only the effect of YH4808

on intragastric pH, but the effect of intragastric pH on the exposure to YH4808.

METHODS

Subjects and clinical study

A first-in-human phase I clinical trial of YH4808 was performed in two parts: single-dose ($n = 83$) and multiple-dose ($n = 40$).[8] Healthy male volunteers who were randomized to a single-dose group received an oral dose of YH4808 at 30, 50, 100, 200, 400, 600, and 800 mg or matching placebo. Healthy male volunteers who were randomized to a multiple-dose group received multiple once-daily oral doses of YH4808 at 100, 200, and 400 mg or matching placebo for 7 days. Plasma samples were collected at 0 (i.e., predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 h after YH4808 administration on days 1 and 7 (multiple-dose part only), and the plasma concentrations of YH4808 were determined using a high performance liquid chromatography-electrospray ionization mass spectrometer (HPLC MS, Agilent 1200 series, Agilent Technologies, Santa Clara, CA; MS/MS, API 3200 Quadrupole, Applied Biosystems/MDS SCIEX, Foster City, CA).[8] Additionally, intragastric pH was monitored in 120 subjects (97.6%) using an ambulatory 24-h pH recorder (Digitrapper pH400 recorder; Medtronic A/S, Skovlunde, Denmark) and a glass electrode.[13] An electrode was inserted in the stomach via the nasal cavity and was positioned 5 cm above the lower esophageal sphincter, and intragastric pH was recorded for 24 h. Intragastric pH was monitored at 0, 0.5, and every hour from 1 to 24 h on day 1 in the single-dose part, on days 1 and 7 in the 100- and 400-mg dose cohorts, and on day 7 in the 200-mg dose cohort in the multiple-dose part.

Population pharmacokinetic–pharmacodynamic dataset

The population PK–PD dataset of YH4808 contained the following data elements: plasma concentrations of YH4808, intragastric pH values after YH4808, and baseline demographic information (age, body weight, height, body mass index [BMI], and drinking status).

Base pharmacokinetic–pharmacodynamic model development

A base PK–PD model of YH4808 was developed in four steps. First, plasma concentrations of YH4808 were fit using a two-compartment model, which was parameterized by the apparent clearance (CL/F, L/h), volumes of distribution of YH4808 in the central (V_C/F, L) and peripheral (V_P/F, L) compartments, intercompartmental clearance (Q/F, L/h), absorption rate constant (K_A, 1/h), and lag time (ALAG1, h), where F is the bioavailability (Figure 1). In addition, concentrations of YH4808 in the effect compartment were modeled using Equation (1):

$$\frac{dC_E}{dt} = K_{EO} \cdot \left(\frac{A_C}{V_C} - C_E \right) \quad (1)$$

where K_{EO} is the elimination rate constant for YH4808 from a hypothetical effect compartment, A_C is the amount of YH4808 in the central compartment, and C_E is the concentrations of YH4808 in the effect compartment. Second, a baseline intragastric pH model was built in the placebo group using a multi-term cosine model to assess the circadian nature of intragastric pH and potential increase in intragastric pH as a result of food intake Equation (2):

$$\text{Baseline intragastric pH}_i = A_{0,i} + \sum_{n=1}^{m} \left[A_{n,i} \cdot \cos\left(\frac{2\pi \cdot (\text{TSLD} - C_{n,i})}{T_n} \right) \right] \quad (2)$$

where $A_{0,i}$, $A_{n,i}$, and $C_{n,i}$ is the mean, amplitude, and phase shift in time, respectively, of intragastric pH for the ith individual, TSLD represents the time elapsed after placebo administration, and T_n is $24*(1/2)^{n-1}$, which coverts time to radian in the nth cosine term. Third, the effect of YH4808 on intragastric pH through C_E was linked using a sigmoidal maximum effect (E_{max}) model Equation (3):

$$\text{Intragastric pH}_i = \text{Baseline intragastric pH}_i + \left(\frac{E_{max} \cdot C_E}{EC_{50} + C_E} \right) \quad (3)$$

where E_{max} is the maximum effect of YH4808 on the intragastric pH, EC_{50} is the concentrations of YH4808 that produces 50% of E_{max}. Fourth, the feedback mechanism of intragastric pH on the PK of YH4808 was characterized using an inhibitory sigmoidal E_{max} model Equation (4):

$$\text{Feedback} = 1 - \frac{EP_{max} \cdot \text{intragastric pH}_i}{EP_{50} + \text{intragastric pH}_i} \quad (4)$$

where EP_{max} is the maximum inhibitory effect of intragastric pH on the PK of YH4808, and EP_{50} is the intragastric pH that produces 50% of EP_{max}. The plasma concentrations and intragastric pH after YH4808 administration were fitted simultaneously using Equations (1–4).

