의학석사 학위논문

Population pharmacokinetic modeling of various combinations of tegoprazan immediate release and delayed release formulations in healthy subjects

건강한 성인에서 테고프라잔 속방형 및 서방형 제제의 다양한 조합에서의 약동학 특성을 예측하기 위한 집단 약동학 모델링

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서울대학교 대학원

의학과 협동과정 임상약리학전공

박 수 연

Master's Thesis of Medical Science

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Submitting a master's thesis of Medical Science

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ABSTRACT

Population pharmacokinetic modeling of various combinations of tegoprazan immediate release and delayed release formulations in healthy subjects

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Introduction: Tegoprazan is a novel potassium-competitive acid blocker used to treat gastric acid-related disease. Although the currently approved dosage regimen of tegoprazan (50 mg once daily) is effective in treatment of gastric acid-related disease, stronger effect is required for patients with severe acid-related diseases. This study aimed to develop a population pharmacokinetic (PK) model of various combinations of tegoprazan immediate and delayed release (IR and DR) formulations in healthy subjects, and to evaluate and predict the

PK of tegoprazan at the optimal ratio of the tegoprazan IR to DR formulations.

Methods: A six-cohort, open-label, randomized, single- and multiple-dose study was performed to evaluate the PK of tegoprazan in healthy male subjects. Subjects in each cohort received various combinations of tegoprazan IR and DR formulations (50, 75, or 100 mg) with single or multiple oral doses once daily for 7-d. Blood samples were collected for 48 and 192 h following single and multiple oral dose of tegoprazan, respectively. A population PK model was developed for tegoprazan IR and DR formulation using the nonlinear mixed-effect modeling approach from Monolix software. A model-based simulation was performed to predict the PK of tegoprazan at dose of 50, 75 and 100 mg, using the optimal ratio of tegoprazan IR and DR, which was determined based on the results of a clinical study.

Results: A 1,398 plasma concentrations from 42 subjects were included in the population PK analysis. A two-compartment model with simultaneous zero-order absorption with different lag times and a linear elimination model appropriately described the PKs of a combination of tegoprazan IR and DR formulation.

The population mean estimates for the PK parameters were as follows: CL/F, 13.9 L/h; V1/F, 55.9 L; V2/F, 58.0 L; $Tk_{0,IR}$, 0.4 h; $Tk_{0,DR}$, 3.6 h; $T_{lag,IR}$, 0.2 h; and $T_{lag,DR}$, 1.2 h. The model was evaluated using bootstrap and visual prediction checks, which showed that it was robust and precise. Furthermore, the simulation results indicated that tegoprazan has a good linear PK profile.

Conclusion: The developed population PK model appropriately described the concentration–time profiles of tegoprazan in healthy subjects, enhancing the understanding of the PK properties of tegoprazan and its DR formulation. Additionally, it has the potential to determine the optimal ratio of tegoprazan IR to DR formulations, which could significantly improve efficacy of tegoprazan. Consequently, a combination of tegoprazan IR and DR at a 1:1 ratio is expected to achieve sufficient gastric acid suppression.

* Part of this work has been published in *British Journal of Clinical Pharmacology* (Park, S., et al., Br J Clin Pharmacol, 2023. doi: 10.1111/bcp.15784.)

Keyword: immediate released formulation, delayed release formulation, population pharmacokinetics, pharmacokinetic modeling

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List of Abbreviations

AIC	Akaike information criteria
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration–time curve
AUC_{inf}	Area under the concentration–time curve from time zero to infinity
AUC_{last}	Area under the concentration–time curve from time zero to the last quantifiable time point
BIC	Bayesian information criteria
BLQ	Below the limit of quantitation
BMI	Body mass index
CI	Confidence interval
CL/F	Total apparent clearance
C_{max}	Maximum plasma concentration
$diffT_{lag}$	Different lag time
DR	Delayed release

ECG	Electrocardiography
F	Relative bioavailability
GERD	Gastroesophageal reflux disease
GMR	Geometric mean ratio
GOF	Goodness-of-fit
IgG	Immunoglobulin G
IIV	Inter-individual variability
IPRED	Individual predicted
IR	Immediate release
IRB	Institutional Review Board
IWRES	Individual weighted residuals
KGCP	Korean Good Clinical Practice
LLOQ	Lower limit of quantification
MCMC	Markov chain Monte Carlo
MR	Modified release

NAB	Nocturnal acid breakthrough
NCA	Non-compartmental analysis
OFV	Objective function value
P-CAB	Potassium-competitive acid blocker
PD	Pharmacodynamic
PK	Pharmacokinetic
PPI	Proton pump inhibitor
PRED	Population predicted
PWRES	Population weighted residuals
Q	Blood flow
Q/F	Apparent inter-compartmental clearance between the central and peripheral compartments
RSE	Relative standard error
SAEM	Stochastic approximation expectation maximization
$t_{1/2}$	Terminal elimination half-life
Tk_0	Duration of zero-order absorption

T_{lag}	Lag time
T_{max}	Time to reach maximum plasma concentration
V1/F	Apparent central volume of distribution
V2/F	Apparent peripheral volume of distribution
VPC	visual predictive check
V_z/F	Apparent volume of distribution

Introduction

1. Study Background

Treatment of gastric acid-related disease, such as gastroesophageal reflux disease (GERD), gastric ulcers, and *Helicobacter pylori* (*H. pylori*) infection, often involves the use of the gastric acid-suppressive agents.[1-4] Although proton pump inhibitors (PPIs) are commonly prescribed as the first-line treatment for these diseases, they have certain limitations that required improvement.[4] One such limitation is the slow onset of action; it may take several days to fully exert their therapeutic effects.[4] Additionally, the frequent occurrence of nocturnal acid breakthrough (NAB), intragastric pH of < 4 for more than 1 h during the night, is another concern despite PPI therapy.[4-7] These limitations highlight the need for alternative treatments that offer faster onset of action and improved NAB control.

Potassium-competitive acid blocker (P-CAB), a novel class of gastric acid-suppressive agents, rapidly inhibit gastric acid secretion and exhibit a longer duration of action. The mechanism of action of P-CABs involves the competitive and

reversible blocking of H+/K+−ATPase (also known as ATP4A), commonly referred to as the gastric proton pump.[8−12]

Tegoprazan, a P−CAB, is used to treat acid−related gastric diseases. It was approved in Republic of Korea in 2018 as an immediate release (IR) formulation marketed under the brand name K−CAB® (HK inno.N Corporation, Republic of Korea).[13] It has also been approved in six other countries across Asia and South America, and is currently under investigation in the United States for the management of erosive esophagitis and nonerosive reflux disease.[14, 15] Compared to other P−CABs and PPIs, tegoprazan demonstrated a relatively fast onset of action and long−lasting suppression of gastric acid.[16] This is attributed to its rapid absorption, with a median time to reach maximum plasma concentration (T_{max}) of 1 h under fasting conditions. Tegoprazan also exhibits a relatively long terminal elimination half−life ($t_{1/2}$) that ranges 3.7−5.4 h.[17, 18] In addition, tegoprazan showed a correlation between systemic exposure and response in terms of gastric acid suppression. This correlation was observed using linear pharmacokinetic (PK) profiles and dose−dependent pharmacodynamic (PD) profiles.[17, 18]

The current approved dosage regimen of 50 mg tegoprazan once daily has been shown to be effective in the treatment of acid-related diseases. However stronger effect is required in patients with severe or PPI-refractory GERD.[19] These patients often experience more severe symptoms or struggle to achieve sufficient symptom control with standard treatment approaches, including PPIs.[20, 21] Furthermore, the frequent occurrence of NAB poses a challenge for patients using PPIs or P-CABs for acid-related conditions.[2, 5, 6, 22-27] To address this clinical need, the development of a new modified release (MR) formulation of tegoprazan is necessary. The MR formulation of tegoprazan was expected to provide enhanced therapeutic effects, potentially leading to improve symptom relief and management. Therefore, by providing stronger efficacy and better symptom control, the limitations of the current treatment options for patients with more challenging cases of acid-related diseases can be addressed.

The delayed release (DR) formulation of tegoprazan was developed as an enteric-coated pellet that release the active ingredients in a pH-dependent manner. In a preclinical study conducted in cynomolgus monkeys, when tegoprazan IR and DR

formulations were co-administrated, the drug plasma concentration reached a plateau after the dissolution of the tegoprazan IR powder.[28] Following a plateau, the plasma concentration slowly declined over time, in contrast to tegoprazan IR alone. These findings are consistent with the in vitro dissolution profile, further supporting the sustained release characteristics of the tegoprazan DR formulation.[28] This suggests that the combination of tegoprazan IR and DR formulations can provide a sustained and prolonged release of the drug, potentially leading to enhanced therapeutic effects and prolonged gastric acid suppression. Therefore, further studies are necessary to determine the optimal ratio of the IR and DR formulations of tegoprazan and to evaluate their effectiveness and safety.

Population PK modeling is a mathematical method that predicts PK by incorporating population variability and individual characteristics such as age, weight, genotype, renal/hepatic function, and concomitant medications.[29-32] This modeling approach provides insights into drug exposure, dosing, and efficacy differences among patient groups, aiding in optimizing dosing regimens and understanding drug-drug interactions.[33]

It is especially useful for special populations, such as pediatrics patients, elderly individuals, and patients with specific diseases who have difficultly conducting clinical trials.[34] Therefore, population PK modeling enables informed decisions regarding drug therapy, with limited data and contributes to personalized and optimized treatment strategies.

2. Purpose of Research

This study aimed to develop a population PK model that reflects the specific formulation characteristics of tegoprazan, including the IR and DR. The PK model included PK data obtained from a phase 1 study that explored the PK and PD of various combinations of tegoprazan IR and DR formulations in healthy subject to evaluate the optimal IR and DR ratio. Based on the population PK model, the PK of tegoprazan at the optimal ratio of the IR and DR formulations was evaluated and predicted. The findings of this study contribute to the characterization of the properties tegoprazan PK, including its absorption and elimination, in healthy subjects.

Method

1. Study design and population

This clinical study was approved by the Institutional Review Board (IRB) of the Seoul National University Hospital (IRB number: B-2006-152-1135, NCT number: NCT04485884). This clinical study was conducted in accordance with the Declaration of Helsinki and Korean Good Clinical Practice (KGCP). Written informed consent was obtained from all subjects before performing any study-related procedures.

Healthy male subjects (aged 19–50 years) with body weight equal to or greater than 55.0 kg and a body mass index (BMI) ranging 18.0-28.0 kg/m^2, were deemed eligible to participants in this study. Subjects who have been diagnosed with *H. pylori* infections were excluded from the study. *H. pylori* infection was determined by testing for IgG antibodies in the serum using an immunology analyzer (IMMULITE® 2000, Siemens Healthineers, Erlangen, Germany). Additionally, subjects with diseases or a history of gastrointestinal disease likely to affect drug absorption, and/or whose total bilirubin, aspartate aminotransferase (AST), or alanine aminotransferase

(ALT) levels were 1.5-fold above the upper normal limits were excluded. The participants were considered to be healthy based on their medical history, physical examination, vital signs, 12-lead electrocardiography (ECG), and clinical laboratory test results at screening.

A six-cohort, open-label, randomized, single- and multiple-dose study was performed to evaluate the PK and PD of tegoprazan in healthy male subject (Figure 1). A total of 42 subjects were planned to complete this study. In single dose study, combination of tegoprazan IR and DR formulations were orally administered once to all randomized subjects in each period; cohort A: two tablets of IR (IR 2), one tablet of IR and one capsule of DR (IR 1 + DR 1), or two capsules of DR (DR 2); cohort B: four tablets of IR (IR 4), two tablets of IR and two capsules of DR (IR 2 + DR 2), or four capsules of DR (DR 4); cohort C: one tablet of IR and two capsules of DR (IR 1 + DR 2), two tablets of IR and one capsule of DR (IR 2 + DR 1), or one tablet of IR and three capsules of DR (IR 1 + DR 3). The washout period was wet for a 7-d between each period.[17] In the multiple dose study, a combination of tegoprazan IR and DR formulations was administered for 7-d to all randomized

subjects; cohort D: one tablet of IR and one capsule of DR (IR 1 + DR 1); cohort E: two tablets of IR and two capsules of DR (IR 2 + DR 2); and cohort F: one tablet of IR and two capsules of DR (IR 1 + DR 2). Blood samples were collected for PK analysis. In the single dose study, blood samples were collected at the following time points: 0 (before dosing), 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, and 48 h after dosing. In multiple dose study, blood samples were collected at 0 (before dosing), 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, and 24 h on day 1, 0 h on day 2–6, and 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6 8, 12, 24, and 48 h on day 7.

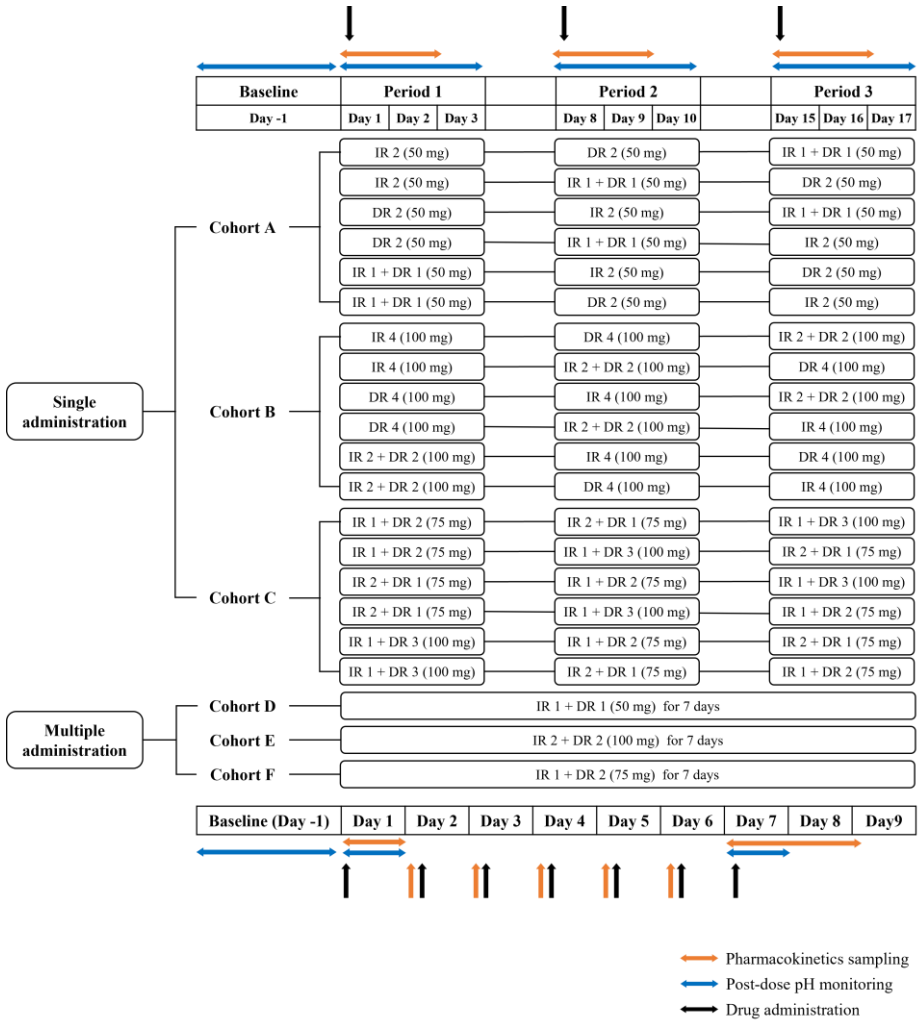


Figure 1 Clinical study design.

