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ARTICLE

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-HT_4) 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 multicompartment 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 $kPCD_t$ (the percent dose of ^{13}C 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.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

YH12852 is a novel, highly selective 5-hydroxytryptamine 4 receptor antagonist under clinical development to treat constipation. Oral YH12852 was safe and well tolerated at 0.05–3 mg for 2 weeks administered once daily.

WHAT QUESTION DID THIS STUDY ADDRESS?

What does the exposure–response relationship of YH12852 and its temporal profile look like? What are the significant covariates for the pharmacokinetic (PK) and pharmacodynamic (PD) parameters of YH12852? What is the recommended dose for YH12852 in its future clinical studies?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

We developed a semimechanistic multicompartment population PK-PD model that describes the time courses of the plasma concentrations and prokinetic effect of YH12852. Furthermore, we showed that the empirical Ghoos model is a special case of the more general semimechanistic multicompartment PD model for gastric emptying. Based on PD simulation experiments, YH12852 is expected to decrease the half time for gastric emptying in a dose-dependent manner over 0.05–5 mg, whereas the results at doses >0.1 mg were extrapolated.

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

A mechanistic exposure–response relationship model for YH12852 and its prokinetic effect can help design a better-informed clinical trial with YH12852.

INTRODUCTION

Functional constipation, also known as chronic idiopathic constipation, is characterized by infrequent bowel movements, unfinished feeling, and hard stools.[1] The pooled global prevalence of functional constipation in adults is 14%.[2] 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.[3]

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.[4,5] Although many laxatives are effective to reduce the symptoms of chronic constipation, 5-hydroxytryptamine 4 (5-HT_4) 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.[6] The benefit-risk profile of 5-HT_4 receptor agonists is closely related to their selectivity for the 5-HT_4 receptor.[7,8] For instance, cisapride, a nonselective 5-HT_4 receptor agonist, was withdrawn from the global market because of concerns over cardiovascular adverse events, whereas prucalopride, the first approved highly selective 5-HT_4 receptor agonist, was not associated with cardiovascular safety issues.[9-11]

YH12852, a novel, highly selective 5-HT_4 receptor agonist, is currently under development as an oral treatment for patients with functional constipation. YH12852 more strongly binds to human 5-HT_4 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-HT_4 receptor over other subtypes of 5-HT receptors (pKi < 7.95).[12] 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.[13] 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 ≤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: Prominence UFLC XR; MS/MS: 5500 QTRAP, AB SCIEX) by BioCore. Plasma samples (200 μl) were mixed with 500 μl 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 μl of 50% methanol, from which 5 μl 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 $kPCD_t$ 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] $kPCD_t$ 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 kPCD-time curve (AUC_{kPCD}) 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 ω^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.[17] 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 χ^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.[18] 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).[19]

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.[20] 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):

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

$$\frac{dA_5(t)}{dt} = \left(K_{45} + \text{SLP} * \text{CONC}\right) * F_{C13} * A_4(t) - K_{56} * A_5(t) \quad (2)$$

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

$$\text{kPCD}_t = \frac{K_{out} * A_6(t)}{60} \quad (4)$$

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_{C13} 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.[20] To make the estimated rate constants physiologically meaningful, we reparameterized the Ghoos model as

$$\text{kPCD}_t = \text{kPCD}_{mag} * \left(\frac{t}{t_{mag,GE}}\right)^{K_s} * e^{-\frac{t}{t_{mag,GE}}} \quad (5)$$

where kPCD_{mag} 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 kPCD_{mag} and $t_{mag,GE}$ lead to the changes in the maximum kPCD (kPCD_{max}) and time to reach kPCD_{max} ($t_{max,GE}$), respectively, when other constants in Equation (5) are fixed. For examples, when $t_{mag,GE}$ and K_s are fixed, kPCD_{max} increases proportionally to kPCD_{mag} while $t_{max,GE}$ is constant regardless of kPCD_{mag}. We assumed that YH12852 either decreases $t_{mag,GE}$ or increases kPCD_{mag} or both. Therefore, the PK-PD relationship between the plasma concentrations of YH12852 and its prokinetic effect, expressed in SLP_1 or SLP_2, was given as Equations (6) and (7), respectively.

