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Original Article

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Pharmacokinetic properties of a new sustained-release pregabalin tablet in subjects with reduced renal function

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ABSTRACT

A new sustained-release (SR) pregabalin tablet, YHD1119, was formulated for once-daily dosing. In the current study, we aimed to evaluate the pharmacokinetics of YHD1119 tablets in patients with reduced renal function. Subjects were grouped by creatinine clearance: > 60 mL/min/1.73m^2 (Cohort A) and 30–60 mL/min/1.73m^2 (Cohort B). Eight subjects in Cohort A received a YHD1119 75 mg tablet (Y75T) and a YHD1119 150 mg tablet (Y150T) in each period, and eight subjects in Cohort B received a Y75T. Non-compartment analysis and population pharmacokinetic analysis using a one-compartment model with first-order elimination and first-order absorption with lag time were performed. Sixteen subjects completed the study. The geometric mean ratio (GMR) (90% confidence intervals [CI]) for maximum concentration (C_{max}), and area under the concentration-time profile from 0 to the last measurable time (AUC_{last}) after Y75T of Cohort B to those of Y75T of Cohort A were 1.2273 (1.0245–1.4701), and 2.4146 (1.8142–3.2138), respectively. The GMR (90% CI) for C_{max}, and AUC_{last} after Y75T of Cohort B to those of Y150T of Cohort A were 0.6476 (0.5229–0.8021), and 1.1471 (0.8418–1.5632), respectively. Simulated steady-steady pregabalin concentrations after once-daily Y75T dosing in subjects with eGFR 45 mL/min/1.73 m^2 were within the range of steady-state concentrations simulated after once-daily Y150T dosing in subjects with eGFR 90 mL/min/1.73 m^2. The total pregabalin exposure of Y75T in patients with moderate renal impairment was comparable with that of Y150T in subjects with near-normal renal function.

Trial Registration: ClinicalTrials.gov Identifier: NCT05012436

Keywords: Pharmacokinetics; Pregabalin; Delayed-Action Preparations; Renal Insufficiency

INTRODUCTION

Pregabalin is an analgesic and anticonvulsant medication that exerts its pharmacological activity by binding to an auxiliary $\alpha_2\delta$ subunit site of certain voltage-dependent calcium

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Conflict of Interest
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Conceptualization: Han S, Lim Y, Yoo H; Data curation: Park M; Formal analysis: Park M, Han S; Investigation: Park M, Choi S, Shin W, Kim A, Yoo H; Project administration: Han S, Yoo H; Supervision: Han S, Han S, Yoo H; Visualization: Park M; Writing - original draft: Park M; Writing - review & editing: Shin W, Kim A, Han S, Kim B, Lim Y, Yoo H.

channels [1,2]. Pregabalin reduces the release of neurotransmitters, such as glutamate, noradrenaline, and substance P, and is thus widely used to treat neuropathic pain, fibromyalgia, and generalized anxiety disorder and as adjunctive therapy for epilepsy [3-5]. Owing to its clinical utility, pregabalin has become widely available in numerous countries, either as an immediate-release (IR) formulation (Lyrica®; Pfizer Inc.) since 2004 or an extended-release (ER) formulation (Lyrica® CR; Pfizer Inc.) since 2017 after approval of the United States Food and Drug Administration. The YHD1119 tablet represents a novel sustained-release (SR) formulation of pregabalin, strategically designed for once-daily dosing akin to Lyrica® CR. Distinguished by its proprietary floating and swelling gastroretentive drug delivery system, the YHD1119 tablets exhibit enhanced bioavailability compared to Lyrica® CR [6,7]. Similar to Lyrica® CR, the SR formulation was developed primarily to meet the demands of patients with chronic neuropathic pain, given that the SR formulation elicits more favorable pharmacokinetic (PK) properties than Lyrica® in terms of controlling disease-related symptoms. Accordingly, in the phase III and post-marketing settings, the YHD1119 tablet, a pregabalin SR tablet, was shown to reduce pain adequately; the reported analgesic effect was found to be non-inferior to that afforded by Lyrica® with extended dosing interval [8,9].