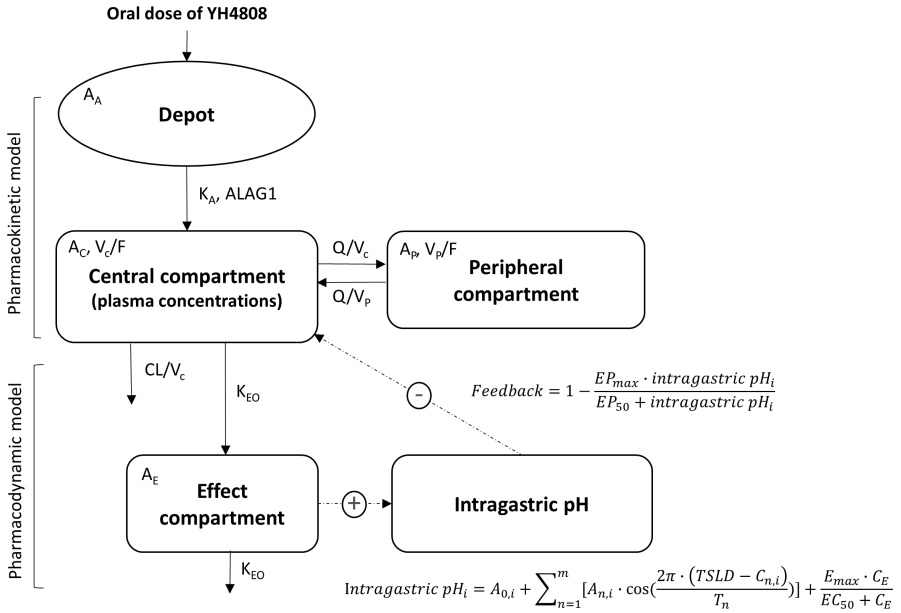

FIGURE 1 Schematic representation of the pharmacokinetic–pharmacodynamic (PK–PD) model of YH4808 with first-order absorption. The plus (+) and minus (−) signs represent the increasing effect of the PKs of YH4808 on intragastric pH and the inhibitory effect of intragastric pH on the PKs of YH4808, respectively. $A_{0,i}$, mean of intragastric for the ith individual; $A_{n,i}$, amplitude of intragastric for the ith individual; C_E, concentrations of YH4808 in the effect compartment; CL/V_C, elimination rate constant; $C_{n,i}$, phase shift in time of intragastric for the ith individual; EC_{50}, concentrations of YH4808 that produces 50% of E_{max}; E_{max}, maximum effect of YH4808 on the intragastric pH; EP_{50}, intragastric pH that produces 50% of EP_{max}; EP_{max}, maximum inhibitory effect of intragastric pH on the PK of YH4808; K_A, absorption rate constant; K_{EO}, rate constant for elimination from the effect compartment; Q/V_C, intercompartmental clearance from the central compartment to the peripheral compartment; Q/V_P, intercompartmental clearance from the peripheral compartment to the central compartment; T_n, $24*(1/2)^{n-1}$ that converts time to radian in the nth cosine term; $TSLD$, time elapsed after placebo administration; V_C/F, apparent volume of distribution in the central compartment; V_P/F, apparent volume of distribution in the peripheral compartment.

Interindividual variability (IIV) and interoccasion variability (IOV) for the PK and PD parameters were estimated using an exponential error model Equation (5):

$$P_i = P_p . \exp\left(\eta_{P_i}\right) . \exp\left(\eta_{p_{i,j}}\right) \tag{5}$$

where P_i is the PK parameter for ith individual, P_p is the typical population value of PK parameter, η_{P_i} is the IIV for the PK parameter in the ith individual, $\eta_{p_{i,j}}$ is the IOV for the PK parameter in the ith individual at the jth occasion. The estimated IIV and IOV were assumed to follow a log-normal distribution with mean 0 and a variance of ω^2. The residual variability (RV) of YH4808 concentration and intragastric pH was evaluated using a combined proportional and additive random effects model and proportional random effects model, respectively.

In every process of model development, decrease in the objective function value (OFV), decrease in the IIV of the PK and PD parameters, visual assessments of diagnostic plots, and biological, physiological, and clinical plausibility of parameter estimates were used as the model selection criteria.

Covariate model development

The continuous covariates were age, body weight, height, and BMI. The categorical covariates were sex and drinking status. The effect of the continuous and categorical covariates was evaluated using Equations (6) and (7), respectively:

$$P_{i,\mathrm{cov}} = P_p . \left[\frac{X_i}{\mathrm{median}\ (X)}\right]^{\theta_{\mathrm{cov}}} \tag{6}$$

$$P_{i,\mathrm{cov}} = P_p . \left(\theta_{\mathrm{cov}}\right)^{Y_i} \tag{7}$$

where $P_{i,\mathrm{cov}}$ is the PK or PDs parameter after incorporating the covariate effect for ith individual, θ_{cov} is the estimated value of covariate X to P_P, and Y_i is a dummy variable that is either 0 or 1 for the reference and non-reference subcategories of a categorical covariate, respectively.

The covariates were entered one by one into the base PK–PD model and retained in the model if OFV was decreased by >3.84 ($p < 0.05$ for $df = 1$). Next, the PK–PD model was refined by removing covariates one by one, and the covariate was put back into the model if OFV increased by >6.64 ($p < 0.01$ for $df = 1$).

Final pharmacokinetic–pharmacodynamic model development

The covariate model was further refined by allowing covariance between the IIV of the PK and PD parameters, resulting in the final PK–PD model.