$$\text{kPCD}_{mag} = \text{kPCD}_{mag,baseline} - \text{SLP}_1 * \text{CONC} \quad (6)$$

$$t_{mag,GE} = t_{mag,GE,baseline} - \text{SLP}_2 * \text{CONC} \quad (7)$$

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_{10}, t_{50}, and AUC_{kPCD} were explored in the PK-PD model development. Continuous covariates were incorporated into the model as follows:

$$P_i = P_{typ} * \left(\frac{\text{Cov}_i}{\text{Cov}_{typ}}\right)^{\theta_{cov}} * e^{\eta_i} \quad (8)$$

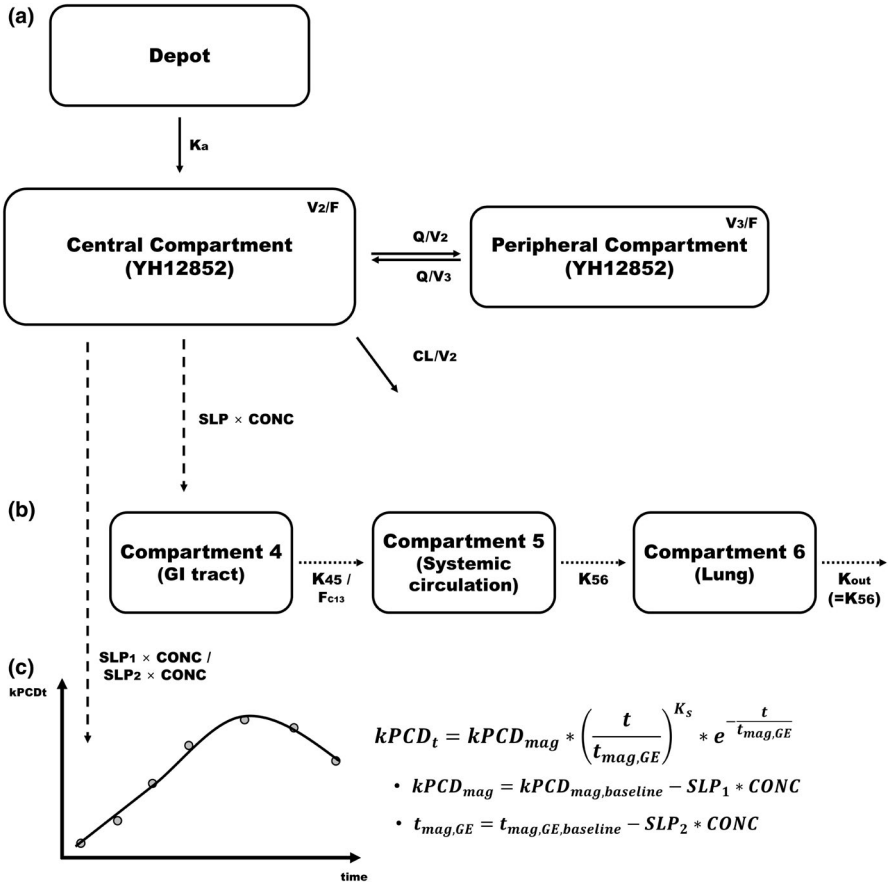

FIGURE 1 Pharmacokinetic (PK)–pharmacodynamic (PD) models to describe the concentration-time profiles of YH12852 and its prokinetic effect. The compartment structures of the (**a**) PK, (**b**) semimechanistic PD, and (**c**) modified Ghoos PD models are shown. Compartments 1–3 are for the PK of YH12852, whereas compartments 4–6 represent the gastrointestinal (GI) tract, systemic circulation, and lung, respectively, in the semimechanistic PK model. *CONC* is the plasma concentration of YH12852 in the central compartment of the PK model. (**a**) Absorption rate constant (K_a), apparent volumes of distribution of the central and peripheral compartments for YH12852 (V_2/F and V_3/F, respectively), total apparent clearance of YH12852 (CL/F), and apparent intercompartmental clearance between the central and peripheral compartments (Q/F) are shown. (**b**) Rate constants for ^{13}C moving from compartment 4 to 5, from compartment 5 to 6, and from compartment 6 to the air (K_{45}, K_{56}, and K_{out}, respectively); fraction of ^{13}C in the Gastric Emptying Breath Test meal that is absorbed (F_{C13}); and slope for the linear PD effect of YH12852 on K_{45} (SLP) are shown. (**c**) Magnitude of kPCD ($kPCD_{mag}$), parameter indicating how fast kPCD (the percent dose of ^{13}C excreted in the exhaled air, multiplied by 1000) values change in the time-kPCD curves in the Ghoos model ($t_{mag,GE}$), baseline $kPCD_{mag}$ ($kPCD_{mag,baseline}$), baseline $t_{mag,GE}$ ($t_{mag,GE,baseline}$), the exponent factor of the Ghoos model (K_s), slope constant for the linear PD effect of YH12852 on $kPCD_{mag}$ (SLP_1), and slope constant for the linear PD effect of YH12852 on t_{mag} (SLP_2) are shown