In a previous well-designed crossover comparative PK study conducted in the healthy Korean population, the PK properties of YHD1119 tablet 300 mg once daily were found to be equivalent to those of Lyrica® 150 mg twice daily under fed (standard meal) conditions at steady-state [10]. The observed half-life did not differ significantly from the value previously reported for both formulations [11]. Although this information is essential to support the development of YHD1119 tablets, it cannot be extrapolated to PK properties in the Korean patient population, particularly those with impaired renal function, which is frequently comorbid with diabetic peripheral neuropathy. Pregabalin undergoes minimal metabolism, with > 90% of its administered amount eliminated unchanged in the urine [12]. Thus, the PK property is influenced by renal function [13], and this aspect is reflected in the label of Lyrica® CR [14].

In the current study, we aimed to elucidate the effects of reduced renal function on the PK properties of pregabalin, administered as YHD1119 tablets. To satisfy the potential need for dose reduction in cases of renal impairment, we also evaluated a low-dose formulation. To achieve this purpose, we 1) investigated the differences in pregabalin exposure according to renal function at the same dose of YHD1119 75 mg tablet (Y75T), 2) evaluated the PK similarity of YHD1119 150 mg tablet (Y150T) in the population with near-normal renal function and Y75T in patients with moderate renal impairment, and 3) performed a population PK analysis (mixed-effect modeling and simulation) to quantitatively assess the relationship between the estimated glomerular filtration rate (eGFR) and pregabalin clearance. Accordingly, we generated additional information on the PKs of YHD1119 tablets in patients with reduced renal function, which was poorly established during initial clinical development.

METHODS

Ethical considerations

This study was conducted at The Catholic University of Korea Seoul St. Mary's Hospital (SSM) and CHA Bundang Medical Center (CBMC) in accordance with the major ethical principles of the Declaration of Helsinki and the Korean Good Clinical Practice guidelines. The protocol was approved by the Institutional Review Board (IRB) of each institution (KC21MDDF0383 for SSM and 2021-05-008 for CBMC). This study was registered at ClinicalTrials.gov

(identifier: NCT05012436). All participants received a detailed explanation from researchers and voluntarily signed a written informed consent form prior to screening.

Subjects

Subjects aged ≥ 19 years and < 75 years with no substantial alterations in renal function within the last three months were eligible for study participation. For screening, medical history, physical examination, vital signs, 12-lead electrocardiogram, and clinical laboratory tests were performed within four weeks before the first administration. Patients with any clinically significant disease conditions or lifestyle factors (e.g., food, caffeine, and/or alcohol consumption) that may impact the PK of pregabalin, abnormal laboratory test results, history of allergies to any component of the investigational product, or history of considerable blood loss (e.g., blood donation or external trauma) were excluded. To determine differences in PK according to renal function, subjects were divided into two groups according to eGFR by Modification of Diet in Renal Disease (MDRD) formula. According to the Lyrica® CR label, dose adjustment is recommended when the eGFR is below 60 mL/min/1.73 m^2. Accordingly, using the same cut-off point at the time of screening, subjects with eGFR > 60 mL/min/1.73 m^2 were enrolled in the near-normal renal function group (Cohort A), and subjects with values ranging between 30–60 mL/min/1.73 m^2 were assigned to the moderate renal impairment group (Cohort B).

Study design

For Cohort A (target n = 8), the schedule was designed as an open, one-sequence, two-period crossover study to obtain pregabalin PK information for both formulations. Subjects were administered a single dose of Y75T (Period 1) or Y150T (Period 2). A four-day washout interval was established between the two periods. The single-sequence design could be justified because the objective was not to compare the results from both periods but to generate information to compare the results from Cohort B. In Cohort B (target n = 8), subjects received Y75T, but 150 mg pregabalin was not administered to minimize safety risk due to increased exposure. To measure the pregabalin concentration, blood samples were collected pre-dose (0 hours) and 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 24, 48, and 72 hours post-dose, regardless of the cohort and period. The subjects were hospitalized during PK sampling, provided with a standard meal 30 min before dosing, and completed their meal within 20 min. Blood samples were handled and analyzed using validated liquid chromatography (Prominence UFLC, Shimadzu, Kyoto, Japan)-tandem mass spectrometry (Triple Quad 5500+ system, SCIEX, Framingham, MA, USA.), using the method by Mandal et al. [15]. The lower limit of quantification was set at 20 ng/mL.

