A population pharmacokinetic-pharmacodynamic model of YH12852, a highly selective 5-hydroxytryptamine 4 receptor agonist, in healthy subjects and patients with functional constipation

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Abstract
YH12852, a novel, highly selective 5-hydroxytryptamine 4 (5-HT4) receptor agonist, is currently under development to treat patients with functional constipation. In this study, we aimed to develop a pharmacokinetic (PK)–pharmacodynamic (PD) model that adequately described the time courses of the plasma concentrations of YH12852 and its prokinetic effect as assessed by the Gastric Emptying Breath Test (GEBT) and to predict the prokinetic effect of YH12852 at higher doses through PD simulation. We used the plasma concentrations of YH12852 from patients with functional constipation and healthy subjects and the GEBT results from healthy subjects obtained from a phase I/IIa trial. The PK-PD modeling and covariate analysis were performed using NONMEM software. The prokinetic effect of YH12852 was described using a semimechanistic multicomartment PD model and an empirical model by Ghoos et al. A two-compartment model with first-order absorption adequately described the observed concentration-time profiles of YH12852. The semimechanistic multicompartment PD model and the revised Ghoos model with two slope parameters adequately described the observed kPCDt (the percent dose of 13C excreted in the exhaled air at minute t after completing the test meal, multiplied by 1000) values. YH12852 accelerated gastric emptying even at low doses of 0.05–0.1 mg, and its prokinetic effect was greater in subjects suffering from more severe functional constipation. The PD simulation experiments revealed that the change from baseline in the half time for gastric emptying induced by YH12852 increased in a dose-dependent manner at 0.05–5 mg although the results at doses >0.1 mg were extrapolated. We also showed that the empirical Ghoos model is a special case of the general semimechanistic multicompartment PD model for gastric emptying.
INTRODUCTION

Functional constipation, also known as chronic idiopathic constipation, is characterized by infrequent bowel movements, unfinished feeling, and hard stools. The pooled global prevalence of functional constipation in adults is 14%. Patients with functional constipation experience significantly poorer quality of life and greater health-related impairments in daily life than patients who do not suffer from functional constipation.

The current clinical practice guidelines for functional constipation recommend lifestyle modifications, such as consuming more fluid and dietary fiber and laxatives as initial interventions, which is of little risk for serious adverse events and low in cost. Although many laxatives are effective to reduce the symptoms of chronic constipation, 5-hydroxytryptamine 4 (5-HT₄) receptor agonists have been developed as prokinetic agents or drugs enhancing gastrointestinal motility for those who did not respond to lifestyle modifications or were not satisfied with laxatives.

The benefit-risk profile of 5-HT₄ receptor agonists is closely related to their selectivity for the 5-HT₄ receptor. For instance, cisapride, a nonselective 5-HT₄ receptor agonist, was withdrawn from the global market because of concerns over cardiovascular adverse events, whereas prucalopride, the first approved highly selective 5-HT₄ receptor agonist, was not associated with cardiovascular safety issues.

YH12852, a novel, highly selective 5-HT₄ receptor agonist, is currently under development as an oral treatment for patients with functional constipation. YH12852 more strongly binds to human 5-HT₄ receptor (pKi, negative decadic logarithm of Ki = 10.3) than prucalopride (pKi = 7.84) and tegaserod (pKi = 8.49) while exhibiting high selectivity for the 5-HT₄ receptor over other subtypes of 5-HT receptors (pKi < 7.95). In a phase I/IIa trial, YH12852 was well tolerated over daily doses of 0.05–3 mg in healthy volunteers and patients with functional constipation. Furthermore, no cardiovascular safety issue was reported in the phase I/IIa trial. YH12852 significantly improved the stool consistency score at all tested doses and increased the average weekly frequency of spontaneous bowel movements at doses of 1, 2, and 3 mg, although a clear dose–response relationship was not observed.