where P_i and P_{typ} are the individual parameter value of the ith 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; θ_{cov} is the exponent reflecting the covariate relationship; and η_i is a normally distributed IIV with a mean of zero and a variance ω_i^2. Cov_{typ} 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}, t_{50}, and AUC_{kPCD} were chosen based on the median of the covariates. The 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:

$$P_i = P_{typ} * \theta_{cov}^{Cov_i} * e^{\eta_i} \quad (9)$$

where Cov_i is sex of an individual patient (0 for male, 1 for female), θ_{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., t_{10}, 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. $kPCD_t$ 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 (t_{50}), time taken for the half of food contents in the stomach to escape it, was estimated from the simulated $kPCD_t$ values using the multiple regression models by Szarka et al. (Table S1).[16] The regression models of Szarka et al. predict the portions of gastric emptying at 45, 90, 120, 150, 180, and 240 min after the ^{13}C-labeled GEBT meal based on the sex, BMI, and $kPCD_t$ 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 $r^2 = 0.68$).[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 $kPCD_t$ 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 t_{10} 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 ^{13}C from the gastrointestinal tract to the lung, adequately described the observed $kPCD_t$ values (Figures 2 and S1). Furthermore, an E_{max} 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 K_{45}. All of the IIV estimates, expressed as coefficients of variation, were less than 35% except for V_3 and SLP (38.6% and 116.2%, respectively; Table 1). IOV was estimated for clearance (CL), V_2, and K_a; the estimates of IOV were low for CL (28.5%) and moderate for V_2 and K_a (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 t_{10} were significant covariates on V_3/F and SLP, respectively. All of the other covariates tested (sex, BMI, baseline t_{50}, and AUC_{kPCD}) 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 $kPCD_t$ values were similar to their respective simulated values (Figure 3). However, the variabilities in $kPCD_t$ in the simulation were overestimated, particularly for

TABLE 1 Parameter estimates of the final pharmacokinetic–pharmacodynamic model for YH12852 and median and 95% confidence intervals from a bootstrap analysis

			95% Confidence Interval		
Parameter	**Estimate**	**η shrinkage (%)**	**Lower**	**Median**	**Upper**
CL/F (L/hr)	88.8	NA	79.8	88.5	96.8
V2/F (L)	1380.2	NA	1040.4	1356.8	1529.4
V3/F (L)	989.7	NA	808.6	980.7	1226.4
Q (L/hr)	137.4	NA	105.6	137.3	175.0
K_a (1/hr)	0.48	NA	0.39	0.47	0.56
F_{C13}	0.22	NA	0.20	0.22	0.25
K_{45} (1/hr)	0.39	NA	0.29	0.41	0.75
K_{56}, K_{out} (1/hr)	0.78	NA	0.58	0.74	0.95
SLP	0.0009	NA	0.00021	0.0012	0.0045
BWT effect on V2/F	0.93	NA	0.29	0.93	1.66
t_{10} effect on *SLP*	3.57	NA	1.20	3.50	11.6
Interindividual variability (%)					
CL/F	39.1	7.1	19.5	32.3	45.6
V2/F	19.4	16.5	6.95	20.2	28.6
V3/F	32.4	16.2	18.3	35.4	40.1
Q	29.4	20.0	7.40	30.2	50.2
K_a	5.0	90.1	0.82	16.4	40.0
F_{C13}	10.3	55.7	0.74	10.2	17.7
K_{56}, K_{out}	22.8	48.4	13.9	21.9	30.6
SLP	110.5	64.6	1.74	99.8	199.2
Interoccasion variability (%)					
CL/F	28.7	31.2	21.3	28.9	34.3
V2/F	44.8	31.7	28.0	51.1	44.8
K_a	50.9	25.5	35.8	48.5	61.9
Proportional residual variability, YH12852 concentrations (%)	17.7	NA	16.9	18.6	21.3
Proportional residual variability, kPCD values (%)	12.5	NA	9.4	11.8	16.4