Model qualification

The final PK–PD model was considered stable if the final PK and PD parameter estimates were similar to the medians of the PK and PD parameters obtained using 100 bootstrap replicates using the original dataset. In addition, visual predictive checks (VPCs) were performed for the final PK–PD model, stratified by the dose of YH4808, to check if there was any model misspecification. To this end, we simulated the PK and PD profiles of YH4808 in 100 virtual subjects using the final PK–PD model and compared the lower 2.5th, median, and upper 97.5th values of the observed and predicted plasma YH4808 concentrations and intragastric pH.

Simulations of YH4808 concentrations and intragastric pH

Using the final PK–PD model of YH4808, a Monte–Carlo simulation was performed 100 times to investigate the PK and PD profiles and percentage of time at pH >4 after YH4808 administration at 100, 200, 400 mg once and twice daily. The percentage of time at intragastric pH >4 by YH4808 was calculated for 24 h on days 1 and 7.

Software

The NONMEM software (version 7.5; Icon Development Solution, Gaithersburg, MD) was used for population PK–PD modeling. The iterative two stage (ITS) and stochastic approximation expectation maximization (SAEM) were the estimation methods. For graphical visualization, R 3.5.1 (R Foundation, Vienna, Austria) was used. Xpose 4.6.1 and the PsN 4.8.1 were used for plots, bootstraps, and VPCs.

RESULTS

Subjects

Plasma concentrations of YH4808 were determined in 79 subjects who received ≥1 dose of YH4808 and completed the study as planned. Intragastric pH recordings were obtained from 76 and 20 subjects, who received YH4808 or placebo, respectively. As a result, a total of 99 healthy male volunteers and their 1560 plasma concentrations of YH4808 and 2919 intragastric pH values were included in the population PK–PD dataset. The age and body weight of subjects ranged from 21 to 41 years and 53.5 to 87.2 kg, respectively (Table 1).

Population pharmacokinetic–pharmacodynamic model

A baseline intragastric pH model was developed using four cosine terms (i.e., four cosine terms which T_n was 24, 12, 6, and 3 h). The final estimates for A_0, A_1, A_2, A_3, A_4, C_1, C_2, C_3, and C_4 were 2.03, 0.29, 0.14, 0.66, 0.32, 7.95, 8.27, 5.37, and 5.00 h, respectively. After fixing these parameters to characterize the baseline intragastric pH, CL/F, V_C/F, K_A, and ALAG1 were estimated to be 221.00 L/h, 121.00 L, 0.95 h^{-1}, and 0.26 h, respectively. The elimination rate constant from the effect compartment (K_{EO}) was 0.06 h^{-1}, implying that steady-state will be attained in ~60 h between the central and effect compartments. The maximum increase in intragastric pH after YH4808 administration (E_{max}) was 4.38 in pH. The EP_{max} by the increased intragastric pH on the exposure to YH4808 was 0.58, implying that the exposure to YH4808 can be reduced by up to 58% (Table 2).

The IIV on PK parameters was relatively small except for CL/F (coefficient of variation expressed as percent [CV%] = 71.7%) and V_C/F (CV% = 118.3%; Table 2). The IIV on E_{max} was also small (CV% = 30.4%). The shrinkages for IIV of all PK and PD parameters were large (≥20%). No IOV improved the model fit or decreased the corresponding IIV on any PK or PD parameters. No covariate was significant on any of the PK or PD parameters.

Model qualification

The four-cosine PD model reasonably described the baseline intragastric pH profiles in the placebo group (Figures S1 and S2). The four-cosine PD model had a lower OFV and better predictive performance in the diagnostic plot assessments than other baseline intragastric pH models using one, two, or three cosine terms (data not shown). Likewise, the final PK–PD model adequately described the PK and PD profiles of YH4808 in individuals (Figure 2). No discernible bias was observed in any of the goodness-of-fit (GOF) plots of YH4808 (Figure S3). In addition, the VPC plots, stratified by the dose of YH4808, showed that most of the observed plasma concentrations of YH4808 and intragastric pH after YH4808 administration were within the 95% predicted intervals (Figure 3).

TABLE 1 Baseline characteristics

Characteristics	Single-dose group	Multiple-dose group	Placebo group	Total	Range
Sex (male), no (%)	55 (100.0)	24 (100.0)	6 (100.0)	85 (100.0)	NA
Age, years[a]	25.9 ± 4.5	24.6 ± 4.4	23.0 ± 2.4	25.3 ± 4.4	20.0–41.0
Body weight, kg[a]	68.5 ± 7.6	67.7 ± 7.8	67.4 ± 5.8	68.2 ± 7.5	53.5–87.2
Height, cm[a]	174.9 ± 5.7	175.0 ± 4.7	176.5 ± 2.9	175.0 ± 5.3	161.5–188.2
BMI	22.4 ± 1.9	22.1 ± 2.1	21.7 ± 1.9	22.2 ± 1.9	17.8–26.6
Drinking, no (%)					
Yes	31 (56.3)	10 (41.7)	4 (66.7)	44 (51.8)	NA
No	24 (43.6)	14 (58.3)	2 (33.3)	41 (48.2)	NA

Abbreviations: BMI, body mass index; NA, not applicable.

[a]The data are presented as mean ± SD.

Moreover, the median of the PK and PD parameters estimated from the bootstrapped datasets was similar to the parameter in the final PK–PD model of YH4808.