IR, immediate release; DR, delay release

2. Plasma concentration analysis

At each sampling point, 4 mL of blood was collected in heparinised tubes. The blood samples were centrifuged at 4℃ and 1910 g for 10 min, after which, the plasma was separated and stored at −70℃ until used for analysis. Plasma tegoprazan concentrations were quantified using validated ultra-performance liquid chromatography (UPLC) tandem mass spectrometry (MS/MS), performed using an ACQUITY UPLC System (Waters Corp., Milford, MA, USA) and a Xevo TQ mass spectrometer (Waters Corp., Milford, MA, USA), with a lower limit of quantification (LLOQ) of 10.0 μg/L. [35]

3. Non-compartment PK analysis

The PK parameters following single and multiple administration of various combination of tegoprazan were calculated and estimated via non-compartmental analysis (NCA) using Phoenix WinNonlin® version 8.3.2 (Certara, Inc., Princeton, NJ, USA). The maximum plasma concentration (C_{max}) and T_{max} were determined from the observed concentrations and times. The area under the concentration-time curve (AUC) from zero to the last quantifiable time point (AUC_{last}) was calculated using the linear-up/log-down trapezoidal method. The AUC from 0 to

infinity (AUC_{inf}) was calculated as $AUC_{last} + C_{last}/\lambda_z$, where C_{last} is the last measurable concentration and λ_z is the terminal elimination rate constant. The apparent volume of distribution during the terminal phase (Vz/F) was estimated as CL/λ_z and the total apparent clearance (CL/F) was calculated as dose/AUC_{inf}. Furthermore, $t_{1/2}$ was analyzed as $\ln 2/\lambda_z$.

4. Population PK model development

The population PK model was developed using a nonlinear mixed effect modeling approach from Monolix software version 2023R1 (Lixoft, Antony, France). The parameters were estimated using the stochastic approximation expectation maximization (SAEM) algorithm combined with a Markov chain Monte Carlo (MCMC) procedure. Tegoprazan plasma concentrations below the limit of quantitation (BLQ) in the absorption and elimination phase were included in the estimation of population parameters using the M4 method.[36−40] The standard errors of the parameter estimates are calculated using stochastic approximation based on the Fisher information matrix. The conditional means and standard deviations were calculated for each individual parameter.

To develop a population PK model for both tegoprazan IR and DR, an initial model was constructed using data from

tegoprazan IR formulation, which is the conventional form of tegoprazan. Subsequently, additional data from DR formulation and the co-administration of IR and DR formulations, were incorporated to further refine and improve the model.

Several potential structural models of orally administrated tegoprazan have been investigated, including one-, two-, or three-compartment models with first- or zero-order absorption with or without lag time, by applying linear elimination. The inter-individual variability (IIV) for each PK parameter was assessed using an exponential error model. The PK parameters were assumed to follow a log-normal distribution, except for IIV, for relative bioavailability (F). For the IIV on F, a logit-normal distribution between 0 and 1 was assumed.

$$P_{i,j} = \theta_j \cdot \exp(\eta_{i,j}) \quad (1)$$

$$log\left(\frac{P_{i,j}}{1-P_{i,j}}\right) = log\left(\frac{\theta_j}{1-\theta_j}\right) + \eta_{i,j} \quad (2)$$

Where P_{ij} is the value of the jth parameter for the ith individual, θ_j is the typical population value of the jth parameter, and $\eta_{i,j}$ is the random variable for the jth parameter for the ith individual, which is normally distributed with a mean of zero and variance

ω^2. Residual error models have been explored using various options, including additive, proportional, and a combination of both. The covariance between random effects was also evaluated. Eta shrinkage was calculated and considered acceptable if the values were less than 30%. The model was considered significantly improved if the OFV in the two nested models decreased by more than 3.84, with $p < 0.05$ and degrees of freedom = 1.

5. Covariate selection

Continuous data (age, height, weight, and BMI) were evaluated as potential covariates. Correlation between continuous covariates and PK parameters were screened using regression analysis. Possible candidate covariates were then tested in the model using power functions normalized to their median values or generally accepted typical value. To determine the covariates to be included in the final population PK model, stepwise forward selection (decreased OFV > 3.84, $p < 0.05$) and backward elimination (increased OFV > 6.63, $p < 0.01$) of each covariate was performed in the basic structural model.

6. Population PK model evaluation

Various models were diagnosed based on both numerical and visual criteria, including parameter precision, comparison of OFV, Akaike information criteria (AIC), Bayesian information criteria (BIC), relative standard errors (RSE), goodness-of-fit plots (GOF), and individual plot. The OFV was calculated as the negative two times the log-likelihood. On the other hand, AIC and BIC are derived from the OFV values and are defined as follows:

$$AIC = OFV + 2P \quad (3)$$

$$BIC = OFV + \log(N) * P \quad (4)$$

Where P is the total number of parameters to be estimated and N is the number of subjects.

The GOF was assessed using several diagnostic scatterplots, including observed vs. population predicted (PRED) concentrations, observed vs. individual predicted (IPRED) concentrations, population weighted residuals (PWRES) vs. PRED, PWRES vs. time, individual weighted residuals (IWRES) vs. PRED, and IWRES vs. time. Visual predictive checks (VPCs) and bootstrap were performed to verify the final model. The

predictive performance of the model was assessed using VPCs, which were stratified by the ratio of tegoprazan IR to DR formulations. Using VPCs, the observed data points were overlaid with the median and 95% confidence intervals (CIs, 5th and 95th percentiles) of 1,000 simulated datasets from the final model. To assess the robustness of the final model, bootstrap analysis was conducted by resampling the dataset 1,000 times. Standard errors for the parameter estimates were obtained and the estimated median values and 95% Cis of each parameter were compared with estimates from the original dataset. The final model was deemed stable when the estimated values were not significantly different, and the 95% CIs were reasonably narrow.

7. Model-based simulation

Model-based simulations were performed based on the final model to predict the concentration profiles of 50, 75, and 100 mg tegoprazan after single and 7-d multiple oral administrations in healthy subjects. Based on the results of a clinical study that investigated the PK and PD of tegoprazan, the optimal ratio of tegoprazan IR to DR formulations was determined for the simulation. In the simulation of multiple administrations, a 7-d

dosing period was considered sufficient to achieve the steady state based on the $t_{1/2}$ of tegoprazan. A total of 1,000 subjects were simulated and the PK parameters were calculated by non-compartmental analysis using PKanalix version 2023R1 (Lixoft, Antony, France).

Results

1. Study population of model dataset

A population PK model for tegoprazan was constructed using 1,398 plasma concentrations obtained from 42 subjects (Table 1). Of these, 702 observations were obtained from 18 Korean subjects and 696 observations were from 24 Caucasian subjects. The age of the study population ranged 20–44 years, height ranged 160.8–198.5 cm, weight ranged 55.5–95.1 kg, and BMI ranged 18.7–26.8 kg/m^2.

Table 1 Demographic characteristics of subjects.

Variables	Total (n = 42)	Korean (n = 18)	Caucasian (n = 24)
Age (years)	26 (20–44)	27 (20–44)	26 (22–39)
Height (cm)	177.5 (160.8–198.5)	174.25 (160.8–194.7)	179.5 (164.5–198.5)
Weight (kg)	69.5 (55.5–95.1)	69.5 (55.6–85.4)	70.1 (55.5–95.1)
BMI (kg/m^2)	22.25 (18.7–26.8)	22.25 (18.7–26.8)	22.15 (19–25.9)

Data were presented as median (min–max).

2. PK analysis

In all dose groups, tegoprazan absorption was delayed with an increase in the DR-to-IR ratio (Table 2). After a single administration of tegoprazan, tegoprazan IR reached C_{max} at a median time of 1 h (range of 0.45-1 h), whereas tegoprazan DR reached C_{max} at a median time of 4.5-7 h (range of 2-8 h) in the tegoprazan 50-100 mg dose range. In particular, when tegoprazan IR and DR were co-administered in a 1:1 ratio following a single administration, the T_{max} of tegoprazan was similar to that of IR alone, with a median T_{max} of 0.7-1 h with a range of 0.5-1 h. In the steady state, the median T_{max} of 50 mg and 100 mg tegoprazan at steady state was 1 h and 2.5 h, respectively (Table S1). The time-concentration of single or multiple oral dose of a combination of tegoprazan IR and DR showed a double-peak profile in the absorption phase, indicating a difference in the release timing of the tegoprazan IR and DR formulations (Figure 2, Figure 3). In addition, C_{max} decreased when DR was administered alone or in combination with IR. However, the overall AUC_{last} was similar to that of IR alone after single and multiple administrations. This suggests that although C_{max} may be reduced by the DR formulation or combination

administration, the total exposure to tegoprazan, as measured by AUC_{last}, remains comparable to that of the IR formulation alone.

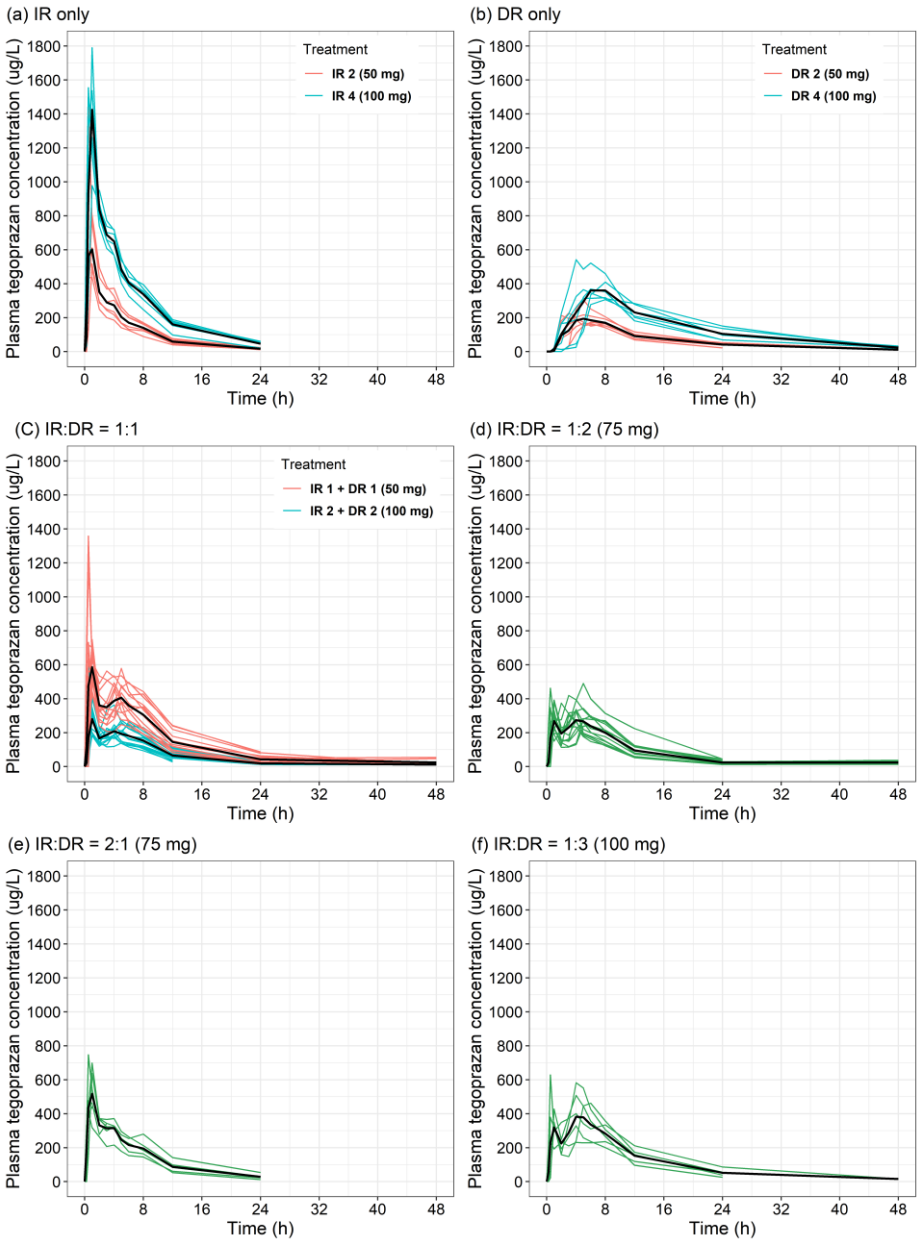


Figure 2 Individual plasma concentrations–time profile following a single oral administration of tegoprazan with (a) IR only, (b) DR only, (c) 1:1 ratio of IR and DR, (d) 1:2 ratio of IR and DR, (e) 2:1 ratio of IR and DR, and (f) 1:3 ratio of IR and DR.