In this study, we aimed to develop a population pharmacokinetic (PK)–pharmacodynamic (PD) model for YH12852 using the PK and PD data observed from the previous clinical trial in healthy subjects and patients with functional constipation. Furthermore, we used the final PK-PD model to predict the change in the gastric emptying half time induced by YH12852 of untested higher doses based on the PD simulation.
METHODS

Clinical study and subjects

The plasma concentrations of YH12852, Gastric Emptying Breath Test (GEBT; Cairn Diagnostics) results, and demographic and clinical covariates were obtained from a randomized, double-blind, placebo-controlled, phase I/IIa study (ClinicalTrials.gov registration no. NCT02538367). Briefly, the study consisted of the multiple dose (MD) and multiple low-dose (MLD) cohorts; 56 subjects (29 healthy volunteers and 27 patients with functional constipation) and 16 healthy subjects were enrolled in the MD and MLD cohorts, respectively. Patients were eligible if they had been diagnosed with functional constipation based on the updated Rome III diagnostic criteria, whereas healthy subjects had to document \( \leq 3 \) spontaneous bowel movements per week for at least 3 months.\(^{14}\) Subjects in the MD cohort randomly received YH12852 at 0.3, 0.5, 1, 2, or 3 mg; prucalopride at 2 mg; or placebo. On the other hand, subjects in the MLD cohort were randomized to 0.05 or 0.1 mg of YH12852 in a ratio of 1:1. In the MD and MLD cohorts, subjects orally received YH12852 once daily after the completion of breakfast for 14 days.

PK sample collection and bioanalysis

In the MD cohort, blood samples were obtained for YH12852 plasma concentration at 0 (i.e., predose), 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, and 24 h postdose on Days 1 and 14. On Day 14, we collected additional blood samples at 36, 48, and 72 h postdose. Furthermore, trough predose blood samples were drawn on Days 5, 10, 12, and 13. In the MLD cohort, blood samples were collected at the same times in the MD cohort on Days 1 and 14, whereas the predose samples were collected only on Days 5 and 13.

YH12852 concentrations were determined in plasma samples using a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) system (LC: Prominance UFLC XR; MS/MS: 5500 QTRAP, AB SCIEX) by BioCore. Plasma samples (200 \( \mu \)l) were mixed with 500 \( \mu \)l of acetonitrile for protein precipitation. The suspension was vortexed and centrifuged. Then, the organic layer was transferred to a glass tube and evaporated under nitrogen. The dry residue was reconstituted in 200 \( \mu \)l of 50% methanol, from which 5 \( \mu \)l of supernatant taken after centrifugation was injected into an LC-MS/MS system. More details on the bioanalysis method can be found elsewhere.\(^{13}\) The lower limit of quantification for bioanalysis was 30 pg/ml.

Gastric emptying breath test

In the MLD cohort, the prokinetic effect of YH12852 was evaluated using the GEBT at baseline and on Day 7. GEBT noninvasively measures the speed of gastric emptying by using a meal containing the stable 13-carbon isotope ([\(^{13}\)C]).\(^{15}\) The test meal containing [\(^{13}\)C]-Spirulina, powdered egg, and saltine crackers was completely or entirely consumed by all subjects in the MLD cohort after an overnight fast. Once ingested, the \(^{13}\)C-labeled GEBT test meal is absorbed in the intestine, and \(^{13}\)C is finally excreted from the lung in the form of \(^{13}\)CO\(_2\), giving rise to the ratio of \(^{13}\)CO\(_2\)/\(^{12}\)CO\(_2\) in exhaled air. GEBT is not only helpful to diagnose delayed gastric emptying but also it is useful to assess the effect of a prokinetic agent without the risk of radiation exposure.

Exhaled air samples were collected at 45, 90, 120, 150, 180, and 240 min after the test meal was fully consumed. The results of the GEBT were reported as a \( k_{PCD} \) value, which is the percent dose of \(^{13}\)C excreted in the exhaled air at minute \( t \) after completing the test meal, multiplied by 1000.\(^{16}\) \( k_{PCD} \) was the pharmacodynamic end point to assess the prokinetic effect of YH12852. Furthermore, time elapsed for gastric emptying by 10% and 50% (\( t_{10} \) and \( t_{50} \), respectively) and the area under the \( k_{PCD} \)-time curve (AUC\(_{k_{PCD}}\)) were estimated. Time for gastric emptying of 50% was also called the “gastric-emptying half time.”

Model development strategies

We used the NONMEM software (version 7.4.3; ICON Development Solutions), and the first-order conditional estimation method with interaction was the estimation method. Concentrations of YH12852 were log-transformed, and the PK-PD models were fitted simultaneously. Visualization of the data set and the results of model diagnostics including goodness-of-fit (GOF) plots and visual predictive checks (VPCs) were performed using R (version 3.5.3; R Foundation for Statistical Computing) and Xpose (version 4.5.3; Uppsala University).