PK assessment and comparison

Each full-PK data was summarized by subject and period using the non-compartmental analysis (NCA) using R (ver 4.0.4, The R Foundation, Vienna, Austria) and the library of NonCompart (ver. 0.5.0, by Kyun-Seop Bae) [16]. C_{max} represents the maximum plasma concentration observed after each dose, and T_{max} represents the sampling time corresponding to C_{max}. AUC_{last} represents the area under the time-concentration curve after dosing until the time of the last observable plasma concentration, calculated using the linear trapezoidal rule. To estimate AUC_{inf} (area under the time-concentration curve extrapolated to infinity), the elimination rate constant (k_e) was first selected as the terminal slope of the time-log-transformed concentration curve with the highest adjusted R^2 value. The resulting AUC_{inf} was $AUC_{last} + C_{last}/k_e$, where C_{last} is the last measurable concentration; the half-life ($t_{1/2}$) was calculated as $\ln 2/k_e$. In addition, we determined the apparent clearance (CL/F) as dose/AUC_{inf} and the apparent volume of distribution (V_z/F) as CL/F/k_e. PK parameters for each cohort and

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period were analyzed using descriptive statistics. For study objectives 1 and 2, primary PK parameters (C_{max} and AUC_{last}) were log-transformed and used for PK comparisons based on bioequivalence (BE) statistics (parallel settings) by utilizing the SasLM Library (ver. 0.8.0, Kyun-Seop Bae) [17].

Population PK analysis

The population PK model was built based on a previously reported model structure, using all available plasma concentration data. First, a one-compartment model with first-order elimination and first-order absorption with lag time was selected as the structural model [18,19]. Although a structural model other than the one selected in the current study may produce a better-fitting outcome, it was not reflected in terms of direct comparability with previous reports. Second, it was reflected that pregabalin clearance is proportional to eGFR. However, owing to the nature of eGFR values, physiologically inappropriate values are occasionally derived depending on laboratory test results. To address these issues, we introduced a breakpoint (the maximum physiologically reasonable eGFR value) previously suggested by Shoji et al. [19]. Finally, because the measured pregabalin concentration values from a substantial number of PK samples obtained in the current study may be below the quantification limit (BQL), the M4 method was employed [20].

Mixed-effect modeling was performed using MonolixSuite (Ver. 2023R1, Simulation Plus, Antony, France). The magnitude of the between-subject variability (BSV) of each model parameter was estimated whenever possible, with post-hoc individual parameters. Inter-occasional variability (IOV) was allowed only for absorption parameters and was tested for significance. Unless specified otherwise, all variability parameters were reflected as having an exponential relationship with the population parameter. Various residual error structures were also tested, and the most appropriate structure was selected as the final structure. Covariate analyses, including demographic variables (age, body weight, height, body mass index, ideal body weight, and cohort), were performed. For forward selection, the level of statistical significance was $p < 0.01$, and for backward elimination, it was $p < 0.001$. The stochastic approximation expectation maximization algorithm was used in modeling procedures.

For model evaluation, nonparametric bootstrapping was performed with 1,000 resampled datasets. After the model was confirmed to be valid with appropriate predictive performance, various simulation results were generated to determine the pregabalin PK profile according to the dosage regimen, dosing period (single-dose or steady-state), and eGFR of the population.

RESULTS

Enrollment outcomes

Sixteen subjects (eight in Cohort A and eight in Cohort B) were enrolled, and all completed the study. The demographic profile of Cohort A was similar to that of Cohort B, except for age, as subjects in Cohort B were older than those in Cohort A (**Table 1**). The actual eGFR median values (minimum–maximum) were 91.5 (79.0–117.0) and 45.5 (36.0–59.0) mL/min/1.73 m^2 for Cohort A and B, respectively.

Comparative PK analysis

Fig. 1 presents the mean plasma concentration of pregabalin versus time in each cohort and period, and the PK parameters is summarized in the NCA results (**Table 2**). In Cohort A, the

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Table 1. Demographic characteristics and baseline eGFR values of study subjects

Variables	Cohort A (n = 8)	Cohort B (n = 8)
Males, No. (%)	8 (100.0)	7 (87.5)
Age, yr, median (minimum–maximum)	38 (21–43)	60 (49–67)
Weight, kg, median (minimum–maximum)	70.6 (46.6–97.0)	73.5 (63.3–80.0)
eGFR,* mL/min/1.73m^2, median (minimum–maximum)	91.5 (79.0–117.0)	45.5 (36.0–59.0)

eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.
*MDRD-eGFR values calculated during screening were used.