Simulations of YH4808 concentrations and intragastric pH

A total of 7900 simulated patient time–concentration-effect profiles (i.e., 100 simulations in 79 subjects), were generated to simulate the PK and PD profiles of YH4808. The observed plasma concentrations and intragastric pH after YH4808 at 400 mg once daily was within the 95% simulated intervals, indicating that a Monte–Carlo simulation using the final PK–PD model adequately predicted the observed PK and PD profiles of YH4808 (Figure 4a, c). In the simulation experiments, a reduced systemic exposure to YH4808 after repeated once-daily administrations was discernible, particularly at >400 mg (Figure 4a). Individual predicted mean percentage of time at pH >4 over 24 h after multiple doses of YH4808 at 100 mg twice daily and 200 mg once daily was 76.3% and 84.7%, respectively.

DISCUSSION

We successfully developed a population PK–PD model of YH4808 that adequately described the plasma concentrations of orally administered YH4808 and their effects on intragastric pH (Figures 2 and 3). The circadian fluctuation in baseline intragastric pH, partly caused by food ingestion, was modeled using four cosine terms, each of which accounted for phase shift and amplitude by 24-, 12-, 6-, and 3-h cycles, respectively.[14,15] Furthermore, the final population PK–PD model incorporated the feedback mechanism to characterize the inhibitory effects of increased intragastric pH on the systemic exposure to YH4808 after its multiple oral administrations, particularly at higher doses (i.e., 400 mg once daily). The PK and PD parameters were precisely estimated and their confidence interval (CI) obtained from bootstrap resampled datasets were relatively narrow (Table 2). The IIV of PK and PD parameters were large, which may have resulted in a large 95% CI around the lower 2.5th and upper 97.5th predicted concentrations or intragastric pH in VPC plots (Figure 3) and slight overprediction of plasma concentrations of YH4808 at day 7 in the simulation (Figure 4a). The adequacy of the final population PK–PD model was confirmed in diagnostic plots, including individual PK and PD, VPC, GOF plots, and eta distribution plots (Figures 2, 3, S3, and S4).

The estimated PK and PD parameters for YH4808 were similar or at least comparable to those derived from phase I clinical trials of YH4808.[8,13] The maximum increase in intragastric pH (E_{max}) by YH4808 was estimated at 4.38 in this study, which was similar to 3.10, the largest difference between placebo and YH4808 at 100 mg twice daily obtained from the first-in-human phase I clinical study.[8] Furthermore, the difference between the estimated *CL/F* from another phase I clinical trial (*CL/F* = 386.25 L/h after YH4808 at 200 mg once daily and 100 and 200 mg twice daily) and this study (*CL/F* = 221.00 L/h; Table 2) was small (165.25 L/h), indicating that the estimated parameters were reliable.[13]

The population PK–PD model of YH4808 incorporated a negative feedback mechanism of increased intragastric pH on the exposure to YH4808. The EP_{max} of intragastric pH on the PK of YH4808 was 0.58, indicating that the systemic exposure to YH4808 after multiple administrations can be reduced by up to 58%. This finding was consistent with the results from the first-in-human phase I clinical trial and PBPK modeling and simulation of YH4808, where the C_{max} and AUC_{0-t} on day 1 were reduced by 56.3%

TABLE 2 Parameter estimates of the final population pharmacokinetic–pharmacodynamic model for YH4808