IR, immediate release; DR, delay release

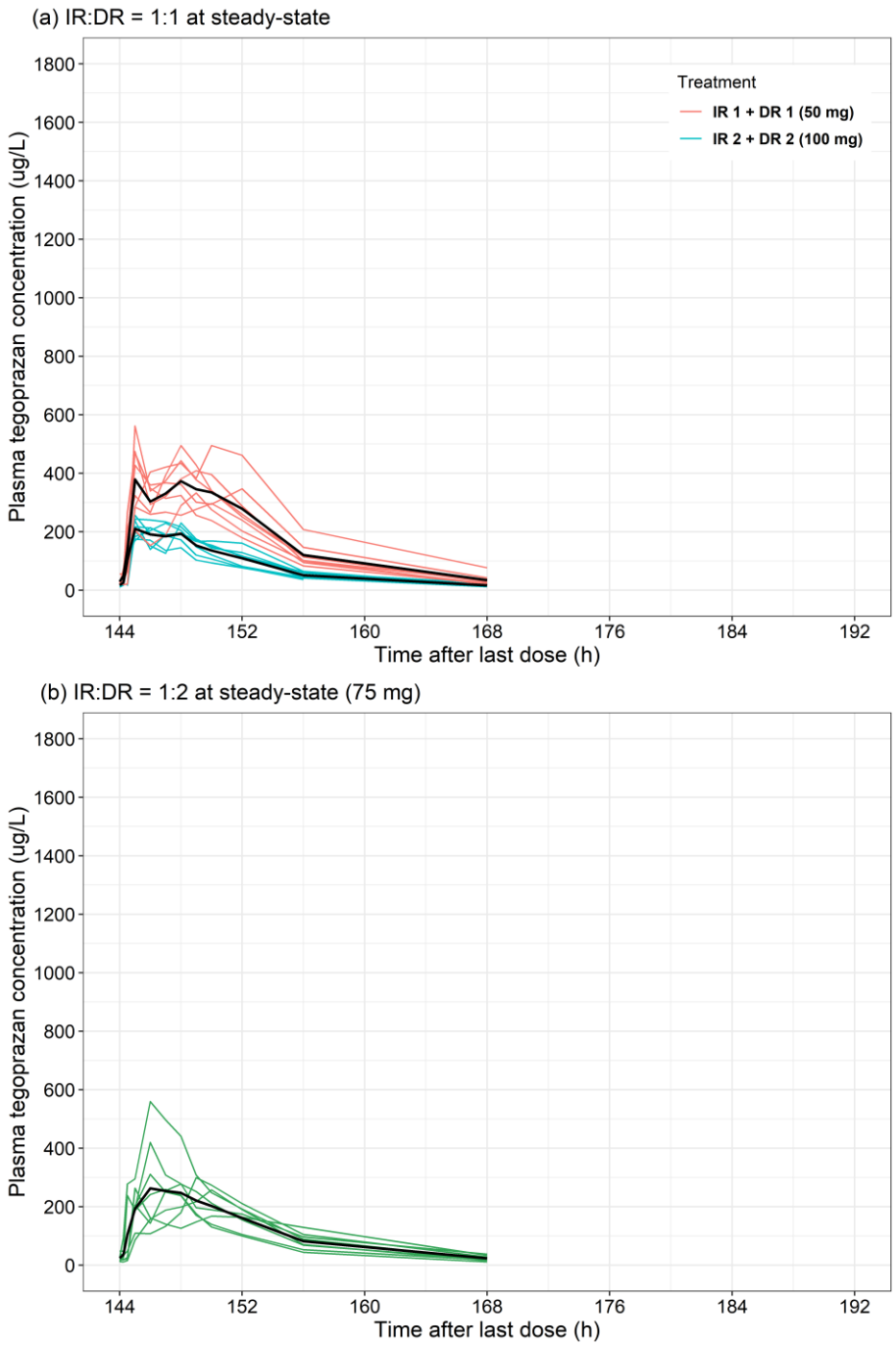


Figure 3 Individual plasma concentrations–time profile following a multiple oral administration of tegoprazan with (a) 1:1 ratio of IR and DR, and (b) 1:2 ratio of IR and DR.

IR, immediate release; DR, delay release

Table 2 Pharmacokinetic parameters after a single oral administration of various tegoprazan immediate and delayed release combinatorial formulations.

Parameter[a]	Tegoprazan 50 mg			Tegoprazan 75 mg		Tegoprazan 100 mg			
	IR 2 (N=6)	IR 1 + DR 1 (N=6)	DR 2 (N=6)	IR 2 + DR 1 (N=6)	IR 1 + DR 2 (N=6)	IR 4 (N=6)	IR 2 + DR 2 (N=6)	IR 1 + DR 3 (N=6)	DR 4 (N=6)
T_{max} (h)	1.00 [0.45–1.00]	1.00 [0.45–1.00]	4.48 [2.00–6.00]	0.73 [0.45–1.00]	2.49 [1.00–5.00]	1.00 [0.45–1.00]	0.73 [0.45–1.00]	3.97 [0.45–8.00]	7.00 [3.97–8.03]
C_{max}, (μg/L)	735.2 ± 365.9	394.0 ± 124.2	212.2 ± 51.5	569.1 ± 143.0	362.9 ± 68.3	1489.6 ± 321.6	903.1 ± 299.8	466.1 ± 143.2	385.2 ± 85.5
GMR[b] (90% CI)	–	0.56 (0.42–0.74)	0.31 (0.23–0.41)	–	–	–	0.59 (0.48–0.73)	0.30 (0.23–0.41)	0.26 (0.21–0.32)
AUC_{last} (μg · h/L)	2972.2 ± 760.7	2857.6 ± 348.1	2640.1 ± 712.8	3486.3 ± 673.9	3449.8 ± 875.3	7137.2 ± 676.4	6639.7 ± 884.7	4526.4 ± 1086.9	5899.4 ± 971.3
GMR (90% CI)	–	0.98 (0.82–1.17)	0.88 (0.74–1.05)	–	–	–	0.93 (0.81–1.05)	0.62 (0.52–0.75)	0.82 (0.72–0.93)
AUC_{inf} (μg · h/L)	3096.6 ± 800.3	3048.0 ± 388.3	2920.6 ± 655.9	3742.4 ± 821.8	3728.0 ± 961.8	7527.4 ± 784.8	7070.5 ± 1045.9	4925.6 ± 986.0	6347.4 ± 825.2
$t_{1/2}$ (h)	5.1 ± 0.3	5.4 ± 0.5	9.4 ± 2.5	5.8 ± 1.1	5.7 ± 0.8	5.6 ± 0.7	8.2 ± 2.6	6.9 ± 1.9	10.4 ± 2.5

Parameter[a]	Tegoprazan 50 mg			Tegoprazan 75 mg		Tegoprazan 100 mg			
	IR 2 (N=6)	IR 1 + DR 1 (N=6)	DR 2 (N=6)	IR 2 + DR 1 (N=6)	IR 1 + DR 2 (N=6)	IR 4 (N=6)	IR 2 + DR 2 (N=6)	IR 1 + DR 3 (N=6)	DR 4 (N=6)
CL/F (L/h)	17.05 ± 4.28	16.65 ± 2.28	17.95 ± 4.5	20.85 ± 4.51	21.14 ± 4.91	13.42 ± 1.52	14.43 ± 2.3	20.89 ± 3.56	16.01 ± 2.35
V_d/F (L)	124.84 ± 28.36	130.42 ± 18.39	231.97 ± 38.95	172.09 ± 32.6	170.91 ± 33.16	107.63 ± 8.93	168.27 ± 50.55	205.34 ± 53.29	235.59 ± 46.27

[a] All parameters are expressed as mean ± standard deviation, except for T_{max}, which is expressed as median [range].

[b] GMR is the ratio of the respective treatments to IR 2 for the 50 mg dose group or the ratio of the respective treatments to IR 4 for the 100 mg dose group.

IR, immediate release; DR, delayed release; GMR, geometric mean ratio; CI, confidence interval; T_{max}, time to reach maximum plasma concentration; C_{max}, maximum plasma concentration; AUC_{last}, area under the concentration–time curve from time zero to the last quantifiable time point; $AUC_{inf,}$ area under the concentration–time curve from time zero to infinity; $t_{1/2}$, terminal elimination half–life; CL/F, apparent clearance; Vd/F, apparent of volume of distribution.

3. Population PK model

Initially, 78 plasma concentrations of tegoprazan were obtained from six subjects to develop a population PK model for tegoprazan IR. The time-concentration profile of tegoprazan IR was appropriately described by a two-compartment model with zero-order absorption with lag time and a linear elimination model (Figure 4, Table S4).

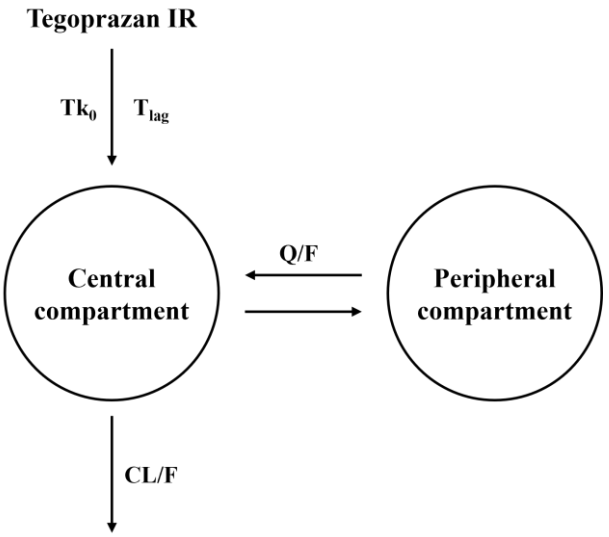


Figure 4 Structural representation of population pharmacokinetic model describing orally administered tegoprazan immediate release formulation.

IR, immediate release; Tk_0, duration of zero-order absorption; T_{lag}, lag time; Q/F, apparent inter-compartmental clearance between the central and peripheral compartments; CL/F, apparent clearance.

Based on the population PK model developed for tegoprazan IR, the most appropriate PK model to explain the combination of tegoprazan IR and DR was a two-compartment model with simultaneous zero-order absorption with different lag times and a linear elimination model with proportional residual variability (Figure 5, Table S5). A total of 1,398 plasma concentrations from 42 subjects were included in the study. Since these two formulations showed differences in release timing with a double-peak profile, we hypothesized that the absorption of the IR and DR formulations would be different. Therefore, tegoprazan IR and DR were constructed using different depots (Figure 5). F was estimated using a logit model based on PK data. The lag time of tegoprazan DR was set as follows:

$$T_{lag,DR} = T_{lag,IR} + diffT_{lag} \quad (5)$$

since absorption of tegoprazan DR formulation showed delayed compared to tegoprazan IR.

The population model estimated the duration of zero-order absorption (Tk_0) approximately 0.38 and 3.35 h for tegoprazan IR and DR, respectively, and lag time of tegoprazan

IR and DR, approximately 0.24 and 1.42 h respectively, which well described the difference absorption phase of tegoprazan IR and DR orally administered. The F values of tegoprazan IR (F_{IR}) and DR (F_{DR}) formulations were estimated to be 94% and 57%, respectively. The final estimates of apparent clearance (CL/F), apparent central volume of distribution (V1/F), apparent peripheral volume of distribution (V2/F), and apparent inter-compartmental clearance between the central and peripheral compartments (Q/F) were 13.86 L/h, 55.9 L, 58.01 L, and 43.87 L/h respectively. The residual variability of the proportional error was 0.24 (2.6% for the RSE). The overall typical parameter value were estimated with a good precision with the RSE of the population PK parameters ranged 0.31–9.68% (Table 3). The IIV of the PK parameters ($Tk_{0,IR}$, $Tk_{0,DR}$, $T_{lag,IR}$, $diffT_{lag}$, CL/F, V1/F, and V2/F) were included assuming log-normal distributions. The PK parameters showed low IIV shrinkage, indicating reduced uncertainty. The eta shrinkage values for $Tk_{0,IR}$, $Tk_{0,DR}$, $T_{lag,IR}$, $diffT_{lag}$, CL/F, V1/F and V2F was −0.8, −7.8, −7.0, −9.5, 1.1, 5.5, and −10%, respectively.

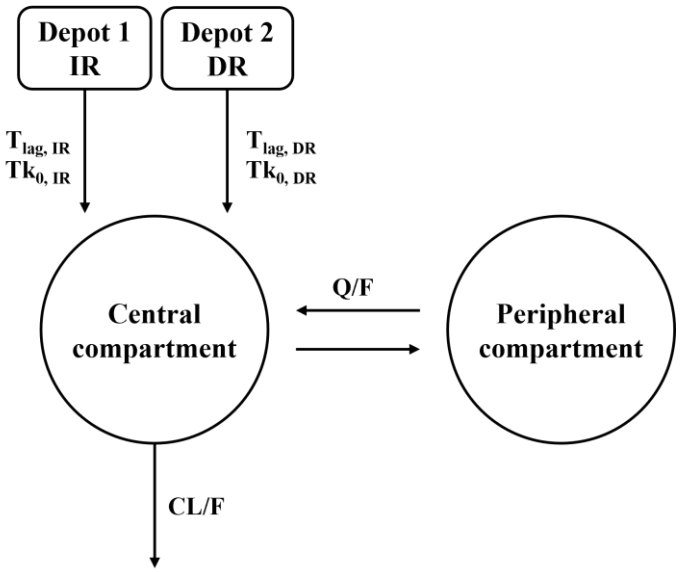


Figure 5 Structural representation of population pharmacokinetic model describing orally administered combination of tegoprazan immediate release and delayed release formulation.

IR, immediate release; DR, delayed release; T_{lag}, lag time, Tk_0, duration of zero-order absorption; ; Q/F, apparent inter-compartmental clearance between the central and peripheral compartments; CL/F, apparent clearance.

Table 3 Parameter estimates and bootstrap results of the final population pharmacokinetic model of tegoprazan immediate release and delayed release formulation.

Parameter	Estimate	RSE (%)	Bootstrap median (95% CI)[a]
Population parameters			
$Tk_{0,IR}$ (h)	0.38	8.5	0.37 (0.264−0.458)
$Tk_{0,DR}$ (h)	3.35	6.63	3.42 (2.823−4.163)
F_{IR}	0.94	0.52	0.92 (0.807−1.0)
F_{DR}	0.57	0.31	0.58 (0.504−0.66)
$T_{lag,IR}$ (h)	0.24	5.0	0.24 (0.21−0.26)
$diffT_{lag}$ (h)	1.2	9.68	1.23 (0.945−1.561)
CL/F (L/h)	13.86	3.61	13.83 (12.118−15.737)
V1/F (L)	55.9	5.31	58.26 (47.647−83.545)
V2/F (L)	58.01	3.04	54.86 (39.229−66.038)
Q/F (L/h)	43.87	6.24	37.71 (4.735−51.576)
Inter−individual variability [b]			
$T_{k0,IR}$ (CV%)	0.5 (52.86)	13.6	0.48 (0.34−0.652)
$T_{k0,DR}$ (CV%)	0.36 (37.06)	14.7	0.35 (0.239−0.449)
$T_{lag,IR}$ (CV%)	0.37 (38.33)	12.25	0.37 (0.27−0.488)
$diffT_{lag}$ (CV%)	0.53 (57.29)	12.07	0.52 (0.422−0.604)
CL/F (CV%)	0.31 (31.6)	8.52	0.3 (0.262−0.335)
V1/F (CV%)	0.34 (34.91)	11.74	0.31 (0.219−0.377)
V2/F (CV%)	0.11 (11.09)	21.64	0.17 (0.092−0.255)
Residual Error			

Parameter	Estimate	RSE (%)	Bootstrap median (95% CI)[a]
Proportional residual error [c] (%)	0.24	2.6	0.23 (0.213–0.255)

[a]Results of bootstrap resampling for 1000 replicates.

[b]Inter–individual variability is presented as standard deviations (coefficient of variation).

[c]Proportional residual error is presented as coefficient of variation.

RSE, relative standard error; CI, confidence interval; $Tk_{0,IR}$, duration of zero–order absorption of tegoprazan immediate release formulation; $Tk_{0,DR}$, duration of zero–order absorption of tegoprazan delayed release formulation; F_{IR}, relative bioavailability of tegoprazan immediate release formulation; F_{DR}, relative bioavailability of tegoprazan delayed release formulation; $T_{lag,IR}$, lag time of tegoprazan immediate release formulation; $diffT_{lag}$, different lag time; CL/F, apparent clearance; V1/F, apparent volume of distribution in the central compartment; V2/F, apparent volume of distribution in the peripheral compartment; Q/F, apparent inter–compartmental clearance between the central and peripheral compartments.

4. Covariate selection

In the final model, several covariates that could describe characteristic specific to subjects and explain the variability were explored to determine the significant effect of tegoprazan on PK. There were no significant covariates affecting the PK parameters.