C_{max} and AUC_{last} elicited by Y75T (Period 1, 873.19 ± 185.86 ng/mL and 9,613.56 ± 2,716.62 h•ng/mL, respectively) were approximately half of those elicited by Y150T (Period 2, 1,678.22 ± 462.94 ng/mL and 20,554.31 ± 7,095.74 h•ng/mL, respectively). In Cohort B, a single-dose administration of Y75T yielded a C_{max} of 1065.16 ± 195.73 ng/mL and AUC_{last} of 23,766.29 ± 9,822.73 h•ng/mL. Accordingly, the geometric mean ratio (GMR) and 90% confidence interval (CI) of Cohort B/Cohort A were 1.2273 (1.0245–1.4701) for C_{max} and 2.4146 (1.8142–3.2138) for AUC_{last} when compared under the same dose condition. The AUC_{last} of Cohort B after Y75T dose was relatively similar to that of Cohort A after Y150T dose, as illustrated by a GMR (90% CI) of 1.1471 (0.8418–1.5632). **Table 3** presents the BE statistics.

The median T_{max} was relatively similar in both groups (5–5.5 hours post-dose) regardless of the period; however, there were significant discrepancies in $t_{1/2}$ and CL/F values between the two groups, although inter-period differences in Cohort A were negligible, given that they were obtained from the same subject group. Although the difference in V_z/F between the two cohorts was relatively small, the half-life in Cohort B was approximately twice that of Cohort A. This finding was consistent with the comparative PK evaluation results, which showed a similar C_{max} (maximum concentration) at the same dose (more dependent on V_z/F),