Parameter	Description	Typical value, median [95% CI, RSE%][a]	Interindividual variability (CV%), median [95% CI][a]	Shrinkage for IIV
CL/F, L/h	Apparent clearance of the YH4808	221.00, 281.58 [152.22–387.05, 23.2]	71.7, 54.0 [31.6–85.5]	33.0
V_C/F, L	Apparent volume of distribution of YH4808 in the central compartment	121.00, 144.75 [62.50–224.44, 31.3]	118.3, 104.0 [84.0–142.6]	25.0
V_P/F, L	Apparent volume of distribution of YH4808 in the peripheral compartment	3800.0, 2089.4 [2000.0–4649.2, 22.7]	48.5, 14.7 [6.0–46.5]	54.0
Q/F, L/h	Apparent inter-compartmental clearance of YH4808 between the central and peripheral compartments	208.00, 200.08 [151.44–310.90, 19.1]	39.1, 25.9 [8.6–62.0]	34.0
$K_{A,}$ 1/h	Absorption rate constant from the administered compartment to central compartment	0.95, 1.18 [0.77–1.47, 12.7]	29.8, 5.9 [2.6–29.2]	48.0
ALAG1, h	Absorption lag-time	0.26, 0.23 [0.22–0.26, 12.1]	15.7, 4.6 [2.6–10.2]	68.0
A_0	Mean intragastric pH	2.03, fixed[b]	36.6, 29.7 [11.8–40.0]	54.0
A_1	Amplitude of intragastric pH on a 24-h cycle	0.29, fixed[b]	127.7, 55.6 [29.3–113.0]	46.0
A_2	Amplitude of intragastric pH on a 12-h cycle	0.14, fixed[b]	137.5, 25.5 [17.2–131.4]	59.0
A_3	Amplitude of intragastric pH on a 6-h cycle	0.66, fixed[b]	53.9, 9.5 [5.2–45.4]	61.0
A_4	Amplitude of intragastric pH on a 3-h cycle	0.32, fixed[b]	12.8, 14.8 [9.9–27.1]	87.0
C_1, h	Phase shift in time of intragastric pH on a 24-h cycle	7.95, fixed[b]	220.9, 10.2 [5.5–204.4]	64.0
C_2, h	Phase shift in time of intragastric pH on a 12-h cycle	8.27, fixed[b]	41.4, 22.2 [11.5–137.1]	72.0
C_3, h	Phase shift in time of intragastric pH on a 6-h cycle	5.37, fixed[b]	22.3, 7.6 [2.4–16.8]	51.0
C_4, h	Phase shift in time of intragastric pH on a 3-h cycle	5.00, fixed[b]	5.4, 1.7 [1.1–3.0]	77.0
E_{max}, pH unit	Maximum effect of PK of YH4808 on the intragastric pH	4.38, 3.00 [3.00–5.52, 19.6]	30.4, 21.4 [5.7–37.0]	58.0
EC_{50}, ng/mL	Concentrations of YH4808 that produces 50% of the maximum effect on the intragastric pH	15.20, 8.00 [8.00–19.67, 31.5]	83.1, 22.4 [14.8–50.1]	53.0
$K_{EO,}$ 1/h	Rate constant for elimination from the effect compartment	0.06, 0.06 [0.03–0.10, 22.2]	129.6, 160.7 [97.6–204.9]	47.0
EP_{max}	Maximum inhibitory effect of intragastric pH on the PK of YH4808	0.58, 0.28 [0.20–0.60, 29.1]	127.7, 126.8 [100.7–146.7]	56.0
EP_{50}, pH unit	Intragastric pH that produces 50% of the maximum inhibitory effect of intragastric pH on the PK of YH4808	2.65, 2.32 [2.00–2.57, 7.4]	118.3, 7.1 [3.4–40.7]	59.0
Prop RUV (PK), %	Proportional error of PK of YH4808	0.37, 0.37 [0.32–0.37, 11.0]	NE	NE
Add RUV (PK), ng/mL	Additive error of PK of YH4808	0.001, fixed	NE	NE
Prop RUV (PD), %	Proportional error of intragastric PH	1.40, 2.70 [1.33–2.75, 19.2]	NE	NE

Abbreviations: CI, confidence interval; CV%, coefficient of variation expressed as percent; NA, not applicable; NE, not estimated; PD, pharmacodynamics; PK, pharmacokinetics; RSE, relative standard error expressed as percent; RUV, residual unexplained variability.

[a]Median value 95% confidence intervals, and relative standard error were derived using 100 bootstrap runs.

[b]The typical value was fixed to a value estimated from the baseline intragastric pH model using the intragastric pH data in the placebo group.

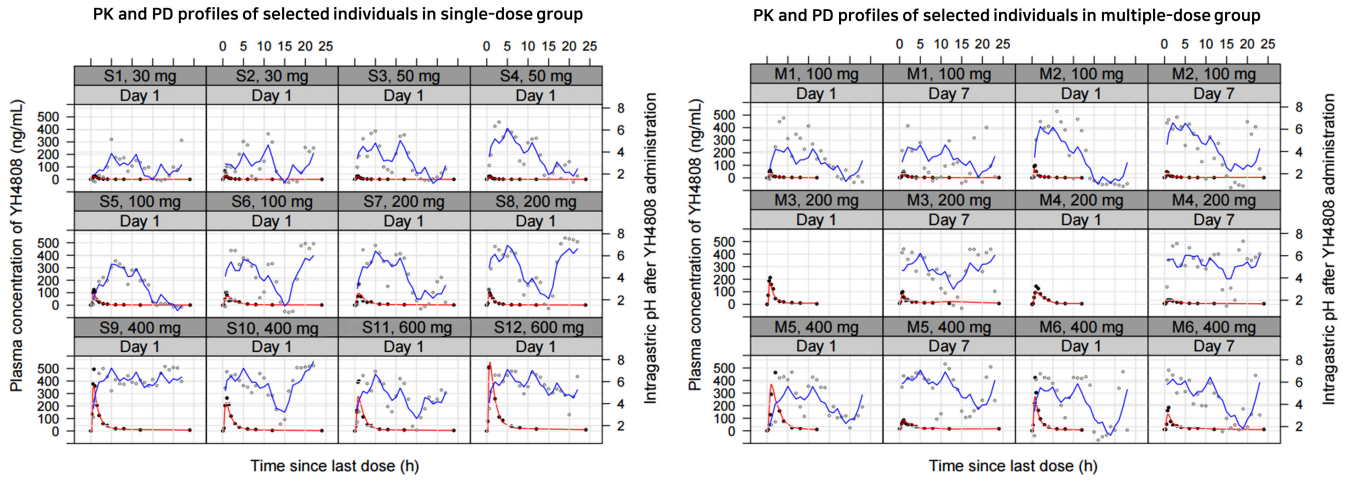

FIGURE 2 Pharmacokinetic (PK) and pharmacodynamic (PD) profiles of selected individuals in the single- and multiple-dose groups. Two individuals per dosage regimens were selected (single-dose: S1 to S12; multiple-dose: M1 to M6). The blue- (—) and red-solid (—) lines denote the predicted concentrations of YH4808 and intragastric pH, respectively, in selected individuals at different dosage regimens. The black solid- (●) and gray empty-circles (○) represent the observed concentrations of YH4808 and intragastric pH, respectively, at different dosage regimens.

and 46.3% on day 7 at 400 mg once daily, respectively.[8,12] Although systemic exposure to YH4808 was reduced after repeated administrations, particularly at higher doses (i.e., 200 mg twice daily and 400 mg once daily), it is unlikely that dose adjustment is necessary. This notion is supported because the predicted effect site concentrations of YH4808 at steady-state were consistently higher than EC_{50} (15.20 ng/ml) over the entire dosing interval when given once or twice daily (Figure S5).