Abbreviations: BWT, body weight; *CL/F*, total apparent clearance; F_{C13}, fraction of ^{13}C in the Gastric Emptying Breath Test meal that is absorbed; K_{45}, rate constant for ^{13}C moving from compartments 4 to 5; K_{56}, rate constant for ^{13}C moving from compartment 5 to 6; K_a, absorption rate constant; K_{out}, rate constant for ^{13}C moving from compartment 6 to the air; kPCD, the percent dose of ^{13}C excreted in the exhaled air, multiplied by 1000; NA, not available; *Q*, intercompartmental clearance; *SLP*, slope for the linear PD effect of YH12852 on K_{45}; t_{10}, times elapsed for gastric emptying by 10%;V_2/F, apparent volume of distribution of the central compartment; V_3/F, apparent volume of distribution of the peripheral compartment.

the 95th percentiles of the predicted $kPCD_t$, 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 $kPCD_t$ 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 $kPCD_t$, in healthy subjects and patients with

TABLE 2 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/m^2		
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

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%.

functional constipation. Evidence showed that the final PK-PD model was stable, that is, the median of the parameters estimated from 300 bootstrapped data sets were close to the final PK-PD parameter (Table 1), no systematic bias was seen in the GOF plots (Figures S1 and S2), and the VPC plots captured most of the observed values for both the concentrations of YH12852 and $kPCD_t$ (Figure 3). *SLP*, a slope constant for the prokinetic effect of YH12852, was significantly greater than zero (0.0012; 95% CI, 0.00021–0.0045; Table 1), indicating that YH12852 accelerates gastric emptying. On the other hand, t_{10} or time elapsed for gastric emptying by 10% was significant on *SLP* (Table 1). t_{10} and t_{50} are known to represent early and overall gastric emptying, respectively.[23] Therefore, the longer the early gastric emptying, the greater the prokinetic effect of YH12852. Furthermore, we showed that once-daily YH12852 is likely to reduce the half time for gastric emptying in a dose-dependent way over a range of 0.05 and 5 mg in healthy subjects, particularly for doses ≥0.5 mg (Figure 4). This finding is generally compliant with the results from the phase I/IIa 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 $kPCD_t$ values particularly when the Ghoos model was parameterized with two *SLPs* (Figures 2 and S1). In the transit PD model, change from baseline in $kPCD_t$ after YH12852 was adequately modeled by a single *SLP* parameter, whereas two separate slope parameters, that is, SLP_1 and SLP_2, were required in the Ghoos model to adequately capture the change in $kPCD_t$ profiles after YH12852 (Figure S3). Moreover, the Ghoos model with a single *SLP* parameter systemically overestimated $kPCD_{max}$ after YH12852. Indeed, the AUC_{kPCD} was consistently overpredicted by the Ghoos model with a single *SLP* parameter, even >100,000 (unitless), suggesting complete absorption and excretion of ^{13}C 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_s 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 $kPCD_t$ in the transit PD model with N transit compartments is the same as those in the Ghoos model, where K_s 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 multicompartment 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 $kPCD_t$ to capture the prokinetic effects of a constipation treatment.

GEBT has been validated against gastric scintigraphy, the gold standard, as a measure of gastric emptying rate.[20,24] The half time for gastric emptying or t_{50}, estimated in GEBT, was highly consistent with t_{50} by scintigraphy.[23] In this study, we simulated changes from baseline in $kPCD_t$ by YH12852 using the final PK-PD model followed by multiple linear regression models. The regression models were initially derived in patients with functional constipation[16] and were subsequently validated in healthy subjects.[24] Also, the half time estimated by those linear regression models showed the highest concordance coefficient with the half time measured by scintigraphy among several proposed mathematical analysis methods.[24] Collectively, the simulated $kPCD_t$ values in this study were adequate to estimate t_{50}.