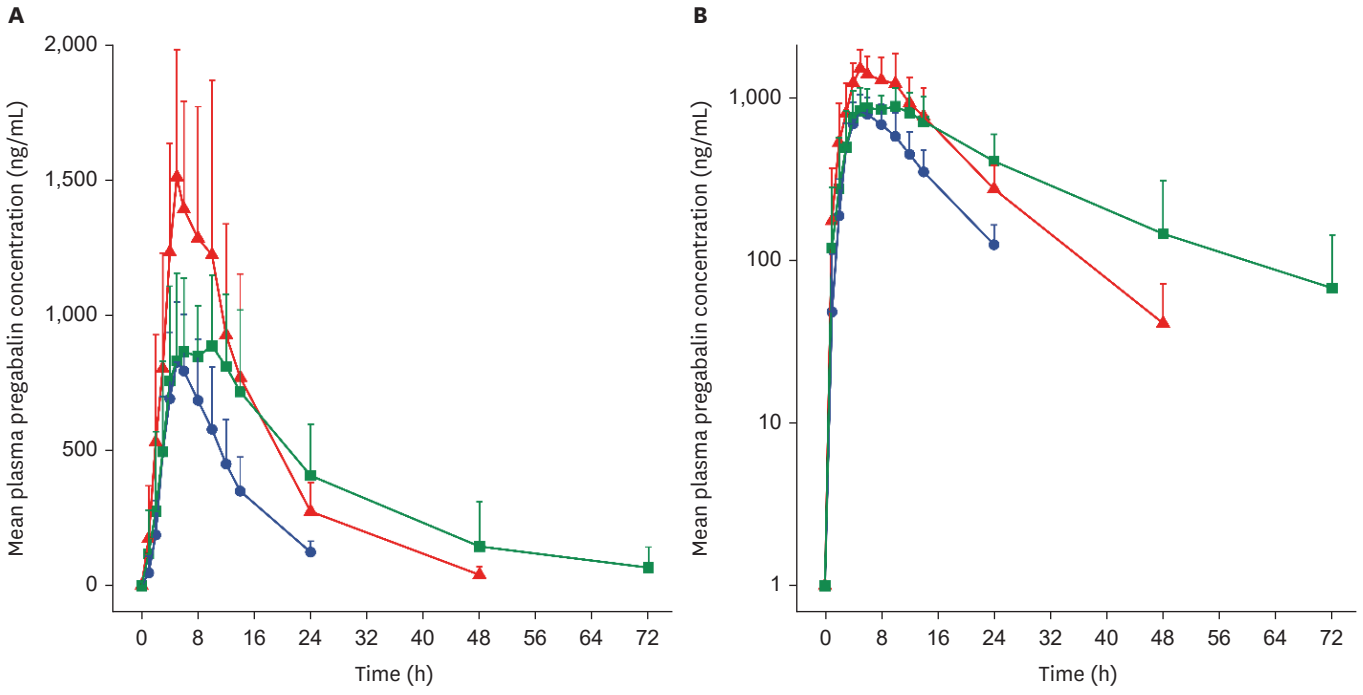

Figure 1. Mean plasma concentration of pregabalin versus time in each cohort and period. Blue: Period 1 of Cohort A (near-normal renal function, YHD1119 75 mg tablet); Red: Period 2 of Cohort A (near-normal renal function, YHD1119 150 mg tablet); Green: Cohort B (moderate renal impairment, YHD1119 75 mg tablet); Panel A: linear scale; Panel B: semi-log scale; Error bar: standard deviation.

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Table 2. Non-compartmental analysis results

PK parameters	Cohort A (n = 8)		Cohort B (n = 8)
	YHD1119 75 mg	YHD1119 150 mg	YHD1119 75 mg
C_{max} (ng/mL)	873.19 ± 185.86	1,678.22 ± 462.94	1,065.16 ± 195.73
AUC_{last} (h·ng/mL)	9,613.56 ± 2,716.62	20,554.31 ± 7,095.74	23,766.29 ± 9,822.73
AUC_{inf} (h·ng/mL)	10,809.64 ± 3,003.51	22,509.18 ± 7,257.88	25,267.91 ± 11,812.65
T_{max} (h)	5.0 (5.0–8.0)	5.0 (4.0–10.0)	5.5 (4.0–14.0)
$t_{1/2}$ (h)	6.69 ± 0.67	7.81 ± 2.96	13.47 ± 4.65
CL/F (L/h)	7.46 ± 2.18	7.31 ± 2.46	3.37 ± 1.07
V_z/F (L)	72.87 ± 25.87	84.82 ± 47.16	60.47 ± 13.60

All values are presented as the mean ± standard deviation, except for $T_{max,}$ which is presented as the median (range).
PK, pharmacokinetic; C_{max}, maximum plasma concentration; AUC_{last}, area under the concentration-time curve from zero to the time of the last quantifiable concentration; AUC_{inf}, area under the concentration-time curve from zero to infinity; T_{max}, time to reach C_{max}; $t_{1/2}$ elimination half-life; CL/F, apparent clearance; V_z/F, apparent volume of distribution.

Table 3. Comparative pharmacokinetics analysis

Group	Geometric mean ratio (90% CI)	
	C_{max}	AUC_{last}
Cohort B (Y75T)/Cohort A (Y75T)	1.2273 (1.0245–1.4701)	2.4146 (1.8142–3.2138)
Cohort B (Y75T)/Cohort A (Y150T)	0.6476 (0.5229–0.8021)	1.1471 (0.8418–1.5632)

All values are geometric mean ratio (90% CI).
CI, confidence interval; C_{max}, maximum plasma concentration; AUC_{last}, area under the concentration-time curve from zero to the time of the last quantifiable concentration; Cohort A, group with near-normal renal function; Cohort B, group with moderate renal impairment; Y75T, single-dose YHD1119 75 mg tablet; Y150T, single-dose YHD1119 150 mg tablet.

whereas the AUC_{last} of Cohort B approximated that observed after a two-fold higher dose administration in Cohort A (more dependent on CL/F).

Population PK analysis

The structural one-compartment model with first-order elimination and first-order absorption with lag time adequately described the dataset, according to the diagnostic plots (plots not shown). Other structural models, including various absorption models and a two-compartment model, were explored; however, no significant model improvement was observed, and there was no compelling reason to justify model replacement. To correlate CL/F with eGFR, alternative relationships, such as exponential and power models, were tested in addition to the linear model. These models exhibited minimal changes in OFV when compared with the linear model. In addition, in the power model, the exponent was estimated to approximate 1, resulting in no discernible difference from the linear model. Therefore, eGFR values were incorporated as time-variant covariates of CL/F in a linear relationship centered on the weighted mean of eGFR up to the breakpoint.