We predict that increased intragastric pH by YH4808 may have led to its lower solubility, further to reduced bioavailability and systemic exposure.[16,17] Weakly basic drugs, such as YH4808, dissolve more readily in the acidic environment in the stomach but when the acidic environment becomes more basic, their solubility can be reduced.[18] Because drugs must be dissolved in the form of an aqueous solution before they reach the absorption site, reduced solubility results in decreased bioavailability.[19] In the case of YH4808, the solubility of YH4808 was reduced from 2.137 to 0.042 mg/ml when intragastric pH was increased from 2.0 to 6.0, resulting in reduced bioavailability and subsequently reduced systemic exposure.[12] Collectively, our analysis supports the notion that reduced absorption and bioavailability as a result of increased intragastric pH is the main cause of the reduced systemic exposure to YH4808 after repeated administration.

The final population PK–PD model was used to simulate percentage of time at intragastric pH > 4 after different dosage regimens of YH4808 (Figure 4). In our simulation experiments, YH4808 at ≥200 mg resulted in a higher percentage of time at intragastric pH > 4 than observed value of esomeprazole at 40 mg once-daily (76.3% time vs. 44.3% time, respectively). This simulation result was consistent with that from the phase I clinical trial of YH4808 where the observed percentage of time after YH4808 at ≥200 mg was higher than that after esomeprazole at 40 mg (70.2% time vs. 44.3% time, respectively).[8] The simulation experiments also showed that the individual predicted mean percentage of time at intragastric pH > 4 after YH4808 administration at 200 mg once daily was 8.4% points higher than that at 100 mg twice daily. The population predicted mean percentage of time after YH4808 at 200 mg once daily was 6.6% points higher than that at 100 mg twice daily (data not shown). These simulation results collectively represent that YH4808 at 200 mg once daily dose regimen would be the most suitable therapeutic regimen for elevating intragastric pH over 24 h. Although simulation experiments were performed using the final population PK–PD model of YH4808, which is based on healthy male volunteers, we believe that simulation results would not be different in patients with gastroesophageal reflux disease because there were no significant differences between healthy subjects and patients with regard to age, smoking status, alcohol, and BMI.[20]

In phase I clinical trials of YH4808, time delay between plasma concentrations of YH4808 and increasing effect of intragastric pH has been shown,[8,13] which may be caused by the uptake of drugs into an effector site (i.e., H+/K+-ATPase).[21,22] Therefore, we assumed that the effect compartment could explain the time needed for YH4808 to attain equilibrium at the effector site, by fully binding it, leading to increasing intragastric pH. As a result, a counterclockwise hysteresis loop could have been collapsed and intragastric pH could be linearly described using effect site concentrations of YH4808 (Figure S6).