5. Model evaluation

The basic GOF plots showed that the final model of tegoprazan IR and DR was appropriate (Figure 6). Bootstrap and VPCs showed good predictive performance for the developed model, and the results indicated that the proposed model was appropriately described and robust with good precision. (Table 3, Figure 7) The VPCs showed that the observed plasma concentration data after the last dose were well within the 5^{th}–95^{th} percentiles of the simulated 1,000–replicate population data. Furthermore, the individual plots predicted using the final PK model fit the observed data well (Figure S4).

The medians and 95% CIs of the PK parameters generated by 1,000 bootstrap replicates were similar to the final PK parameter estimates, indicating that the final model was

stable and adequately represented the data(Table 3). Therefore, the final model was robust and precise in characterizing the PK properties of tegoprazan IR and DR.

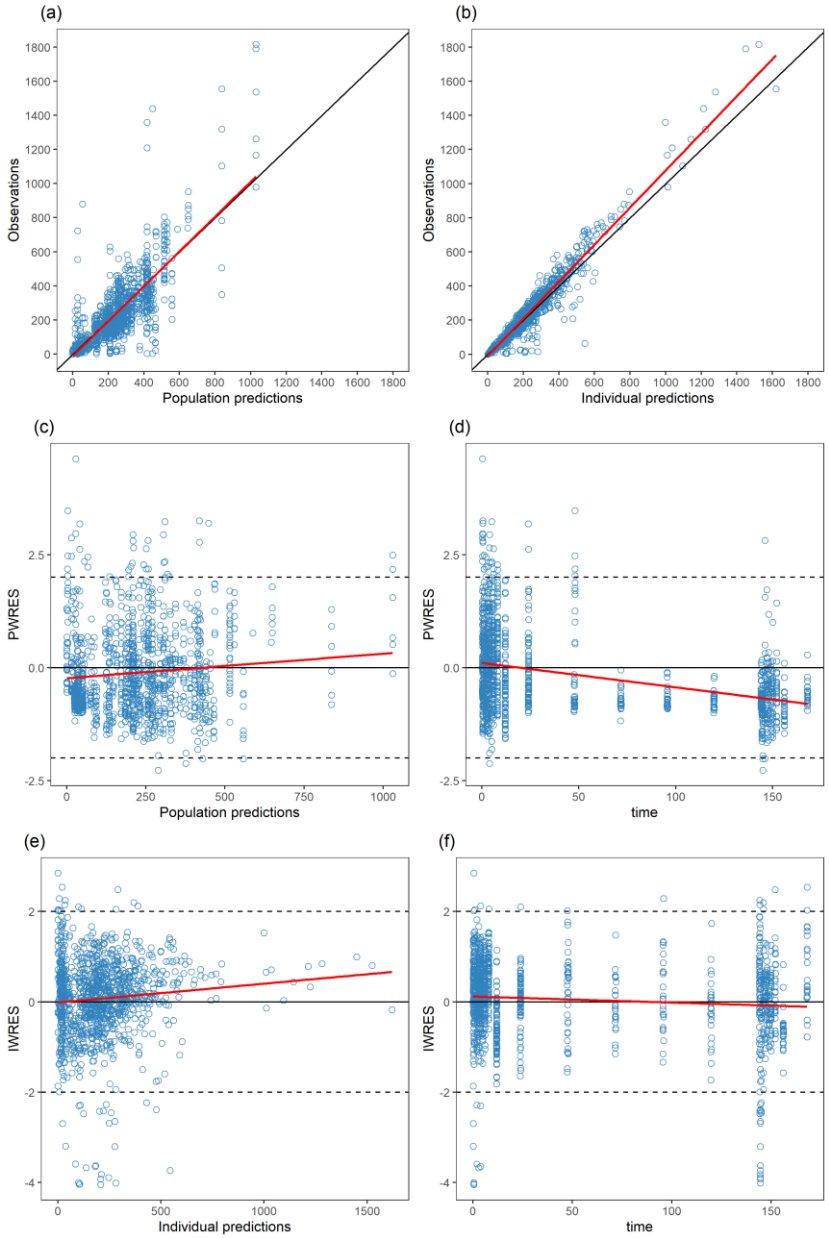


Figure 6 Basic goodness-of-fit plots of final combination tegoprazan model of (a) observations vs. PRED, (b) observations vs. IPRED, (c) PWRES vs. PRED, (d) PWRES vs. time, (e) IWRES vs. PRED, and (f) IWRES vs. time.

PRED, population predictions; IPRED, individual predictions; PWRES, population weighted residuals; IWRES, individual weighted residuals.

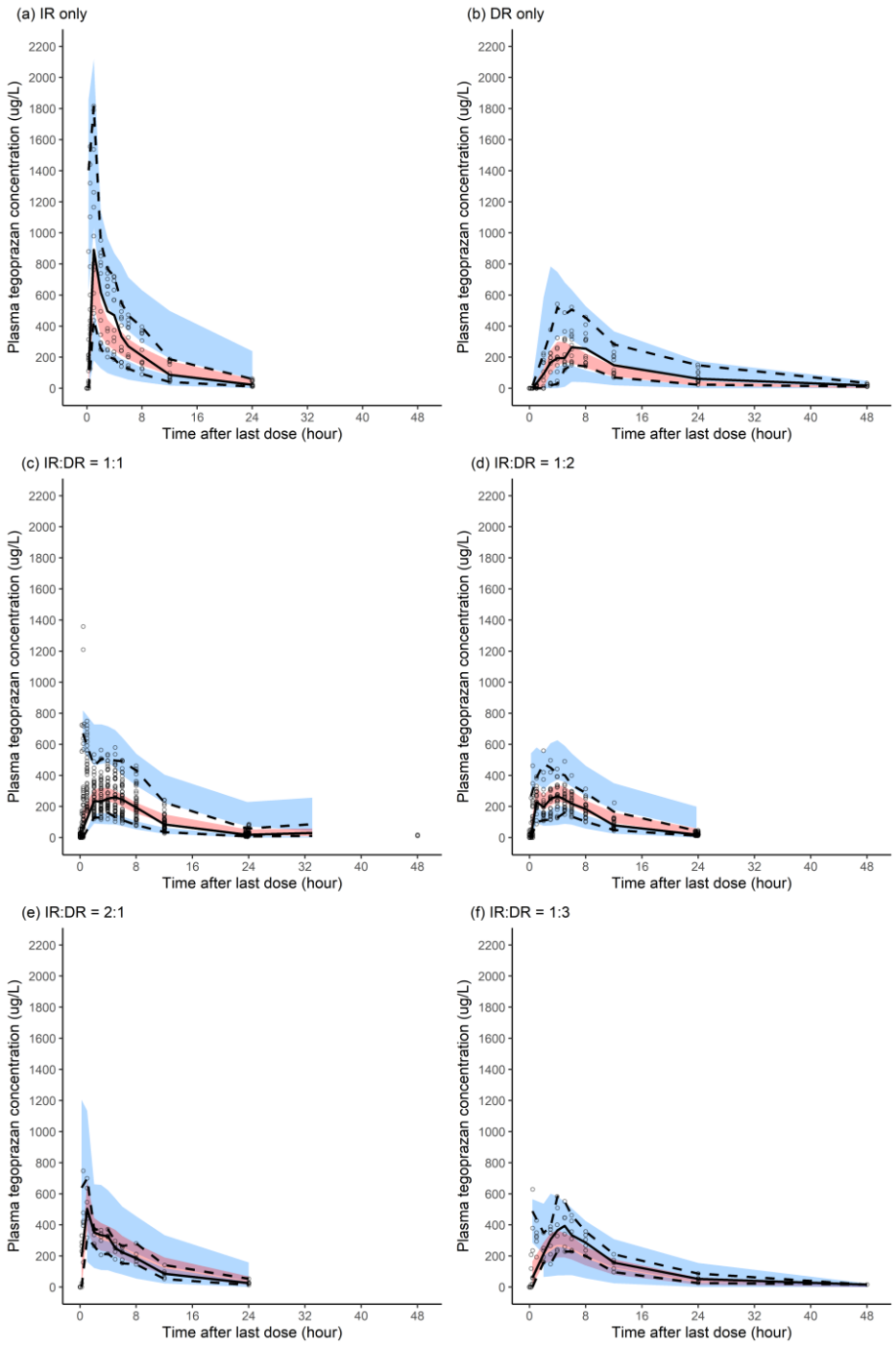


Figure 7 Visual predictive check plot of the final population pharmacokinetic model for tegoprazan after the last dose of (a) IR only, (b) DR only, (c) 1:1 ratio of IR and DR, (d) 1:2 ratio of

IR and DR, (e) 2:1 ratio of IR and DR, and (f) 1:3 ratio of IR and DR.

A total of 1000 simulations were run. The blue-shaded areas represent the 95% confidence intervals of 5th and 95th percentiles of the simulated data, whereas the dash black lines represent the 5th and 95th percentiles of the observed data and solid black lines represent the 50th percentiles of the observed data. IR, immediate release formulation; DR, delayed release formulation.

6. Simulation of combination tegoprazan

The population PK model was applied to predict the concentration profiles of 50, 75, and 100 mg of tegoprazan in a 1:1 ratio of IR and DR formulations, which was determined to be the optimal ratio based on the PK and PD results of a clinical study. Predictions were made for both single and 7-d multiple oral doses in healthy subjects (Figure 8, Table 4). The median C_{max} and AUC_{0-48h} of tegoprazan after single dosing were 478.04 μg/mL and 4035.21 h·μg/mL respectively, and for tegoprazan 75 mg in the IR and DR 1:1 ratio formulation after 7-d multiple oral doing, the median $AUC_{tau,144-168}$ was 4061.93 h·μg/mL. The simulation results suggested that tegoprazan has a good linear PK profile (Figure 9).

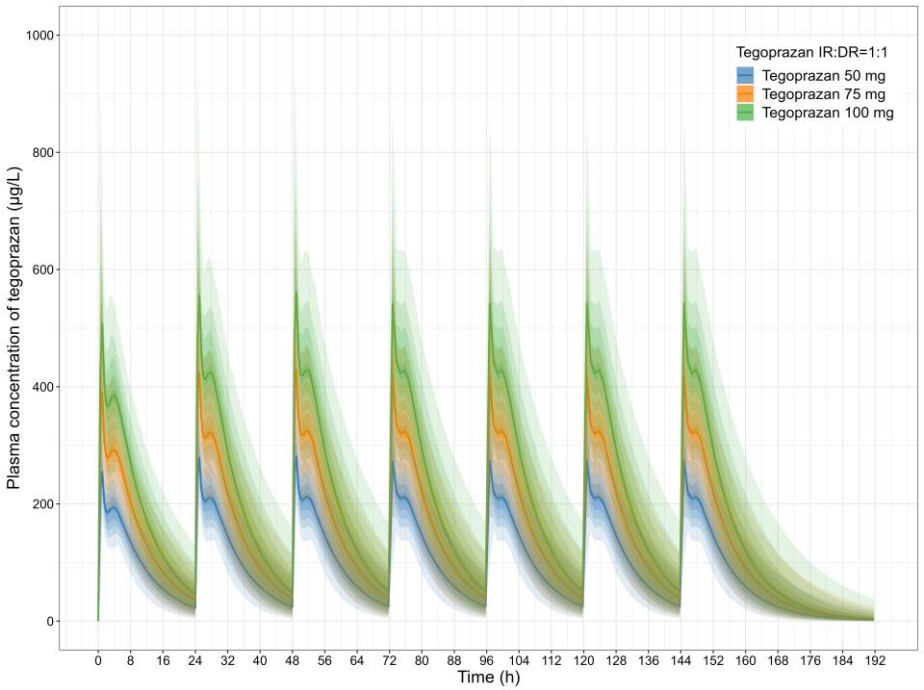


Figure 8 Simulated median concentration-time profile of combination of tegoprazan immediate release and delayed release formulation with a 1:1 ratio in healthy subjects after single and 7-d multiple dosing regimen.

IR, immediate release; DR, delayed release

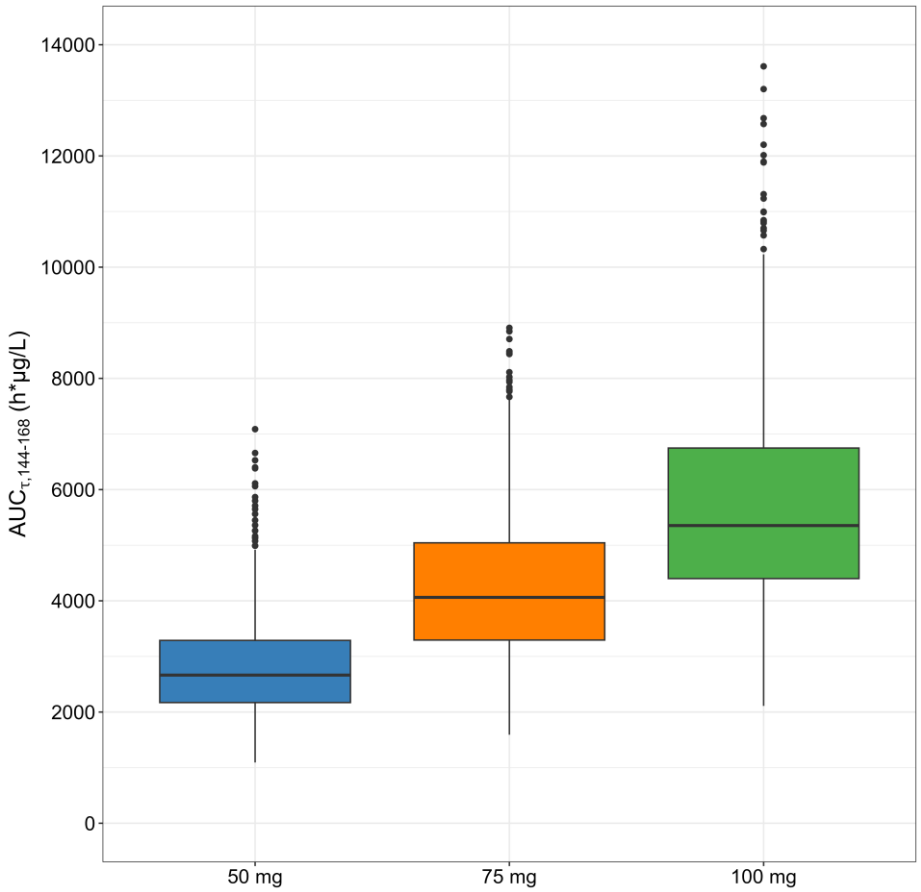


Figure 9 Simulated $AUC_{tau,144-168}$ of combination of tegoprazan immediate release and delayed release formulation with a 1:1 ratio in healthy subjects after 7-d multiple dosing regimen.

$AUC_{tau,144-168h}$, area under the concentration-time curve from time 144 to 168 h after multiple administration

Table 4 Simulated PK parameters of combination of tegoprazan immediate release and delayed release formulation with a 1:1 ratio in healthy subjects after single and 7-day multiple dosing regimen.