Interindividual variability (IIV) and interoccasion variability (IOV) were assumed to be log-normally distributed with a mean of zero and a variance of \( \omega^2 \). Occasion was defined as a set of sampling times clearly separated between two adjacent occasions (i.e., 1 for Day 1 and 2 the other). To describe residual variability, three residual error models (additive, proportional, and combined additive and proportional) were tested. We chose the models based on physiological plausibility, GOF plots, decrease in the objective function value (OFV), the precision of estimated PK parameters, and the reductions in both residual variability and IIV. Also, we ruled out a model that was associated with a large shrinkage.
because it may obscure the relationships between the random effects and covariate. When comparing the nested models, a decrease in OFV >6.63 between the full and reduced models, corresponding to a significance level of 1% with a single degree of freedom in the $\chi^2$ distribution, was considered statistically significant, and the model with a significantly smaller OFV was selected for further development.

**Population PK model**

One-compartment and two-compartment PK models with first-order elimination were tested. Also, we tested the following three absorption models: first-order models, combined zero-order and first-order models, and sequential linked zero-order and first-order models. A mixture model on the absorption rate constant ($K_a$) was also tested to explain a large interindividual variability in $T_{max}$ (the time to maximum plasma concentration).

**Population PK-PD model**

The prokinetic effect of YH12852 was described using two models (Figure 1): a semimechanistic multicompartment PD model and an empirical model by Ghoos et al. Assuming compartments 1–3 are reserved for the PK of YH12852 and compartments 4, 5, and 6 correspond to the gastrointestinal tract, systemic circulation, and lung, respectively. Then, the semimechanistic multicompartment PD model can be written in Equations (1) to (4):

$$\frac{dA_4(t)}{dt} = - (K_{45} + SLP \times CONC) \times A_4(t) \quad (1)$$

$$\frac{dA_5(t)}{dt} = (K_{45} + SLP \times CONC) \times F_{CL3} \times A_4(t) - K_{56} \times A_5(t) \quad (2)$$

$$\frac{dA_6(t)}{dt} = K_{56} \times A_5(t) - K_{out} \times A_6(t) \quad (3)$$

$$k_{PCD} = \frac{K_{out} \times A_6(t)}{60} \quad (4)$$

where $A_i(t)$ is the amount of $^{13}$C in compartment $i$ at time $t$; $K_{45}$, $K_{56}$, and $K_{out}$ are the rate constants for $^{13}$C in the test meal transferred from compartment 4 to 5, 5 to 6, and 6 to the air, respectively; SLP represents a slope for the linear PD effect of YH12852 on $K_{45}$; $F_{CL3}$ is the fraction of $^{13}$C in the test meal that is eventually absorbed; and CONC is the concentrations of YH12852 in the central compartment of the PK model. In Equation (4), 60 was used to divide the numerator to convert the time unit from min to h. Because we did not observe the amount of $^{13}$C in compartment 5, $K_{56}$ and $K_{out}$ were not independently identifiable. Thus, we assumed that $K_{56}$ was identical to $K_{out}$. The initial values of compartments 5 and 6, that is, $A_5(0)$ and $A_6(0)$, respectively, were 0, whereas the initial amount of $^{13}$C in compartment 4 was set to 100,000 because kPCD (the percent dose of $^{13}$C excreted in the exhaled air, multiplied by 1000) is the percent dose of $^{13}$C excreted in the exhaled air multiplied by 1000, that is, 100*1000. In addition to the linear model of YH12852 concentration on kPCD (Equations 1 and 2), we tested if an $E_{max}$ model could have better described the prokinetic effect of YH12852.

Next, we fit an empirical model proposed by Ghoos et al. to describe the amount of $^{13}$C appearing in breath sample per unit time. To make the estimated rate constants physiologically meaningful, we reparameterized the Ghoos model as

$$k_{PCD} = k_{PCDmag} \times \left(\frac{t}{t_{mag,GE}}\right)^{K_s} \times e^{-\frac{t}{t_{mag,GE}}} \quad (5)$$