Covariate analysis failed to yield any additional covariates that impacted parameters. Variability was allowed for CL/F and V_z/F as BSV and T_{lag} as IOV. Despite the high correlation between CL/F and V_z/F, it was not included in the final model, considering the small sample size in accordance with the parsimony principle of creating a model that satisfactorily explains the dataset while remaining as simple as possible. The residual variability was represented using a proportional error model. **Table 4** summarizes the estimation results of the final model. The ratio of the maximum to minimum eigenvalues of the correlation matrix was 4.87, indicating that the final model estimates were stable and not influenced by ill-conditioning.

The final model was validated using diagnostic plots, nonparametric bootstrapping, and a visual predictive check. **Fig. 2** presents the goodness-of-fit plots of the final PK model.

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Table 4. Population pharmacokinetics parameter estimates

Parameters	Estimate	RSE (%)	Median (95% CI)*
Fixed effect			
T_{lag}, h	0.889	16.2	0.900 (0.613–1.19)
k_a, h^{-1}	0.347	8.02	0.341 (0.233–0.470)
V_d/F, L	61.7	5.24	61.3 (49.3–71.8)
CL/F, L/h	5.55	6.67	5.55 (4.81–6.32)
Breakpoint, mL/min/1.73 m^2	91.2	4.38	Fix†
Between-subject variability			
V_d/F, CV (%)	0.147 (14.8)	22.1	0.140 (0.0233–0.229)
CL/F, CV (%)	0.242 (24.6)	19.1	0.233 (0.139–0.324)
Inter-occasional variability			
T_{lag}, CV (%)	0.726 (83.3)	19.5	0.688 (0.480–1.013)
Residual variability			
Proportional error	0.286	5.16	0.287 (0.241–0.331)

*Medians and 95% CIs were calculated using nonparametric bootstrapping.
†The breakpoint was estimated but subsequently fixed during nonparametric bootstrapping.
Breakpoint, the maximum physiologically reasonable eGFR value, up to which CL/F increases with eGFR.
RSE, relative standard error; CI, confidence interval; CV, coefficient of variation; eGFR, estimated glomerular filtration rate.

The plots of observations versus population or individual predictions showed a central tendency toward the identity line (y=x) without major bias. There was no systematic trend with regard to time or predictions in plots of IWRES (individual weighted residuals) versus time or PWRES (population-weighted residuals) versus individual predictions. The final model was internally validated using nonparametric bootstrapping. The breakpoint was fixed at the estimated value of 92.10 during the nonparametric bootstrap, owing to the limited sample size. The median values and 95% prediction intervals (2.5 and 97.5 percentile points) for each parameter estimate from the 1000 bootstrap datasets were comparable with each parameter estimate (**Table 4**). A visual predictive check plot revealed that the average prediction matched observed concentration-time courses and that the variability was within the expected range for pregabalin (**Fig. 3**). The 10, 50, and 90% quantiles of observed data are included in the 90% prediction intervals, as presented by the final model for the 10, 50, and 90% quantiles.

To establish steady-state concentration profiles with once-daily dosing of Y75T or Y150T, simulations were conducted using the representative eGFR value of each Cohort, selected as 45 and 90 mL/min/1.73 m^2 for Cohort A and B, respectively. The simulated median plasma pregabalin concentration versus time is shown in **Fig. 4**. Notably, the simulated steady-state concentrations after once-daily Y75T dosing in subjects with eGFR 45 mL/min/1.73 m^2 were within the range of steady-state concentrations observed after once-daily Y150T dosing in subjects with eGFR 90 mL/min/1.73 m^2.

DISCUSSION

To establish the PK characteristics of the YHD1119 tablet in patients with moderate renal impairment and determine the dosage regimen, the current study was meticulously designed, encompassing two cohorts covering a distinct range of renal function. Unlike typical PK investigations in patients with impaired renal function, we merged normal renal function and mild impairment into a single cohort, considering the present practice with pregabalin formulations, in which the dosage adjustment is not employed for patients with mild renal impairment [14,21]. Additionally, a cohort with severe renal impairment was not included