Parameter[a]	Tegoprazan 50 mg (IR 25 mg and DR 25 mg)	Tegoprazan 75 mg (IR 37.5 mg and DR 37.5 mg)	Tegoprazan 100 mg (IR 50 mg and DR 50 mg)
C_{max} (μg/mL)	313.98 (133.06-697.33)	478.04 (153.05-1123.51)	625.73 (278.01-1534.47)
AUC_{0-48h} (h·μg/mL)	2628.85 (1088.14-5900.82)	4035.21 (1591.03-8195.61)	5318.14 (2111.44-12095.56)
$AUC_{tau,144-168h}$ (h·μg/mL)	2664.09 (1093.31-7086.68)	4061.93 (1592.38-8908.5)	5353.44 (2110.47-13611.29)

[a] All parameters are expressed as median (min-max).

IR, immediate release; DR, delayed release; GMR, geometric mean ratio; C_{max}, maximum plasma concentration; AUC_{0-48h}, area under the concentration-time curve from time zero to 48 h after administration; $AUC_{tau,144-168h}$, area under the concentration-time curve from time 144 to 168 h after multiple administration.

Discussion

Overcoming the limitations associated with PPIs has become an important challenge in the management of GERD.[3] To address these limitations, various modifications to PPI formulations have been developed, including dexlansoprazole MR (Dexilant™, Takeda Global Research & Development Center, Inc., Deerfield, IL, USA), a modified dual-release formulation of dexlansoprazole, the R-enantiomer of lansoprazole, belonging to the PPI class.[41] Dexlansoprazole MR exhibits delayed drug exposure, with multipeak plasma concentration-time profiles, and greater gastric acid suppression as a result of prolonged gastrointestinal absorption.[41] Furthermore, dexlansoprazole MR 30 mg is effective in treating symptomatic GERD in patients with moderate-to-very severe nocturnal heartburn.[42] However, despite these formulation modifications, certain limitations of PPIs remain to be addressed, including a slow onset of action attributable to the specific mechanism of action that necessitates acid activation.[28] In addition, even a high dose of dexlansoprazole MR failed to provide adequate control of nighttime pH > 4, which requires improvement.[43] It is consequently anticipated that tegoprazan can overcome the

current limitations of modified PPIs, whilst conferring similar benefits based on a dual-release MR formulation consisting of a combination of IR and DR formulations.

In the present study, we developed a population PK model specifically for a tegoprazan IR formulation. The purpose of this model was to gain insights into the PK characteristics of conventional tegoprazan formulation. The conventional tegoprazan IR formulation was well characterized by a two-compartment model with zero-order absorption with lag time and a linear elimination. Based on this tegoprazan IR model, we constructed a final model for the combination of tegoprazan IR and DR formulations using data from 42 healthy subjects. The final model, a two-compartment PK model with simultaneous zero-order absorption with different lag times and a linear elimination, adequately described the PK profiles of both tegoprazan IR and DR formulations, as well as their combination. This conclusion is supported by the high precision observed in the GOFs, VPCs, and bootstrap results. Furthermore, we conducted simulations for a combination of tegoprazan at doses of 50, 75, and 100 mg with a 1:1 ratio of IR and DR formulations. In a clinical study, a 1:1 ratio of tegoprazan IR and DR

formulations resulted in stronger gastric acid suppression, suggesting that this is as the optimal ratio. The simulated PK parameters were similar to those observed in a clinical study, indicating that our model accurately described the PK profiles of the tegoprazan IR and DR formulation in healthy subjects.

The occurrence of a double peak in the absorption phase when the tegoprazan IR and DR formulations were co-administered was well captured by the model's incorporation of different lag times (T_{lag}) for the IR and DR formulations. The tegoprazan DR formulation was designed to be released in a pH-dependent manner, making it dissolve relatively slowly compared with the IR formulation. Therefore, when tegoprazan IR and DR formulations were co-administered, tegoprazan IR was initially released as an active pharmaceutical ingredient, followed by the subsequent release of tegoprazan DR. This information provides valuable insights into the combined administration of IR and DR tegoprazan formulations. By administering both formulations together, gastric acid suppression could be maintained for a longer duration than with tegoprazan IR alone. These findings are supported by the results of a clinical study and population PK modeling, indicating the potential benefits of the combination of

tegoprazan IR and DR in achieving sustained gastric acid suppression.

In our study, we evaluated clinical factors such as age, height, weight, and BMI as potential covariates for the PK parameters of tegoprazan. However, we found that these factors had no significant effect on the PK parameters. This suggests that variations in age, height, weight, and BMI do not warrant dose adjustment for tegoprazan. These findings are consistent with the available efficacy and safety data for tegoprazan, indicating that these factors have no effect on the efficacy or safety of tegoprazan.[17, 19]

The results of a clinical study indicated that the combination of tegoprazan IR and DR at a 1:1 ratio showed promising efficacy as an alternative to the conventional tegoprazan IR formulation, providing adequate gastric acid suppression. The combination of tegoprazan IR and DR at a 1:1 ratio formulation induced sustained gastric acid suppression for 24 h with systemic exposure, similar to that observed with marketed tegoprazan (Table 2, Figure S2). Specifically, 100 mg of a combination of tegoprazan IR and DR formulations demonstrated adequate gastric acid suppression in clinical study.

However, although tegoprazan does not exhibit hepatotoxicity, caution is warranted regarding high-dose administration because of previous experience with other P-CABs such as SCH28080, YH48080, and AZD0865. [4, 44-46] Therefore, further evaluation of combination of tegoprazan IR and DR formulation in a 1:1 ratio at doses ranging 50-100 mg was required in clinical study. In this study, we conducted simulations to assess the PK profiles of a combination of tegoprazan IR and DR formulations at doses of 50-100 mg following single- and multiple-dose regimens in healthy subjects. The simulated results showed that exposure to a combination of tegoprazan IR and DR at a 1:1 ratio was similar between the 50 and 100 mg after single and multiple administrations, respectively, which is consistent with the findings from the clinical study. Furthermore, the simulations revealed the PK profiles for 75 mg tegoprazan in a combination at a 1:1 ratio of IR and DR formulations, which were not evaluated in the clinical study. Given the clear exposure-response relationship and expected response using the E_{max} model (Figure S5),[17, 18] it can be concluded that 75 mg of tegoprazan IR and DR in a 1:1 ratio formulation would achieve sufficient gastric acid suppression.

However, this study has several additional considerations. First, this population PK model was based solely on data from healthy subjects and did not include data from patients with acid-related gastric diseases such as GERD. It is likely that the absorption profiles of tegoprazan would differ between healthy subjects and patients with gastrointestinal diseases. Secondly, the pooled data used to construct the model were insufficiently large. Although a valid model was developed using the data from this clinical study, including additional data from other clinical studies would enhance the robustness and generalizability of the population PK model. Third, the model only included male subjects. Although gastric acid secretion is generally similar between the sexes,[47-49] it is possible that there may be differences in the PK profiles of tegoprazan between males and females. Therefore, further studies that include female subjects are essential to evaluate the potential impact of sex on the PK characteristics of tegoprazan and ensure the generalizability of the model to both male and female populations. Finally, the model included only PK data and did not incorporate PD information. Although the model does not directly incorporate PD data, the known relationship between tegoprazan

dose, exposure, and response allows for a reasonable extrapolation of its gastric acid suppression capabilities. Consequently, it is necessary to include patients with GERD or other gastrointestinal conditions and female in the PK model. By doing so, population PK modeling can be validated, and a more comprehensive understanding of the PK characteristics of tegoprazan can be obtained by considering the influence of sex and specific disease populations.

Conclusion

This study is the first attempt to evaluate a population PK model for tegoprazan that incorporates its absorption characteristics. Notably, the model included the co-administration of a tegoprazan DR formulation, enabling the prediction of the PK profiles for various combinations of tegoprazan IR and DR formulations. The developed population PK model, employing a two-compartment model with simultaneous zero-order absorption with different lag times and a linear elimination, effectively elucidated the PK of tegoprazan IR and DR formulations. This model has the potential to determine the optimal ratio of tegoprazan IR to DR formulations, which can significantly enhance the clinical efficacy and treatment outcomes of tegoprazan for gastric acid-related disorders. Consequently, a combination of tegoprazan IR and DR at a 1:1 ratio is expected to achieve sufficient gastric acid suppression.

Supplementary Material

1. PK parameter after multiple administration

Table S1 Pharmacokinetic parameters after 7-day multiple oral administration of various tegoprazan immediate and delayed release combinatorial formulations.

Parameter[a]	50 mg IR 1 + DR 1 (N=8)	75 mg IR 1 + DR 2 (N=8)	100 mg IR 2 + DR 2 (N=8)
$T_{max,ss}$ (h)	1.0 [1.0-4.0]	2.5 [1.0-6.0]	2.5 [1.0-6.0]
$C_{max,ss}$ (μg/L)	225.3 ± 24.4	330.8 ± 106.5	444.0 ± 88.5
$AUC_{tau,144-168h}$ (μg · h/L)	1876.7 ± 314.2	2667.7 ± 580.5	4060.9± 928.5
$t_{1/2,ss}$ (h)	5.3 ± 1.1	5.7 ± 1.0	5.4 ± 0.8
CL_{ss}/F (L/h)	27.3 ± 4.7	29.18 ± 5.7	25.6 ± 5.2
$V_{d,ss}/F$ (L)	206.4 ± 47.4	239.57 ± 50.8	197.2 ± 43.1
PTF (%)	1645.7 ± 519.3	1813.4 ± 632.9	1720.9 ± 577.9
Accumulation ratio	1.1 ± 0.1	1.0 ± 0.1	1.1 ± 0.2

[a] All parameters are expressed as mean ± standard deviation, except for $T_{max,ss}$, which is expressed as median [range].

IR, immediate release; DR, delayed release; $T_{max,ss}$, time to reach maximum plasma concentration at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; $AUC_{tau,144-168h}$, area under the concentration–time curve from time 144 to 168 h after multiple administration; $t_{1/2,ss}$, terminal elimination half-lifeat steady state; CL_{ss}/F, apparent clearance at steady state; $V_{d,ss}/F$, apparent of volume of distribution at steady state.

2. PD in clinical study

- Method of PD evaluation

The 24-hour intragastric pH was monitored using a Digitrapper^{TM} pH-Z recorder (Medtronic, Inc., Dublin, Ireland) and VersaFlex® pH Catheters (Alpine Biomed Corp., Natus Medical Inc., Pleasanton, CA, USA) on a day before the first administration (Day -1) and retained as the as baseline. And then it was measured on Day 1, 8, and 15 following single administration, and on Day 1 and 7 following multiple administration. The pH catheter, which was approximately 6 mm in diameter, was inserted through the nose into gastrointestinal tract and connected to a recorder. To reduce discomfort during catheter insertion and to minimize foreign body sensation, 10% lidocaine (Angelcaine Spray, Dong In Dang Pharmaceutical Co., Ltd., Republic of Korea), was used as an anaesthetic. Given the inconvenience caused by 24-h intragastric pH monitoring and the lack of significant changes in intragastric pH during this short periods[50, 51], the baseline intragastric pH was measured only during the first period. Intragastric pH values were recorded every second, and the parameters observed for 24-hour and night-time period (i.e., percentage of the time above pH 4 (%

Time pH ≥ 4), median pH, and mean pH) were determined for each subject. The % Time pH ≥ 4 was compared in 50 mg and 100 mg dose group in the same manner of PK using the Wilcoxon signed–rank test or Mann–Whitney test, and 95% CIs for the difference in median % Time pH ≥ 4 of each treatment compared to IR were calculated.

- Results of PD

Intragastric pH profiles at baseline were similar among cohorts, with the mean ± standard deviation values for baseline intragastric pH being 2.38 ± 0.22, 2.24 ± 0.37, 2.39 ± 0.61, 2.37 ± 0.59, 2.27 ± 0.22, and 2.28 ± 0.33 in cohort A, B, C, D, E, and F, respectively.

Tegoprazan promoted a rapid suppression of gastric acid secretion in all treatments, the mean intragastric pH reached above 4 approximately 1 h following administration. However, in groups treated with DR alone (i.e., DR 2 and DR 4), intragastric pH remained less than 4 until 4 h, having initially reached values above 4 immediately following administration (Figure S1).

As the dose increased, the duration of gastric acid suppression also increased (Figure S4). In the 50 mg dose group

following single administration, gastric acid suppression following treatment with IR 1 + DR 1 tend to be longer than that following treatment with IR alone, although the difference was not statistically significant (% Time pH ≥ 4: 59% for IR 1 + DR 1 vs. 52% for IR 2, $P = 0.2188$, median difference (95% CI): 7.7% (−6.92–22.27)). In the 100 mg dose group following single administration, IR 2 + DR 2 showed statistically greater gastric acid suppression than IR alone (% Time pH ≥ 4: 85% for IR 2 + DR 2 vs. 70% for IR 4, $P < 0.05$, median difference (95% CI): 13.3% (8.92–22.19)) (Figure S2 and Table S2). Following multiple administrations, gastric acid suppression was found to be similar to that observed after single administration (Table S3).

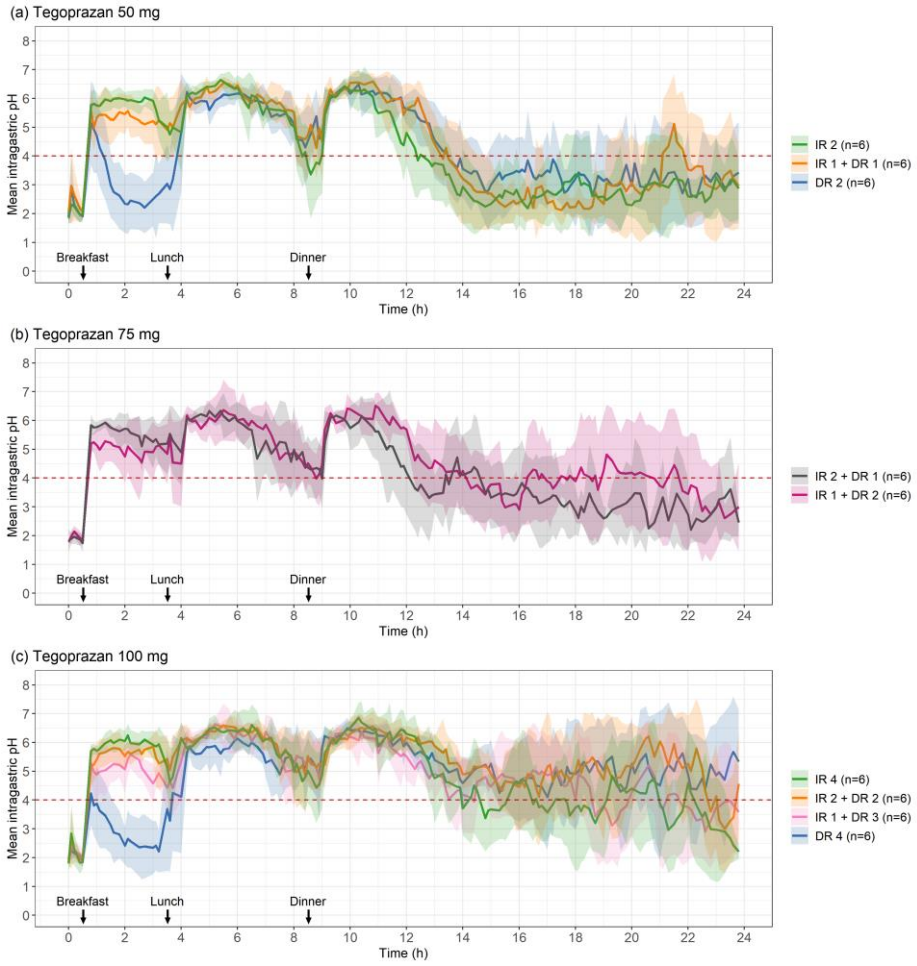


Figure S1 Mean intragastric pH–time profiles following a single oral administration of various tegoprazan immediate and delayed release combinatorial formulations of (a) 50 mg, (b) 75 mg, and (c) 100 mg.