where $k_{PCDmag}$ and $t_{mag,GE}*$ denote the magnitude of kPCD and a constant as to how fast kPCD values change in the time-kPCD curves, respectively; $K_s$ is the power term of the Ghoos model that determines the shape of kPCD-time curve; and $t$ is time (minute) after the end of test meal consumption. The changes in kPCDmag and $t_{mag,GE}$* lead to the changes in the maximum kPCD ($k_{PCDmax}$) and time to reach $k_{PCDmax}$ ($t_{max,GE}$*), respectively, when other constants in Equation (5) are fixed. For examples, when $t_{mag,GE}$* and $K_s$ are fixed, kPCDmag increases proportionally to kPCDmag while $t_{max,GE}$* is constant regardless of kPCDmag. We assumed that YH12852 either decreases $t_{mag,GE}$* or increases kPCDmag or both. Therefore, the PK-PD relationship between the plasma concentrations of YH12852 and its prokinetic effect, expressed in SLP1 or SLP2, was given as Equations (6) and (7), respectively.

$$k_{PCDmag} = k_{PCDmag, baseline} - SLP_1 \times CONC \quad (6)$$

$$t_{mag,GE} = t_{mag,GE, baseline} - SLP_2 \times CONC \quad (7)$$

**Covariate analysis**

The covariates included age, sex, body weight, body mass index (BMI), blood test results of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and blood urea nitrogen (BUN) tests. The effects of baseline $t_{typ}$, $t_{50}$, and $AUC_{kPCD}$ were explored in the PK-PD model development. Continuous covariates were incorporated into the model as follows:

$$P_i = P_{typ} \times \left(\frac{Cov_i}{Cov_{typ}}\right)^{\theta_{cov}} \times e^{\eta_i} \quad (8)$$
where \( P_i \) and \( P_{typ} \) are the individual parameter value of the \( i \)th subject and the typical value in the population, respectively; \( Cov_i \) and \( Cov_{typ} \) are the individual value of a given covariate and its median or typical value, respectively; \( \theta_{cov} \) is the exponent reflecting the covariate relationship; and \( \eta_i \) is a normally distributed IIV with a mean of zero and a variance \( \omega_i^2 \). Covtyp for age, body weight, BMI, \( t_{10} \), \( t_{50} \), and AUC_{kPCD} were 27.6 years, 59.2 kg, 22.0 kg/m\(^2\), 30 min, 100 min, and 140 (unitless), respectively. Baseline \( t_{10} \) and \( t_{50} \) of subjects at baseline were determined by interpolating the portions of gastric emptying at given timepoints. The portions of gastric emptying were estimated through the multiple regression models by Szarka et al.\( ^{16} \) using kPCD\(_t \) values at baseline and each subjects’ covariates (e.g., sex and BMI). On the other hand, \( Cov_{typ} \) for AST, ALT, and BUN were 15 U/L, 10 U/L, and 10 mmol/L, respectively. Sex was incorporated into the model as follows:

\[
P_i = P_{typ} \times \theta_{cov}^{Cov} \times e^{\eta_i}
\]

where \( Cov_i \) is sex of an individual patient (0 for male, 1 for female), \( \theta_{cov} \) is the proportional constant reflecting the effect of sex on parameter \( P_i \), and the meanings of the rest of the variables are the same as in Equation (8).

We used the forward-addition and backward-elimination methods for the covariate analysis, and candidate covariates were identified through empirical Bayes estimate–based
model diagnostics. A candidate covariate was considered significant when a decrease in OFV after adding the covariate was >6.63 (p = 0.01, d.f. = 1). In the backward elimination, the covariate was retained in the model if OFV was increased by >10.83 (p = 0.001, d.f. = 1) after removing the covariate. For an efficient covariate search, we performed the covariate analysis on the PK model first and then on the PK-PD models.

**Model validation**

We evaluated the final PK and PK-PD models using the bootstrap resampling method and VPCs. Furthermore, the 95% confidence interval (CI) of the PK and PK-PD parameters were derived such that the 2.5th and 97.5th percentiles of the refit parameters using 300 bootstrapped data sets were the lower and upper CI bounds, respectively. The final PK and PK-PD parameters were considered stable if they were close to the median of the refit parameters using 300 bootstrapped data sets. The VPCs were both prediction corrected and variability corrected and stratified by the several covariates (e.g., t10, sex, weight, and dose) to rule out a possible model misspecification.

**PK-PD simulation**

To determine an optimal dose for the phase II trial with YH12852, we simulated the prokinetic effect of YH12852 based on the final PK-PD model. A total of 1050 virtual subjects randomly and equally received once-daily YH12852 at 0.05, 0.1, 0.5, 1, 2, 5, and 10 mg for 2 weeks. kPCD1 values were determined from the virtual subjects whose PK-PD parameters were within the 95% CIs of the respective parameters (Table 1).