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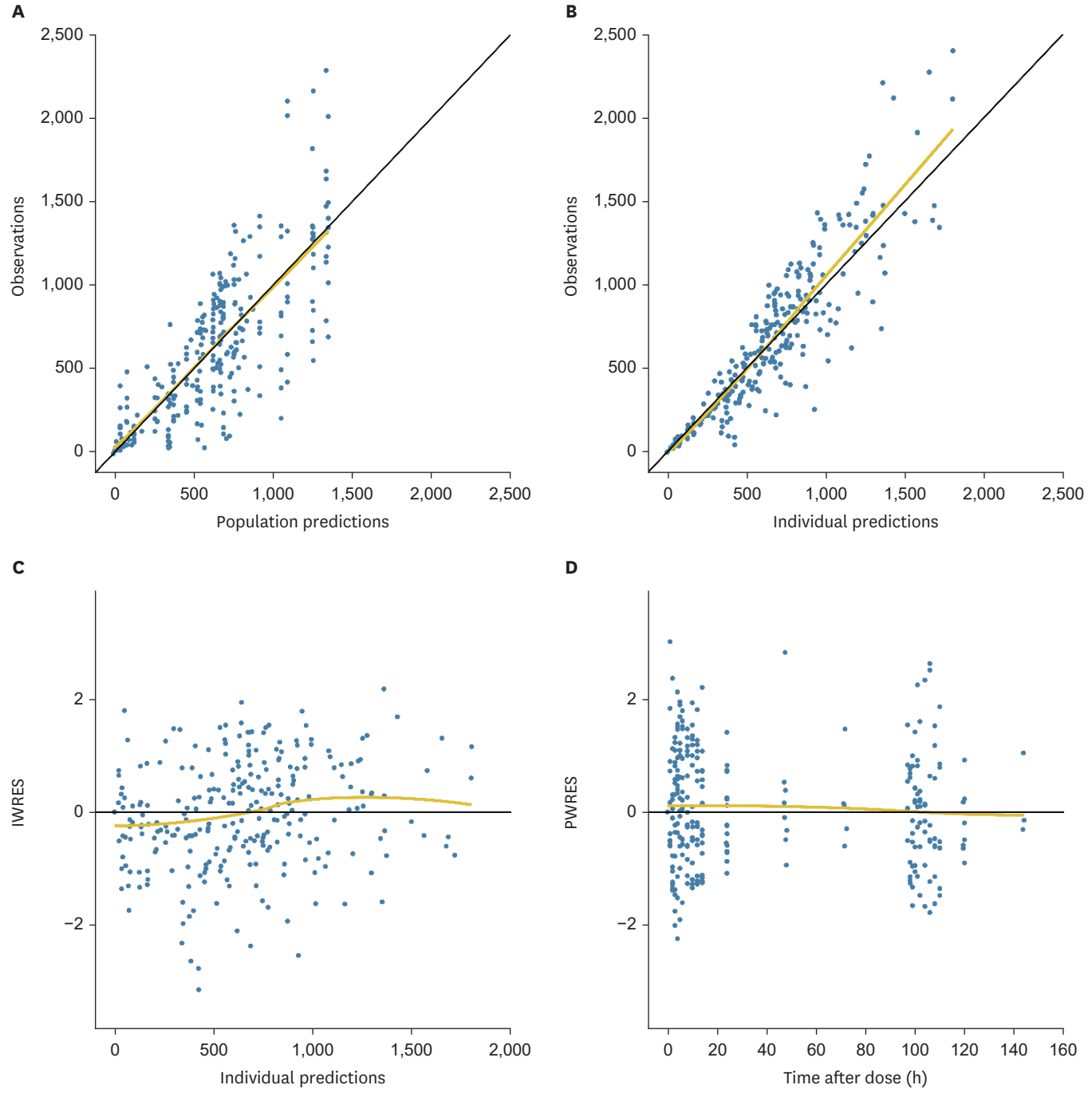

Figure 2. Basic goodness-of-fit plots of the final model. Blue dots: observed concentrations; Black lines: y = x or y = 0; Yellow lines: spline; Panel A: Scatterplot of observations versus concentrations of population prediction; Panel B: Scatterplot of observations versus concentrations of individual prediction; Panel C: Scatterplots of individual weighted residuals (IWRES) versus individual prediction; Panel D: Scatterplots of population-weighted residuals (PWRES) versus time after dose.

because a daily dosing regimen has been previously established for Lyrica® capsules [21]. The selected design factors, including sampling points and dosing intervals, effectively addressed the objectives of the current study. Blood sampling was conducted up to a 72-hour period post-dose, which was approximately five times the half-life. Prior to reaching C_{max}, four sampling points were collected, eliciting an in-depth assessment of absorption and distribution phases.