The background shadow represents standard deviation. The time of meals was presented using arrows. IR, immediate release; DR, delayed release.

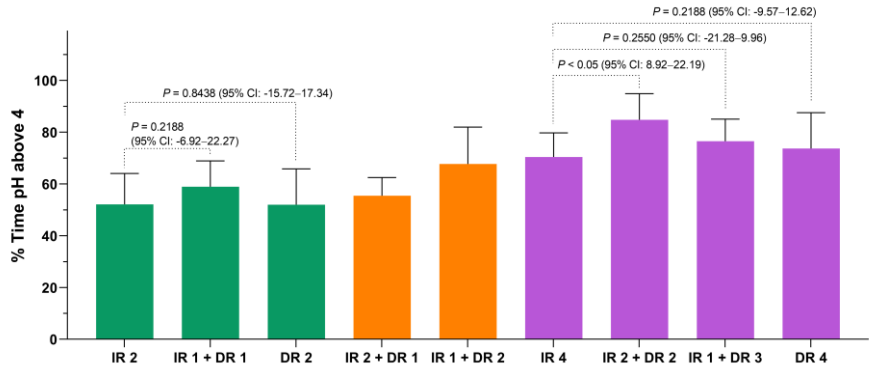


Figure S2 Mean percentage of the time above pH 4 (% Time pH ≥ 4) for 24 h following a single oral administration of various tegoprazan immediate and delayed release combinatorial formulations.

The error bars represent standard deviation. IR, immediate release; DR, delayed release.

Table S2 Pharmacodynamic parameters following a single oral administration of various tegoprazan immediate and delayed release combinatorial formulations

Parameter[a]	Tegoprazan 50 mg			Tegoprazan 75 mg		Tegoprazan 100 mg			
	IR 2 (N=6)	IR 1 + DR 1 (N=6)	DR 2 (N=6)	IR 2 + DR 1 (N=6)	IR 1 + DR 2 (N=6)	IR 4 (N=6)	IR 2 + DR 2 (N=6)	IR 1 + DR 3 (N=6)	DR 4 (N=6)
% Time pH ≥ 4 (%)	52.13 ± 11.96	58.91 ± 10.03	51.99 ± 13.81	55.46 ± 7.00	67.75 ± 14.19	70.44 ± 9.31	84.79 ± 10.13	76.55 ± 8.49	73.73 ± 13.84
Median pH	4.01 ± 1.06	4.74 ± 0.64	3.84 ± 1.01	4.44 ± 0.61	4.81 ± 0.58	5.32 ± 0.53	5.81 ± 0.22	5.24 ± 0.42	5.25 ± 0.71
Mean pH	4.19 ± 0.43	4.37 ± 0.40	4.12 ± 0.58	4.27 ± 0.29	4.57 ± 0.42	4.91 ± 0.43	5.40 ± 0.33	4.92 ± 0.38	4.94 ± 0.52

[a]All parameters are expressed as mean ± standard deviation

IR, immediate release; DR, delayed release; % Time, pH ≥ 4, percentage of the time above pH 4.

Table S3 Pharmacodynamic parameters following multiple oral administration of various tegoprazan immediate and delayed release combinatorial formulations

Parameter[a]	50 mg IR 1 + DR 1 (N=8)	75 mg IR 1 + DR 2 (N=8)	100 mg IR 2 + DR 2 (N=8)
Single administration			
% Time pH ≥ 4 (%)	54.68 ± 9.96	69.41 ± 15.4	54.56 ± 14.46
Median pH	4.34 ± 1.04	5.17 ± 0.96	4.36 ± 1.36
Mean pH	4.3 ± 0.43	4.92 ± 0.67	4.36 ± 0.64
Multiple administration			
% Time pH ≥ 4 (%)	61.76 ± 13.02	81.86 ± 14.76	66.26 ± 20.29
Median pH	4.65 ± 0.93	5.62 ± 0.44	4.8 ± 1.11
Mean pH	4.4 ± 0.5	5.32 ± 0.56	4.73 ± 0.83

[a]All parameters are expressed as mean ± standard deviation

DR, delayed release; IR, immediate release; % Time, pH ≥ 4, percentage of the time above pH 4.

3. PK–PD relationship

- Method of PK–PD relationship evaluation

The PK–PD relationship was evaluated using the sigmoid E_{max} model consisted by AUC (i.e., AUC_{last} in single administration or AUC_{tau} in multiple administration) and % Time pH ≥ 4 for 24 h following each administration.

$$E = \frac{E_{max} \times AUC^{\gamma}}{EC_{50}{}^{\gamma} + AUC^{\gamma}}$$

The parameters including drug effect (E), maximum effect (E_{max}), half maximal effective concentration (EC_{50}) and Hill coefficient (γ) was estimated using PROC NLIN in SAS® Version 9.4 (SAS Institute Inc., Cary, NC, USA).

- Results of PK–PD relationship

The relationship between PK and PD was observed to show an increase in % Time pH ≥ 4 for 24 h, which then reached a plateau as AUC increased following each administration. The results revealed that the exposure–response correlation was well–fitted to the sigmoid E_{max} model. The E_{max}, EC_{50} and γ were estimated as 80.1 %, 1991 μg·h/L, and 2.6, respectively (Figure S3).

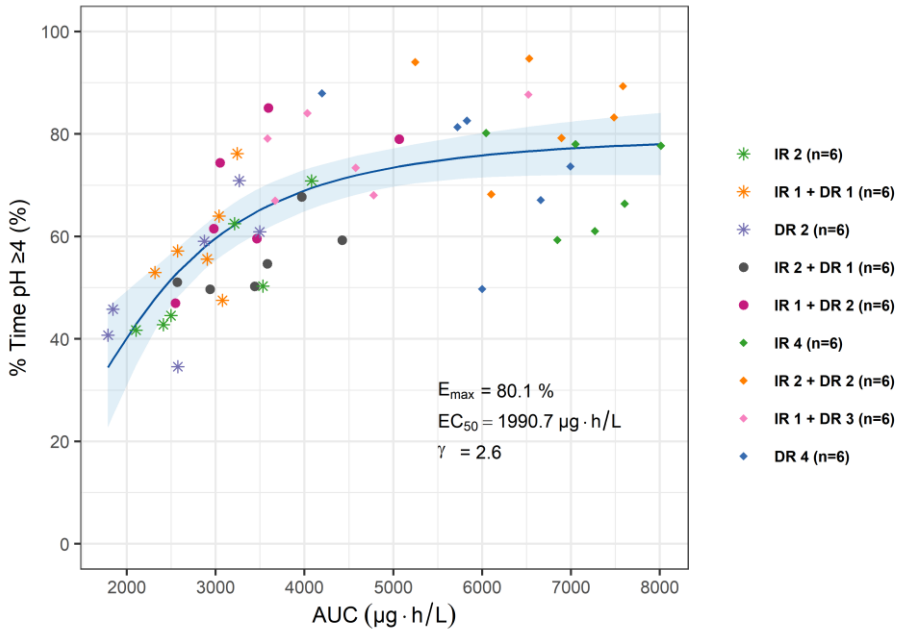


Figure S3 PK–PD relationships of tegoprazan. Mean percent of the time above pH 4 (% Time pH ≥ 4) for 24 h is plotted vs. AUC following each administration

IR, immediate release; DR, delayed release.

4. Monolix macro code for struct the final PK model

```
DESCRIPTION:

input = (Tk01, Tk02, F1, F2, Tlag1, diffTlag2, Cl, V1, Q, V2)


EQUATION:

odeType = stiff

; Parameter transformations

V = V1

k = Cl/V1

k12 = Q/V1

k21 = Q/V2

Tlag2 = Tlag1 + diffTlag2


PK:

compartment(cmt = 1, volume = V1, concentration = Cc)

depot(adm=1, target=Cent, p=F1, Tlag=Tlag1, Tk0=Tk01)

depot(adm=2, target=Cent, p=F2, Tlag=Tlag2, Tk0=Tk02)

absorption(cmt=1, Tlag=Tlag1, Tk0=Tk01, p=F1, adm=1)
```

```
absorption(cmt=1, Tlag=Tlag2, Tk0=Tk02, p=F2, adm=2)

peripheral(k12, k21)

elimination(cmt = 1, k)


EQUATION:

; Initial condition

t_0 = 0

Cent_0 = 0

Peri_0 = 0


;--Ordinary Differential Equations

ddt_Cent = - k*Cent + k21*Peri - k12*Cent

ddt_Peri = k12*Cent - k21*Peri

Cc = Cent/V1


OUTPUT:

output = (Cc)
```

5. Population PK model development process

Table S4 Development process of population pharmacokinetic model of tegoprazan immediate release formulation.

Model	Description	OFV	AIC	BIC
One-compartment with linear elimination				
111	First-order absorption	788.47	802.47	805.87
112	First-order absorption with lag time	714.94	732.94	737.3
121	Zero-order absorption	780.23	794.23	797.62
122	Zero-order absorption with lag time	727.83	745.83	750.19
Two-compartment with linear elimination				
211	First-order absorption	747.5	769.5	774.83
212	First-order absorption with lag time	619.89	645.89	652.19
221	Zero-order absorption	723.54	745.54	750.87
222	Zero-order absorption with lag time (final)	581.6	607.6	631.29
Three-compartment with linear elimination				
311	First-order absorption	749.09	779.09	786.36
312	First-order absorption with lag time	617.97	651.97	660.21

Model	Description	OFV	AIC	BIC
321	Zero-order absorption	723.8	753.8	761.08
322	Zero-order absorption with lag time	528.32	562.32	570.56

OFV, observation function value; AIC, Akaike information criterion; BIC, Bayesian information criterion

Table S5 Development process of population pharmacokinetic model of tegoprazan immediate release and delayed release formulation.

Model	IIV	OFV	△OFV	AIC	△AIC	BIC	△BIC	Condition number[a]
Zero-order absorption with lag time and zero-order absorption with different lag time								
101 (base)	$Tk_{0,IR}$, ka, F_{IR}, F_{DR}, $T_{lag,IR}$, $diffT_{lag}$, CL/F, V1/F, Q/F, V2/F	6942.37	0	6984.37	0	7033.86	0	482.06
102	$Tk_{0,IR}$, ka, $T_{lag,IR}$, $diffT_{lag}$, CL/F, V1/F, V2/F	6947.49	5.12	6983.49	41.12	7025.91	83.54	13.47
103	$Tk_{0,IR}$, ka, $T_{lag,IR}$, $diffT_{lag}$, CL/F, V1/F	6950.38	8.01	6984.38	42.01	7024.44	82.07	7.93
Zero-order absorption with lag time and zero-order absorption with different lag time								
201 (base)	$Tk_{0,IR}$, $Tk_{0,DR}$, F_{IR}, F_{DR}, $T_{lag,IR}$, $diffT_{lag}$, CL/F, V1/F, Q/F, V2/F	6963.08	0	7005.08	0	7054.57	0	130.35
202	$Tk_{0,IR}$, $Tk_{0,DR}$, $T_{lag,IR}$, $diffT_{lag}$, CL/F, V1/F, V2/F	6962.42	−0.66	6998.42	−6.66	7040.84	−13.7	4.95

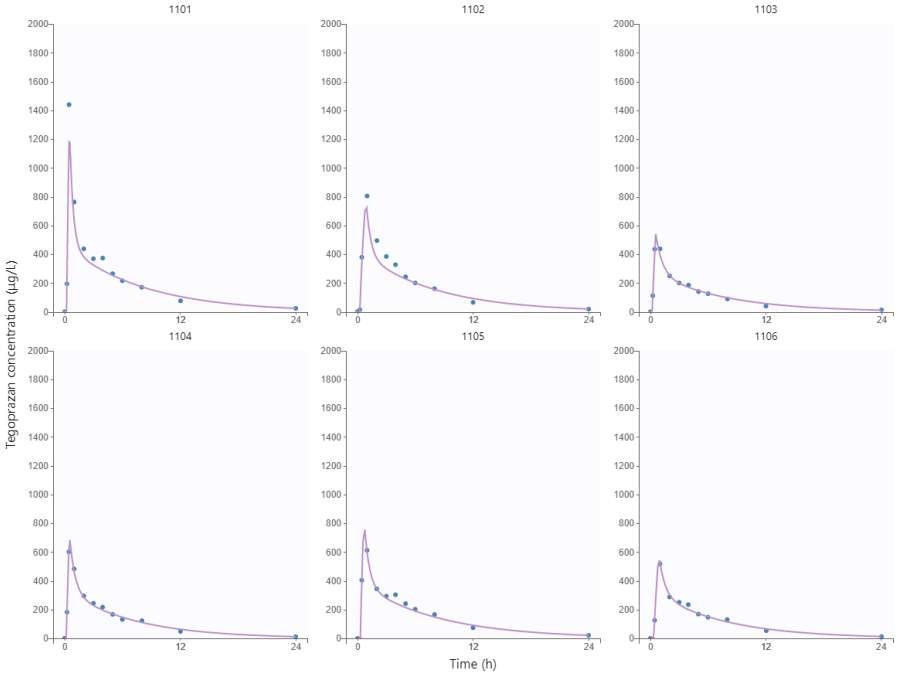
Model	IIV	OFV	△OFV	AIC	△AIC	BIC	△BIC	Condition number[a]
203 (final, adjust initial estimates)	$Tk_{0,IR}$, $Tk_{0,DR}$, $T_{lag,IR}$, $diffT_{lag}$, CL/F, V1/F, V2/F	6958.29	−4.79	6994.29	−10.8	7036.71	−17.9	8.87

[a]Condition number is computed as the ratio of the highest and lowest eigenvalues.