In the simulation experiments, the half time for gastric emptying (t50), time taken for the half of food contents in the stomach to escape it, was estimated from the simulated kPCD1 values using the multiple regression models by Szarka et al. (Table S1). The regression models of Szarka et al. predicted the portions of gastric emptying at 45, 90, 120, 150, 180, and 240 min after the 13C-labeled GEBT meal based on the sex, BMI, and kPCD1 values. Because the regression model by Szarka et al. included the sex and BMI of patients as covariates, we derived BMI from the simulated sex and body weight of virtual patients using a linear regression model (adjusted r² = 0.68) [21,22].

In this PK-PD simulation, we relied on the following two assumptions: (1) the systemic exposure to YH12852 is dose-proportional over 0.05–3 mg and untested higher doses of 5 and 10 mg and (2) the prokinetic effect of YH12852 follows the linear PD model on low doses (i.e., 0.05 and 0.1 mg) over 0.5–10 mg.

**RESULTS**

**Data set and study population**

The final PK-PD data set included 1287 plasma concentrations of YH12852 and 196 kPCD1 values obtained from 49 subjects in the MD and MLD cohorts and 14 subjects in the MLD cohort, respectively. A total of 71.4% of the subjects were women, and the mean age was 27.3 years (Table 2). The baseline t10 of the subjects in the MLD cohort was 30.3 ± 15.5 min (mean ± standard deviation).

**Population PK-PD model**

A two-compartment model with first-order absorption adequately described the observed concentration-time profiles of YH12852 (Figure 1). Of the two PD models we tested, the semimechanistic multicompartment PD model, which physiologically integrates the transfer of 13C from the gastrointestinal tract to the lung, adequately described the observed kPCD1 values (Figures 2 and S1). Furthermore, an Eₘₐₓ PD model did not improve the model fit or reduce OFV significantly compared with a linear slope model. Therefore, we chose the semimechanistic multicompartment linear PD model as the final PD model, and the GOF plots showed that observations were comparable with the model predictions and no systematic deviations were noted (Figures S2 and S3).

The estimated parameters from the final PK-PD model fell within the 95% CIs of the parameters obtained by bootstrap analysis (Table 1). IIV was estimated for all of the fixed parameters except for Kₐ5. All of the IIV estimates, expressed as coefficients of variation, were less than 35% except for V₃ and SLP (38.6% and 116.2%, respectively; Table 1). IOV was estimated for clearance (CL), V₂, and Kₐ; the estimates of IOV were low for CL (28.5%) and moderate for V₂ and Kₐ (48.1% and 48.9%, respectively; Table 1). The median bootstrap estimates were close to the parameters estimated from the full analysis data set (by <10% except for SLP; Table 1).

Body weight and baseline t₁₀ were significant covariates on V₃/F and SLP, respectively. All of the other covariates tested (sex, BMI, baseline t₅₀, and AUCₑ₅₀ₐₚ) did not decrease OFV by >6.63 (p = 0.01) from the reduced model or minimally reduced IIV of the respective parameters and therefore were not retained in the final PK-PD model.

**Model validation**

The VPC plots grouped by occasion showed that the median and 5th and 95th percentiles of the observed YH12852 concentrations and kPCD1 values were similar to their respective simulated values (Figure 3). However, the variabilities in kPCD1 in the simulation were overestimated, particularly for
the 95th percentiles of the predicted kPCD₄, possibly because of a large variability in SLP. Likewise, the similarity between the observations and simulations was noted when the VPCs were separately done by significant covariate (body weight and baseline \( t_{10} \)), dose, and sex, which was required for kPCD₄ regression (Figure S4 and S5).

**PK-PD simulation**

The half time for gastric emptying or \( t_{50} \) decreased as the dose of YH12852 was increased from 0.05 to 5 mg. All of the decreases in \( t_{50} \) between any two doses were significantly different after the Bonferroni adjustment (\( p \)-value < 0.0001) except for the comparison between 5 and 10 mg (Figure 4).

**DISCUSSION**

We developed a semimechanistic multicompartment PK-PD model that adequately described the time courses of the plasma concentrations of YH12852 and its prokinetic effect, assessed using kPCD₄ in healthy subjects and patients with
We showed that once-daily YH12852 is likely emptying, the greater the prokinetic effect of YH12852. A mechanistic than the revised Ghoos model, whereas both models doses of 1–3 mg.