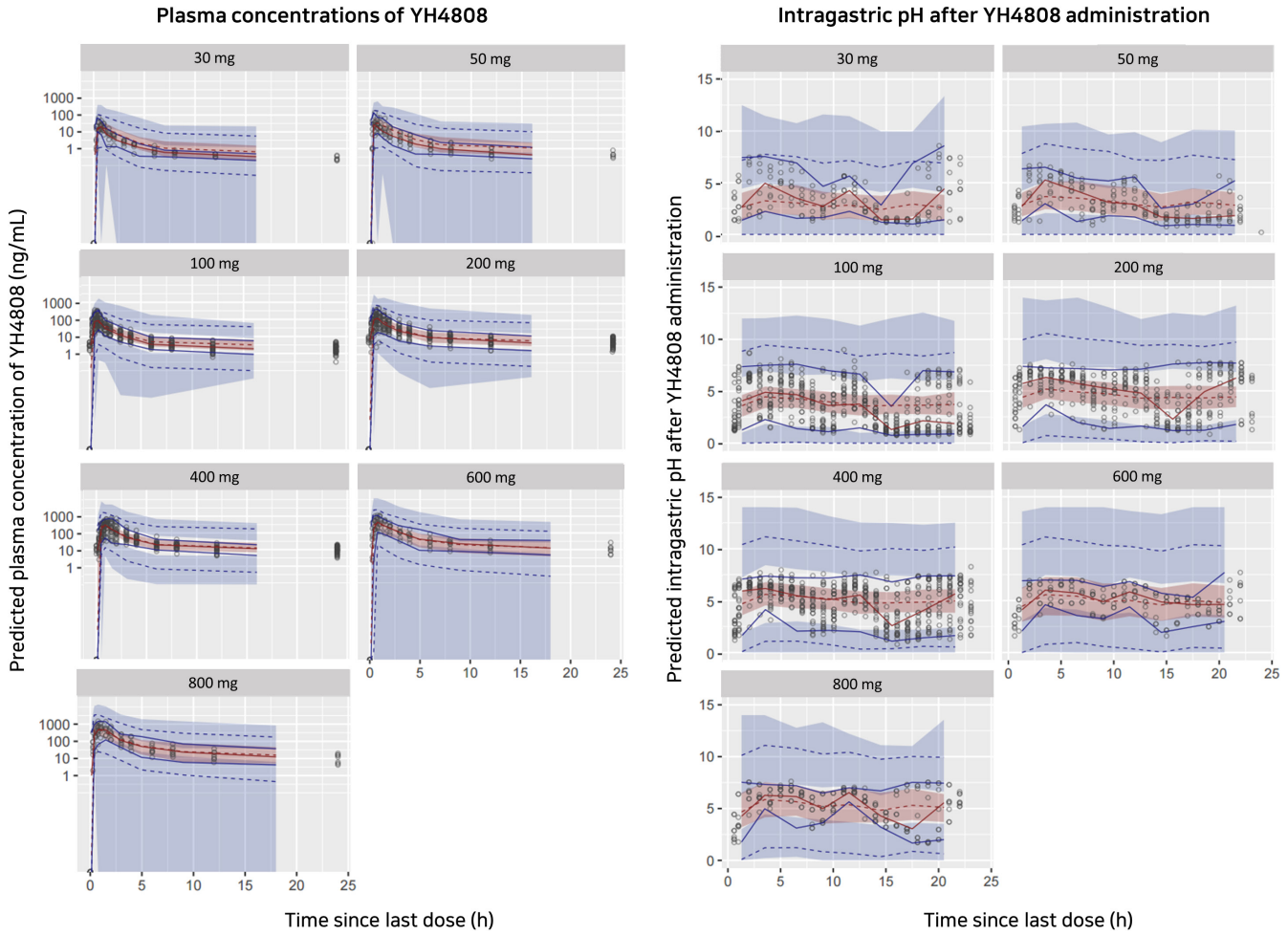

FIGURE 3 Visual predictive check (VPC) plots of the final population pharmacokinetic–pharmacodynamic model of YH4808. The VPC plots were stratified by the dose of YH4808. The empty circles (○) represent the observed plasma YH4808 concentrations or intragastric pH after YH4808 administration. The solid (—) and dashed (– – -) red lines denote the median values of the observed and predicted plasma YH4808 concentrations or intragastric pH, respectively; the solid (—) and dashed (– – -) blue lines are the lower 2.5th and 97.5th values of the observed and predicted plasma YH4808 concentrations or intragastric pH, respectively; and the shaded areas indicate the 95% confidence intervals around the lower 2.5th, median, and upper 97.5th predicted concentrations or intragastric pH, respectively. The vertical axis for the concentrations of YH4808 is drawn in the logarithmic scale.

We successfully modeled how the PKs and PDs of P-CABs including YH4808 were linked both ways in that not only PKs drove PDs, but PDs also affected the PKs. To the best of our knowledge, no previous population analysis incorporated negative feedback mechanism by increased intragastric pH onto the reduced systemic exposure to acid reducing agents including P-CABs, PPIs, and H_2 receptor antagonists.[23]

This study had three major limitations. First, the population PK–PD model of YH4808 was developed solely in healthy male volunteers with a limited range of body weight (53.5–87.2 kg). Relatively homogenous populations, such as healthy volunteers, may preclude us from identifying significant covariates on the PK and PK–PD parameters of YH4808, as seen in this study (Figure S7). A clinical study with vonoprazan, another novel P-CAB, demonstrated that sex and body weight was significant on K_A and CL, respectively.[24] Because various covariates including sex and body weight can be significant for the PK and PK–PD of YH4808, requiring dosage adjustment for, further clinical studies are warranted to study the effects of those covariates. Second, although the final PK and PD parameters could have been changed if all of the model parts were fit simultaneously, amplitude and phase shift parameters were first estimated in the placebo group to characterize the baseline intragastric pH and then fixed in the final PK–PD analysis. This approach was chosen mainly to save computational time before a model was successfully converged. Third, an indirect model was not tested in our experiment although it could be mechanistically more plausible. Instead, we thought that an effect compartment could explain the time needed for YH4808