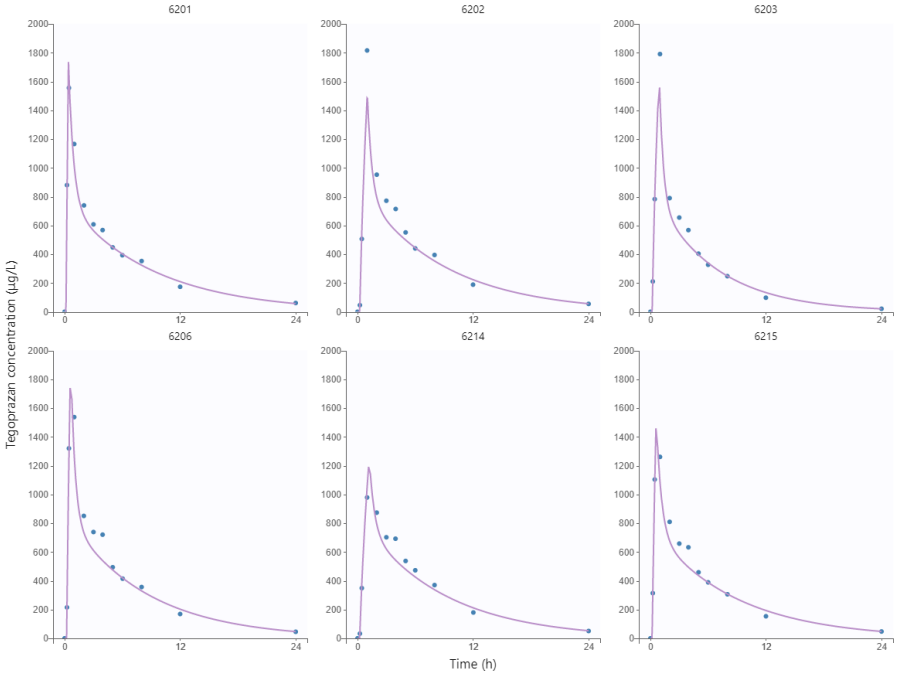
OFV, observation function value; AIC, Akaike information criterion; BIC, Bayesian information criterion; RSE, relative standard error; $Tk_{0,IR}$, duration of zero−order absorption of tegoprazan immediate release formulation; $Tk_{0,DR}$, duration of zero−order absorption of tegoprazan delayed release formulation; F_{IR}, relative bioavailability of tegoprazan immediate release formulation; F_{DR}, relative bioavailability of tegoprazan delayed release formulation; $T_{lag,IR}$, lag time of tegoprazan immediate release formulation; $diffT_{lag}$, different lag time; CL/F, apparent clearance; V1/F, apparent volume of distribution in the central compartment; V2/F, apparent volume of distribution in the peripheral compartment; Q/F, apparent inter−compartmental clearance between the central and peripheral compartments.

6. Individual fitting plots for the final PK model

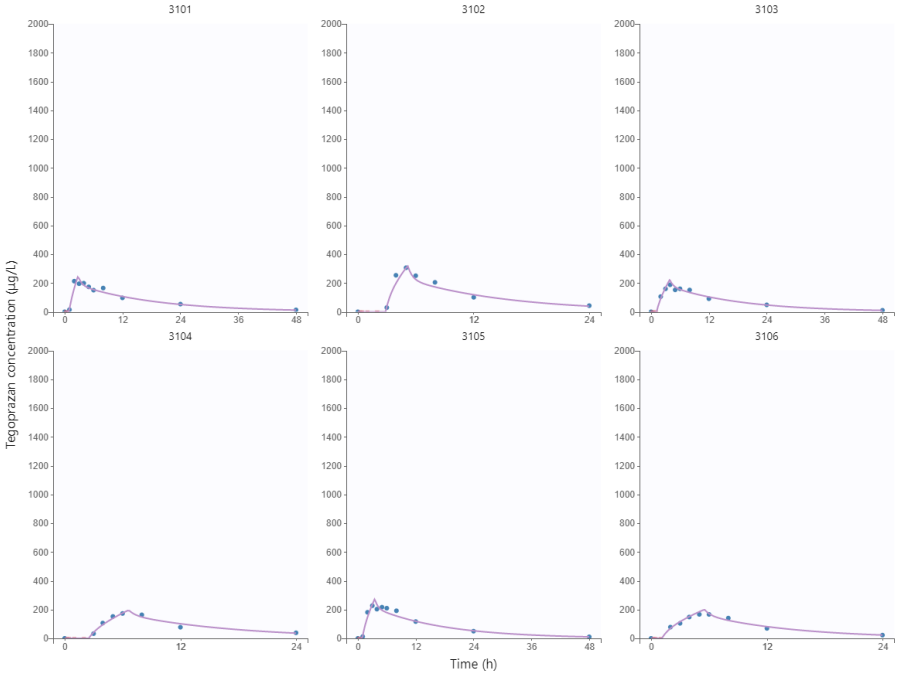
(a) IR 2 (50 mg)



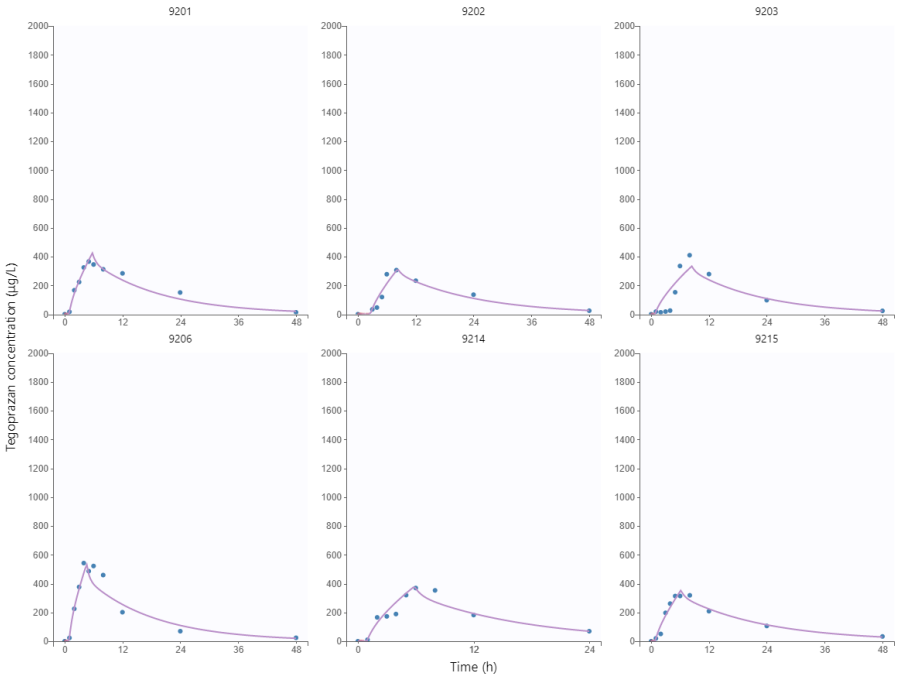
(b) IR 4 (100 mg)



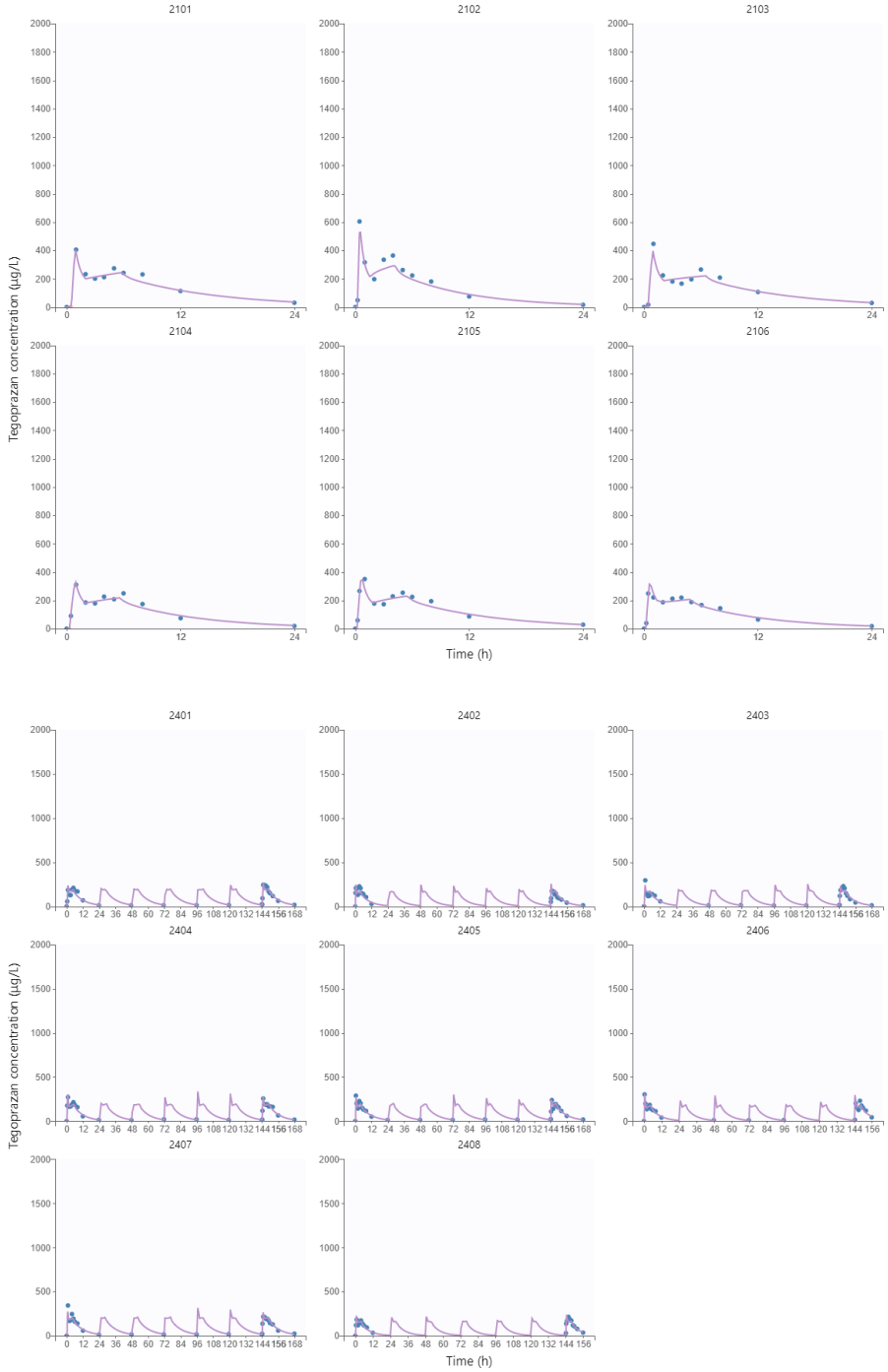
(c) DR 2 (50 mg)



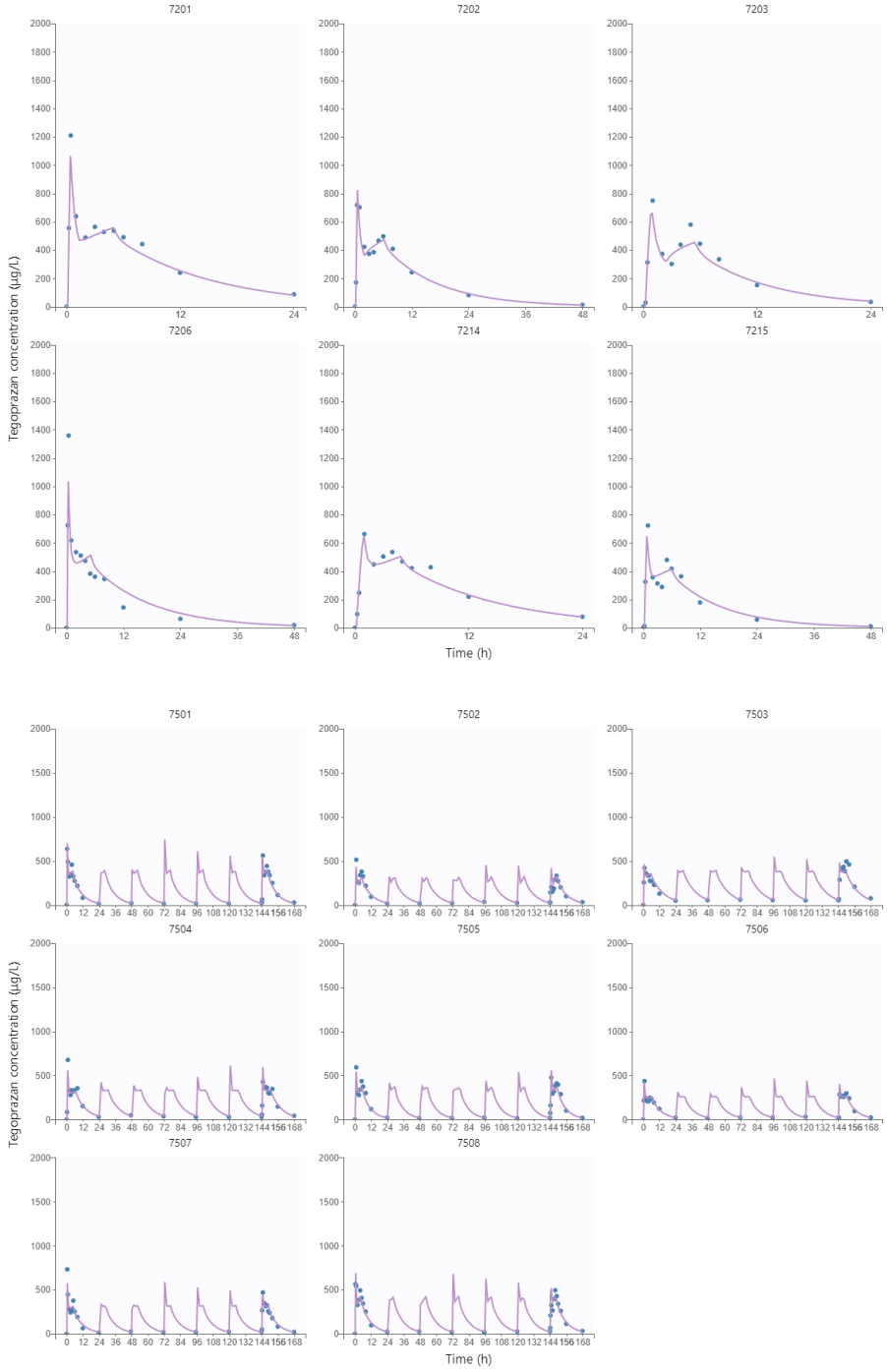
(d) DR 4 (100 mg)