In this study with YH12852, where it significantly increased the average weekly frequency of spontaneous bowel movements at doses of 1–3 mg.

The final transit PD model for YH12852 was more mechanistic than the revised Ghoos model, whereas both models adequately described the observed kPCD1 values particularly when the Ghoos model was parameterized with two SLPs (Figures 2 and S1). In the transit PD model, change from baseline in kPCD1 after YH12852 was adequately modeled by a single SLP parameter, whereas two separate slope parameters, that is, SLP1 and SLP2, were required in the Ghoos model to adequately capture the change in kPCD1 profiles after YH12852 (Figure S3). Moreover, the Ghoos model with a single SLP parameter systemically overestimated kPCDmax after YH12852. Indeed, the AUCkPCD was consistently overpredicted by the Ghoos model with a single SLP parameter, even >100,000 (unitless), suggesting complete absorption and excretion of 13C in the test meal, which is practically not possible.

In fact, the Ghoos model is a specific case of the more general transit model that assumes all of the transfer rate constants $K_{i(i+1)}$ being identical as $K_0$ (Supplementary Method S1). Under this assumption, $K_s$ and $t_{mag,GE}$ in the Ghoos model become equal to the number of transit compartments minus one and the inverse of $K_0$, respectively, in the transit PD model. Furthermore, the estimated $K_i$ from the Ghoos model, 1.94, suggests that three transit compartments were appropriate for modeling the prokinetic effect of YH12852. It is because the predicted kPCD1 in the transit PD model with N transit compartments is the same as those in the Ghoos model, where $K_i$ is equal to (N-1) under the previous assumption (Table S2). Moreover, the estimated value of $t_{mag,GE}$ was similar to the inverse of the average rate constants in the final PK-PD model (1.64 vs. 1.54 h; Tables 1 and S2). All of those findings support the notion that the semimechanistic multi-compartment PK-PD model for YH12852 in this study was not only physiologically more plausible but also was a general form of the Ghoos model. This may explain why the empirical Ghoos model has been frequently used in describing the time course of kPCD1 to capture the prokinetic effects of a constipation treatment.

Abbreviations: BMI, body mass index; MD, multiple dose; MLD, multiple low dose; NA, not available; SD, standard deviation; $t_{10}$, times elapsed for gastric emptying by 10%.

### Baseline characteristics of subjects by cohort

| Characteristic     | MD cohort, N=35 | MLD cohort, N=14 |
|--------------------|-----------------|------------------|
| **Sex, n (%)**     |                 |                  |
| Female             | 24 (68.6)       | 11 (78.6)        |
| Male               | 11 (31.4)       | 3 (22.4)         |
| **Age, y**         |                 |                  |
| Mean ± SD          | 28.6 ± 7.7      | 24.2 ± 3.6       |
| Range              | 19–53           | 19–31            |
| **Weight, kg**     |                 |                  |
| Mean ± SD          | 60.4 ± 8.2      | 58.2 ± 8.1       |
| Range              | 45.9–78.8       | 46.8–77.3        |
| **BMI, kg/m²**     |                 |                  |
| Mean ± SD          | 22.0 ± 1.8      | 21.6 ± 2.1       |
| Range              | 19.0–24.8       | 18.2–25.0        |
| **Health status, n (%)** |           |                  |
| Functional constipation | 17 (48.6)    | 0 (0.0)          |
| Healthy            | 21 (51.4)       | 14 (100.0)       |
| **Baseline $t_{10}$, min** |               |                  |
| Mean ± SD          | NA              | 30.3 ± 15.5      |
| Range              | NA              | 11.1–59.4        |

**TABLE 2**

The final transit PD model for YH12852 was more mechanistic than the revised Ghoos model, whereas both models adequately described the observed kPCD1 values particularly when the Ghoos model was parameterized with two SLPs (Figures 2 and S1). In the transit PD model, change from baseline in kPCD1 after YH12852 was adequately modeled by a single SLP parameter, whereas two separate slope parameters, that is, SLP1 and SLP2, were required in the Ghoos model to adequately capture the change in kPCD1 profiles after YH12852 (Figure S3). Moreover, the Ghoos model with a single SLP parameter systemically overestimated kPCDmax after YH12852. Indeed, the AUCkPCD was consistently overpredicted by the Ghoos model with a single SLP parameter, even >100,000 (unitless), suggesting complete absorption and excretion of 13C in the test meal, which is practically not possible.