In GEBT, the rate-limiting step of $^{13}CO_2$ excretion is the gastric emptying of the ^{13}C-labeled test meal.[25] In our semimechanistic PK-PD model, K_{45} was 50% lower than K_{56} and

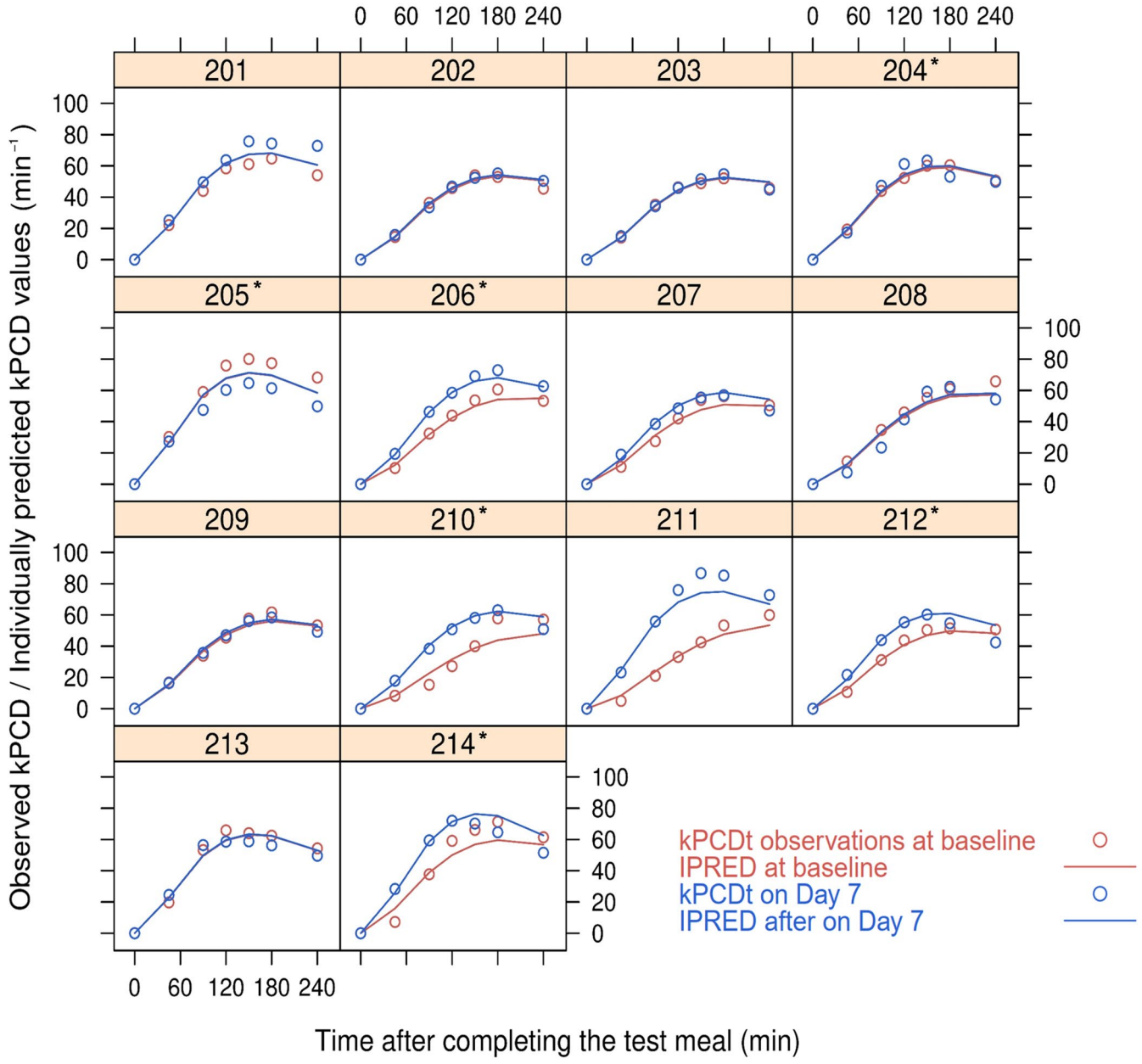

FIGURE 2 Individual $kPCD_t$-time profiles by the final semimechanistic pharmacokinetic–pharmacodynamic model. The circles and lines represent the observed and the individual model-predicted $kPCD_t$ values, respectively. Red circles and lines denote the observed and predicted $kPCD_t$ at baseline, and the blue circles and lines denote the observed and predicted $kPCD_t$ 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: $kPCD_t$, the percent dose of ^{13}C excreted in the exhaled air at minute t after completing the test meal, multiplied by 1000; kPCD, the percent dose of ^{13}C excreted in the exhaled air, multiplied by 1000; IPRED, individual prediction

K_{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 $kPCD_t$ 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 $kPCD_t$ 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