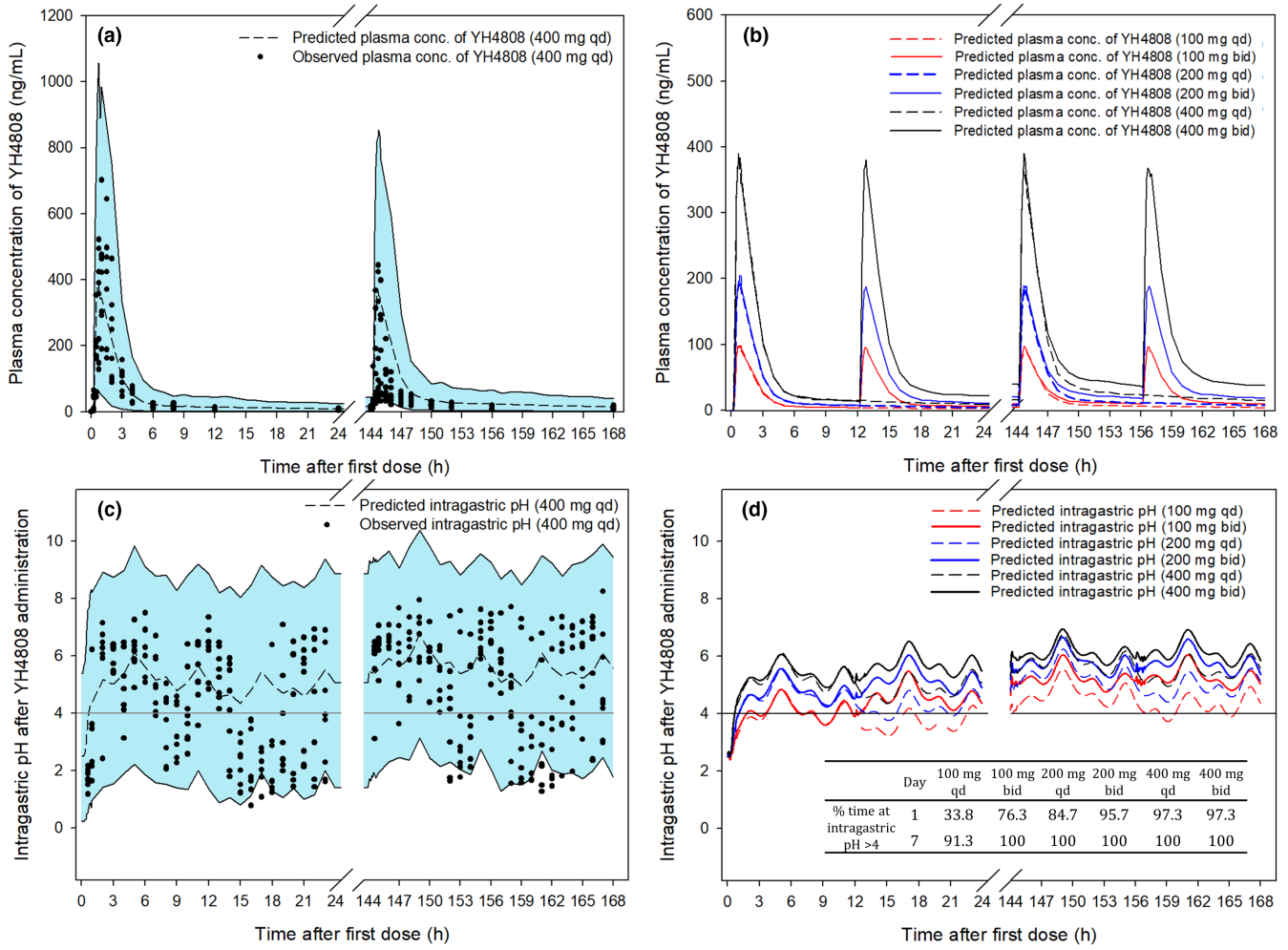

FIGURE 4 Simulated pharmacokinetic and pharmacodynamic profiles of YH4808: simulated plasma concentrations and intragastric pH after YH4808 at 400 mg once daily versus time after first dose (plots a and c, respectively); simulated plasma concentrations and intragastric pH after YH4808 at different dosage regimens vs. time after first dose (plots b and d, respectively). The dashed (– – -) line in plots a and c denotes the predicted mean concentrations of YH4808 and intragastric pH, respectively, after YH4808 at 400 mg once daily. The shaded areas in plots a and c indicate the 95% simulated intervals around the mean predicted plasma concentration of YH4808 and intragastric pH after YH4808 administration, respectively. The circles (●) in plots a and c represent the observed plasma YH4808 concentrations and intragastric pH after YH4808 administration, respectively. Each solid (—) and dashed (– – -) line in plots b and d denotes the simulated mean concentrations and mean intragastric pH at different dosage regimens, respectively. The inlet table in plot d shows the percentage of time at intragastric pH > 4 at different dosage regimens on days 1 and 7. Gray solid line in plots c and d shows the intragastric pH at 4. All simulated plots (plots a–d) are drawn on the linear scale.

to attain equilibrium at the effector site, leading to increasing intragastric pH. Exploring a more mechanistic model such as indirect response model is something that could be pursued further.

In conclusion, we developed a population PK–PD model of YH4808 that adequately described its plasma concentrations, intragastric pH, and their mutual effects in healthy volunteers. Our study clarified the negative feedback mechanism of intragastric pH on the PK of YH4808. Based on our simulation experiments and supporting evidences from a phase I clinical trial of YH4808, YH4808 at 200 mg once daily was the most suitable therapeutic regimen for elevating intragastric pH over 24 h.

AUTHOR CONTRIBUTIONS

T.K.C., H.A.L., K.R.L., S.B.J., K.S.Y., and H.L. wrote the manuscript. T.K.C., H.A.L., S.B.J., K.S.Y., and H.L. designed the research. T.K.C., H.A.L., K.R.L., S.B.J., K.S.Y., and H.L. performed the research. T.K.C. and H.L. analyzed the data.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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