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**Abbreviations:** BMI, body mass index; MD, multiple dose; MLD, multiple low dose; NA, not available; SD, standard deviation; $t_{10}$, times elapsed for gastric emptying by 10%.
$K_{\text{out}}$ (0.39/h vs. 0.78/h; Table 1), suggesting that gastric emptying of the $^{13}$C-labeled test meal is truly rate limiting. The fraction of absorbed $^{13}$C contained in the test meal was 0.22 or 22% (Table 1). Because absorbed $^{13}$C might have been excreted via other routes than exhalation, the estimate could have been slightly larger.

This study had a couple of limitations. First, we assumed the concentration of YH12852 linearly affects $SLP$. Because we measured the $k_{\text{PCD}}$ values only in the MLD cohort, the range of YH12852 plasma concentrations was relatively narrow. This allowed us to link the concentrations of YH12852 with $k_{\text{PCD}}$ in a linear way, thereby supporting our approach. Thus, although an $E_{\max}$ model did not improve the model fit or significantly reduce OFV than the simpler linear mode, an $E_{\max}$ model could have better described the overall exposure–response relationship of YH12852 if a wider narrow range of dose was incorporated for PK-PD analysis. Second, we assumed that the PK-PD relationship identified in healthy

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**FIGURE 2** Individual $k_{\text{PCD}}$-time profiles by the final semimechanistic pharmacokinetic–pharmacodynamic model. The circles and lines represent the observed and the individual model-predicted $k_{\text{PCD}}$ values, respectively. Red circles and lines denote the observed and predicted $k_{\text{PCD}}$ at baseline, and the blue circles and lines denote the observed and predicted $k_{\text{PCD}}$ on Day 7. The healthy subject administered 0.1 mg YH12852 is marked by *, whereas the subject administered 0.05 mg YH12852 was not marked. Abbreviations: $k_{\text{PCD}}$, the percent dose of $^{13}$C excreted in the exhaled air at minute $t$ after completing the test meal, multiplied by 1000; $k_{\text{PCD}}$, the percent dose of $^{13}$C excreted in the exhaled air, multiplied by 1000; IPRED, individual prediction.
Subjects of the MLD cohort (0.05–0.1 mg) would be maintained at higher doses (1–10 mg). Because the prokinetic effect of YH12852 could become saturated at a certain point as the dose is increased, caution needs to be exercised not to overestimate the prokinetic effect of YH12852 at doses greater than 0.1 mg (Figure 4). Third, we performed our simulation experiments using the PK-PD model developed only in healthy subjects, not in patients diagnosed with functional constipation. However, those healthy subjects also had to report ≤3 spontaneous bowel movements per week for at least 3 months. Therefore, they experienced functional constipation to some extent. To support this notion, the mean baseline $t_{50}$ of those healthy subjects was 94.8 min (data not shown), indicating that their gastric emptying was also delayed (i.e., >86 min). Fourth, we used the 95% CIs as the sampling boundaries for the PK parameters in the simulation experiments. However, the 95% prediction intervals would be more appropriate because they are wider than the 95% CIs by accounting for both the uncertainty of the PK parameters and their random variation. Therefore, our simulation experiments might not have captured all of the variability, although they could still have showed the typical behaviors. Lastly, we assumed that the PK linearity of YH12852 would be maintained at doses >3 mg.13

In conclusion, the time courses of the plasma concentrations of YH12852 and its prokinetic effect were adequately described using a semimechanistic multicompartment PK-PD model. Based on PD simulation, YH12852 at 0.05–5 mg is expected to decrease the half time for gastric emptying in a dose-dependent manner. We showed that the empirical Ghoos model is a special case of the general semimechanistic multicompartment PD model for gastric emptying. Our study
not only clarifies the mechanism of the prokinetic effects by YH12852 but also provides the reason why the simple and empirical Ghoos model has been used so successfully for describing kPCd.

CONFLICT OF INTEREST
Seong Bok Jang is an employee of Yuhan Corporation. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS
S.K., H.A.L., S.B.J., and H.L. wrote the manuscript. S.B.J. and H.L. designed the research. S.K., H.A.L., S.B.J., and H.L. performed the research. S.K. and H.L. analyzed the data.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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