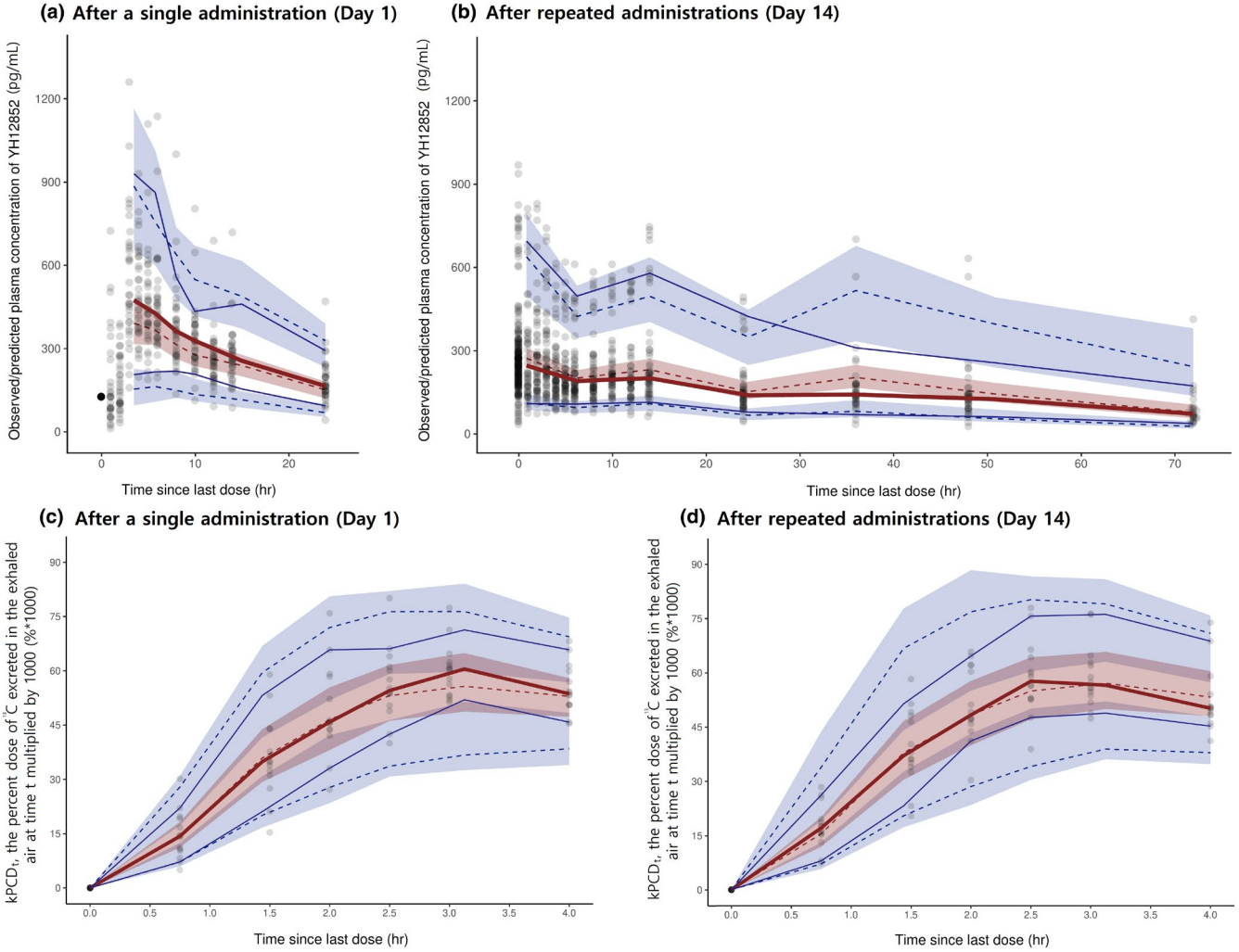

FIGURE 3 Prediction-corrected and variability-corrected visual predictive check plots group by occasion for the final population pharmacokinetic–pharmacodynamic model of YH12852. The observed and predicted concentrations of YH12852 on (**a**) Day 1 and (**b**) Day 14 are plotted. Similarly, the observed and predicted kPCD (the percent dose of ^{13}C excreted in the exhaled air, multiplied by 1000) values on (**c**) Day 1 and (**d**) Day 14 are plotted. The gray circles represent the observed values, and the solid and dashed lines depict the 95th, 50th, and 5th percentiles of the observed and predicted values, respectively. The shaded areas denote the 95% confidence intervals for the 95th, 50th, and 5th percentiles of the predicted values