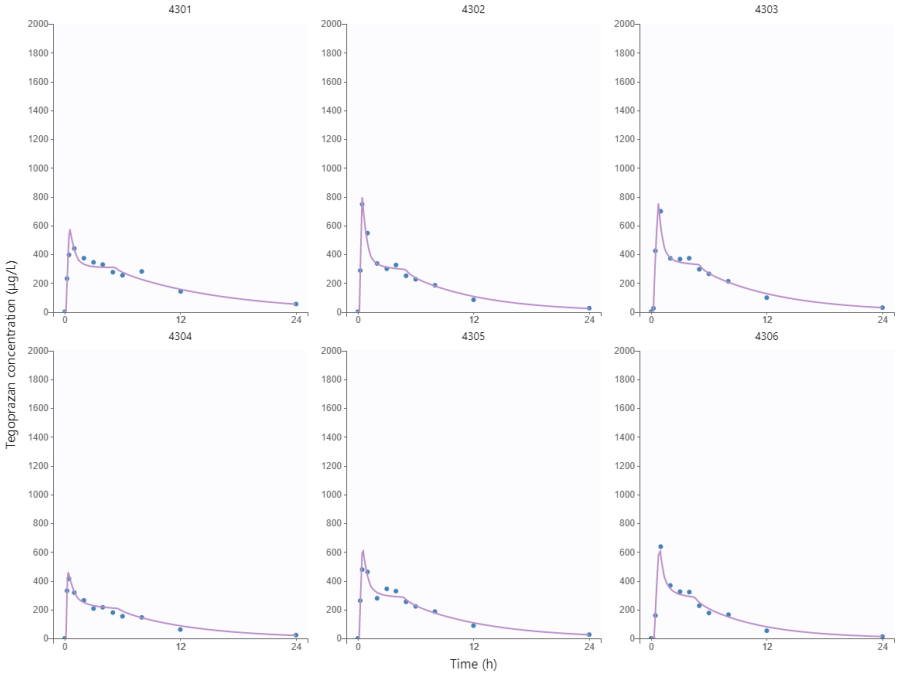
(e) IR 1 + DR 1 (50 mg)



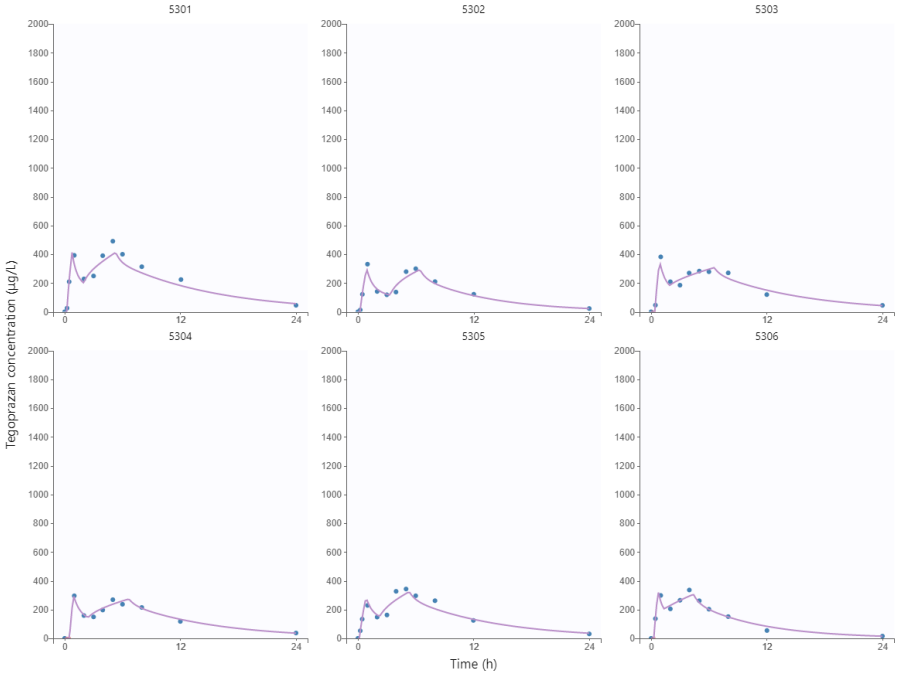
(f) IR 2 + DR 2 (100 mg)

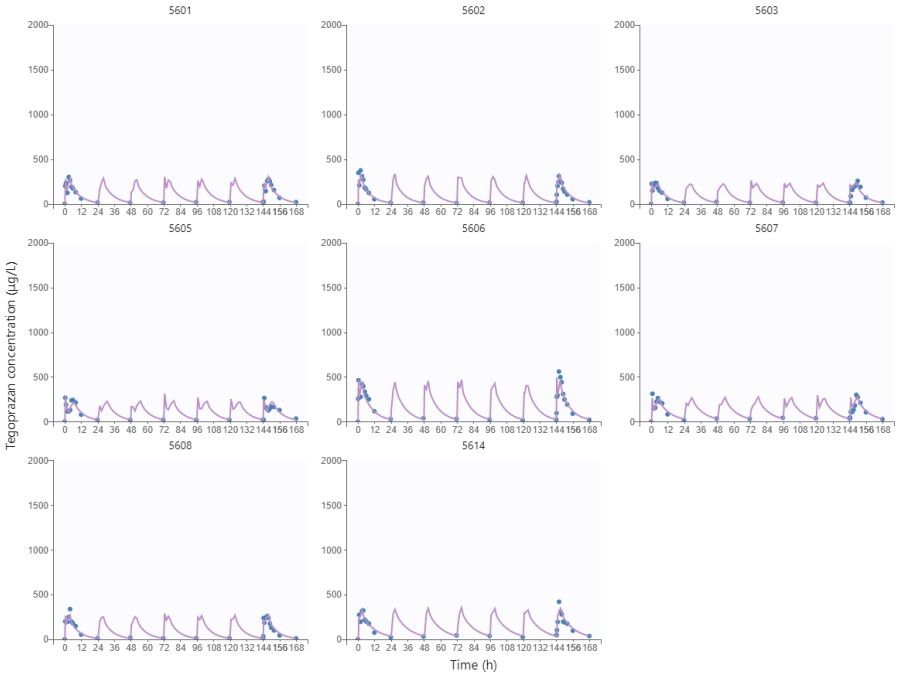


(g) IR 2+ DR 1 (75 mg)

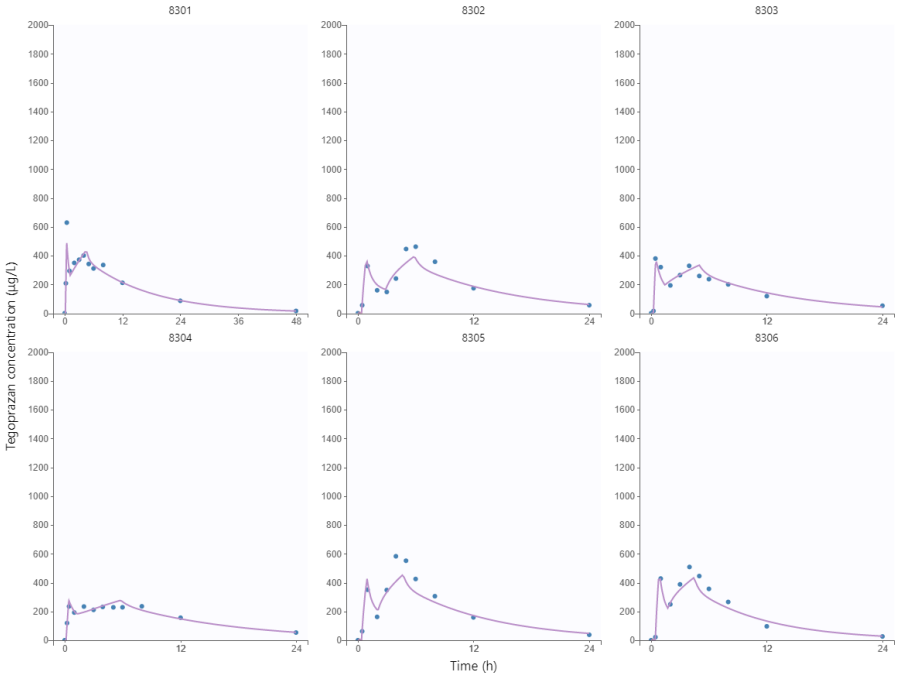


(h) IR 1 + DR 2 (75 mg)





(i) IR 1 + DR 3 (100 mg)



7. Basic goodness-of-fit plots of normal normalized prediction distribution errors for final model.

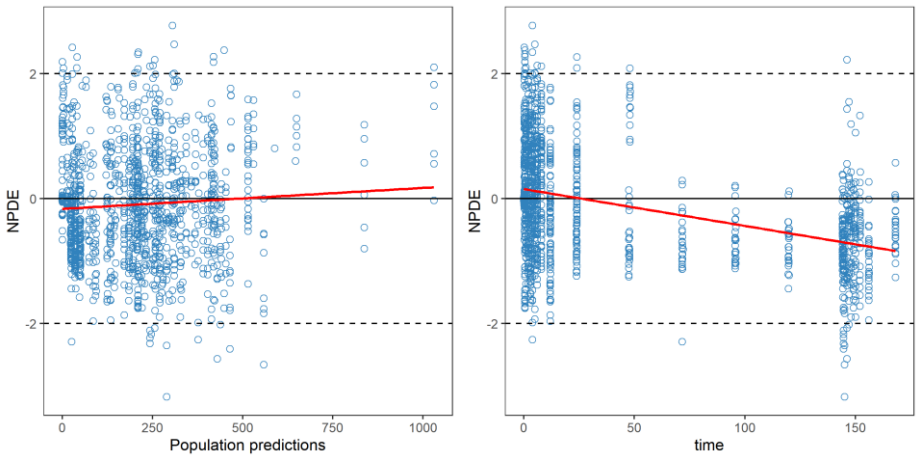


Figure S4 Basic goodness-of-fit plots of normal normalized prediction distribution errors for final model. (a) normalized prediction distribution errors (NPDE) vs. population predictions, (b) NPDE vs. time

8. Expected response of tegoprazan using E_{max} model at 1:1 ratio of tegoprazan IR and DR formulation.

Based on the simulated exposure (Figure 9, Table 4), the expected response of tegoprazan using the E_{max} model at a 1:1 ratio of tegoprazan IR and DR formulation was evaluated at doses of 50, 75, and 100 mg (Figure S5). The results of expected response suggested that combination of tegoprazan IR and DR formulation at a dose of 75 mg could provide sufficient gastric acid suppression.

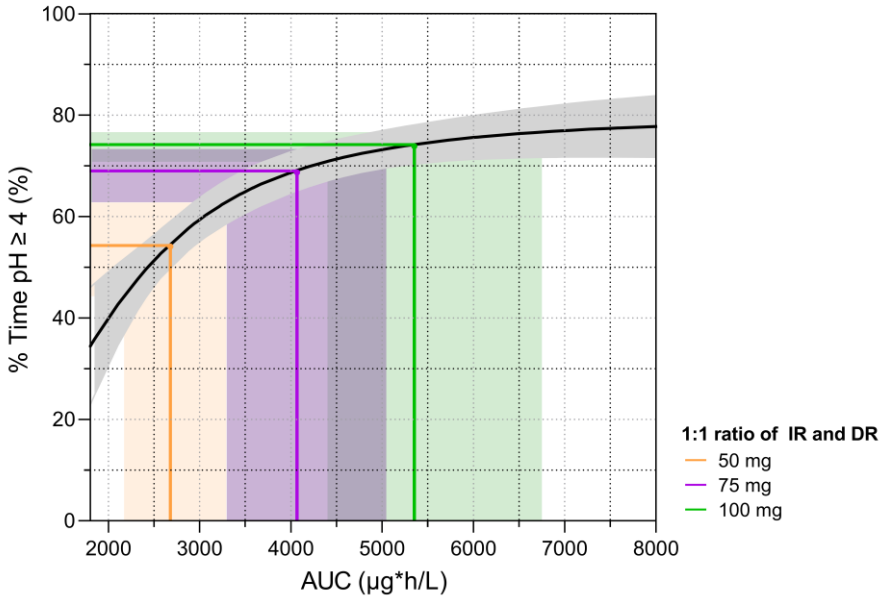


Figure S5 Expected response of tegoprazan using the E_{max} model at a 1:1 ratio of tegoprazan IR and DR formulation by 50, 75, and 100 mg, based on the simulated exposure.

The shaded area represents the interquartile range by dose. DR, delayed-release; IR, immediate-release.

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Abstract in Korean

서론: 테고프라잔은 위식도 역류 질환과 같은 위산 관련 질환을 치료하기 위해 사용되는 새로운 포타슘 경쟁적 위산 분비 차단제이다. 현재 승인된 테고프라잔 50 mg 1일 1회 복용법은 위산 관련 질환의 치료에 효과적이지만, 중증 위산 관련 질환을 가진 환자들에게는 더 강력한 효과가 필요하다. 따라서 본 연구는 건강한 대상자에서 테고프라잔 속방형 및 서방형 제제의 다양한 조합의 집단 약동학 모델을 수립하여 최적의 비율에서의 테고프라잔의 약동학을 평가하고 예측하고자 한다.

방법: 건강한 성인 남성을 대상으로 테고프라잔의 약동학을 평가하기 위하여 6-코호트, 공개, 무작위배정, 단회 및 반복 투여 시험을 진행하다. 시험대상자들은 각 코호트 별로 테고프라잔 속방형 및 서방형 제제의 다양한 조합(50, 75, 100 mg)을 단회 또는 7일동안 1일 1회 반복 경구 투여하였다. 테고프라잔 단회 및 반복 경구 투여 후 최대 48시간 및 192시간까지 혈액 샘플이 수집되었다. 집단 약동학 모델은 테고프라잔 속방형 및 서방형 제형에 대해 모노릭스 소프트웨어(버전 2023R1)의 비선형 혼합 효과 모델링 접근법을 사용하여 개발되었다. 또한, 임상시험 결과를 바탕으로 선정된 최적의 속방형 및 서방형 제제의 비율에서 테고프라잔 50, 75, 100 mg의 약동학을 예측하기 위한 모델 기반 시뮬레이션을 수행하였다.

결과: 집단 약동학 분석을 위하여 총 42명의 시험대상자에서 1,398개

의 혈장 농도가 포함되었다. 테고프라잔 속방형 및 서방형 제제의 다양한 조합의 약동학은 서로 다른 지연 시간을 가진 동시 0차 흡수와 선형 제거 모델로 이루어진 2구획 모델로 적절하게 설명되었다. 최종 모델로부터 측정된 약동학 파라미터들의 집단 대표 평균 값은 다음과 같다; 겉보기 청소율(CL/F): 13.9 L, 중심 구획의 겉보기 용적(V1/F): 55.9 L, 구획의 겉보기 용적(V2/F): 58.0 L, 속방형의 흡수 시간($Tk_{0,IR}$): 0.4 h, 서방형의 흡수 시간($Tk_{0,IR}$): 3.6 h, 속방형의 흡수 지연 시간($T_{lag,IR}$): 0.2 h, 서방형의 흡수 지연 시간($T_{lag,DR}$): 1.2 h. 모델은 bootstrap과 시각적 예측 검사(VPC)를 통해 평가되었으며, 그 결과 개발된 모델이 견고하고 정확한 것을 보여주었다. 또한 시뮬레이션 결과 테고프라잔은 선형 약동학 프로파일을 따르는 것으로 나타났다.

결론: 개발된 모델은 건강한 성인에서 테고프라잔의 시간별 농도-시간 프로파일을 잘 설명함으로써 테고프라잔 및 테고프라잔 서방형 제제의 약동학 특성에 대한 이해를 높일 수 있었다. 또한, 개발된 모델은 테고프라잔 속방형 및 서방형 조합의 최적 비율을 결정하는 잠재력을 가지고 있다. 결과적으로 1:1 비율의 테고프라잔 속방형과 서방형 제제는 충분한 위산 억제를 달성할 수 있을 것으로 기대된다.

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주요어: 속방형, 서방형, 집단 약동학, 약동학 모델링

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