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).[16] 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

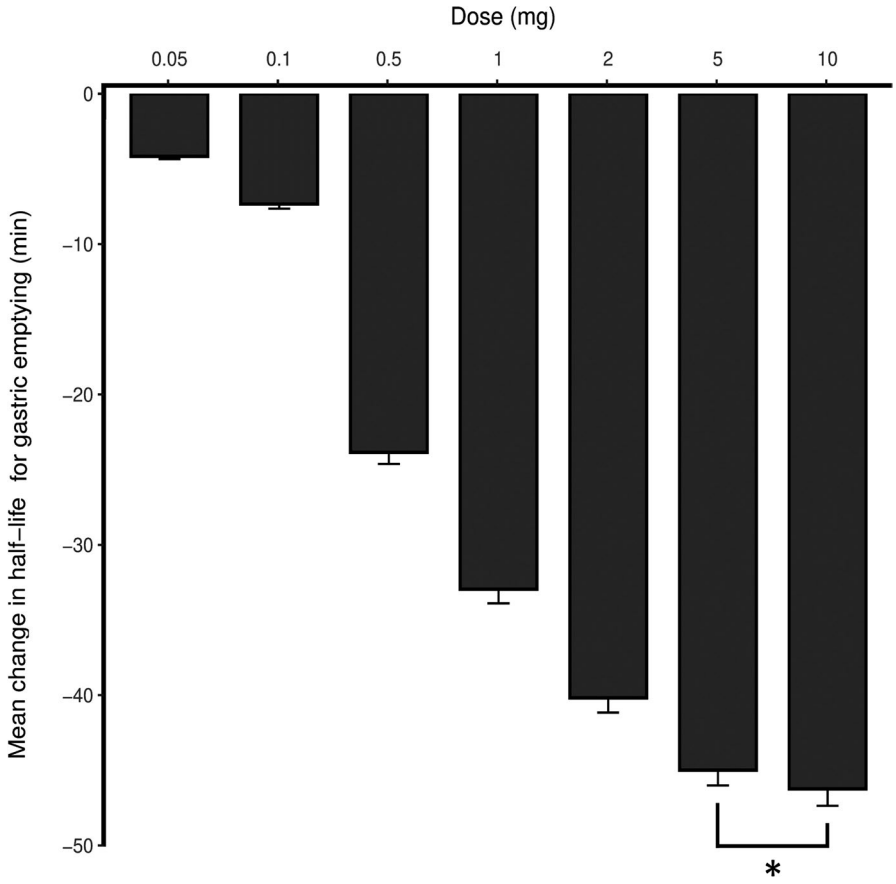

FIGURE 4 Simulated mean decreases in t_{50} from baseline by dose after once-daily YH12852 for 2 weeks. The error bars denote the standard deviations. Changes in t_{50} between any two doses were significantly different (Bonferroni-adjusted p-value <0.001) except for the comparison between 5 mg and 10 mg, marked by *

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 $kPCD_t$.

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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