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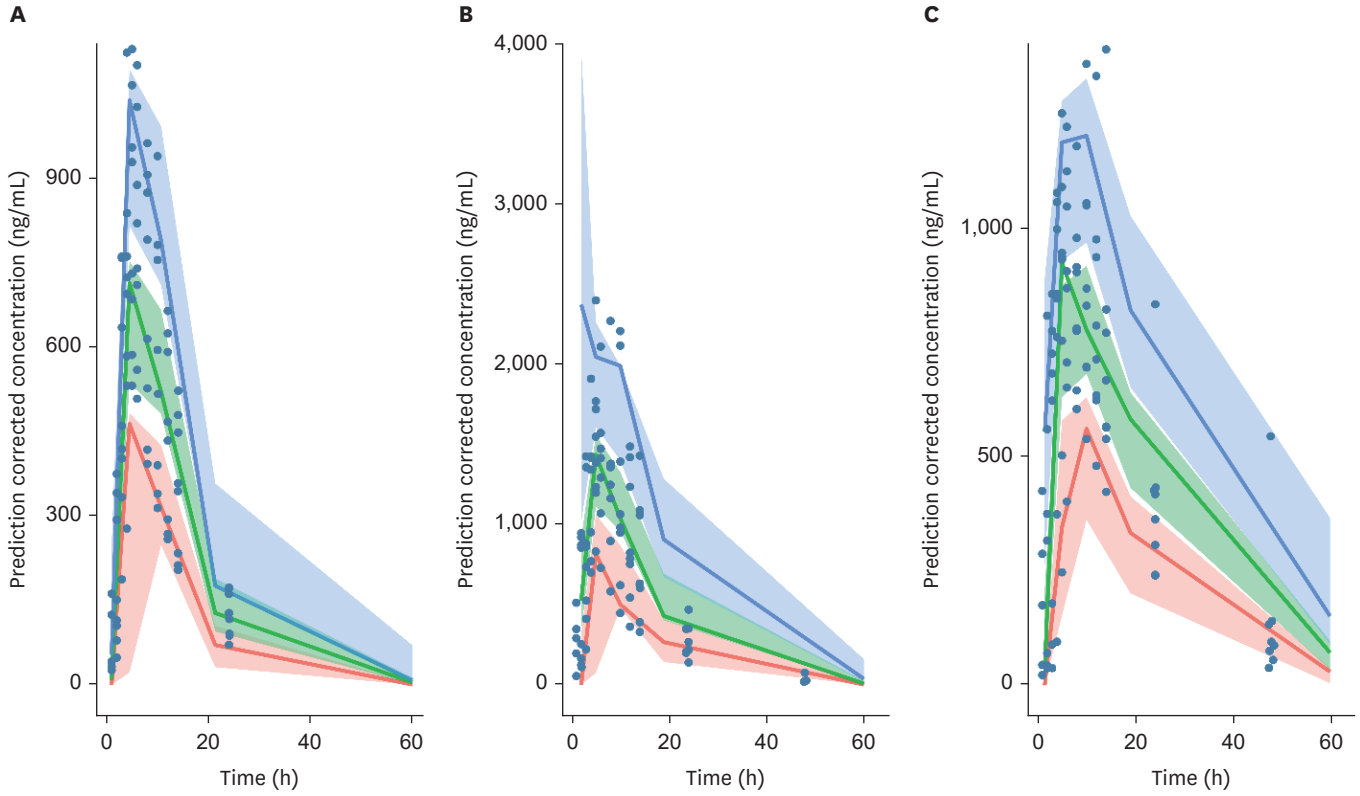

Figure 3. Prediction corrected visual predictive check plots stratified by cohort and period. Blue dots: observed concentrations; Lines: 10th, 50th, and 90th percentiles of observed data; Shades: 90% prediction intervals of simulated 10th, 50th, and 90th percentiles; Panel A: Period 1 of Cohort A (near-normal renal function, YHD1119 75 mg tablet); Panel B: Period 2 of Cohort A (near-normal renal function, YHD1119 150 mg tablet); Panel C: Cohort B (moderate renal impairment, YHD1119 75 mg tablet).

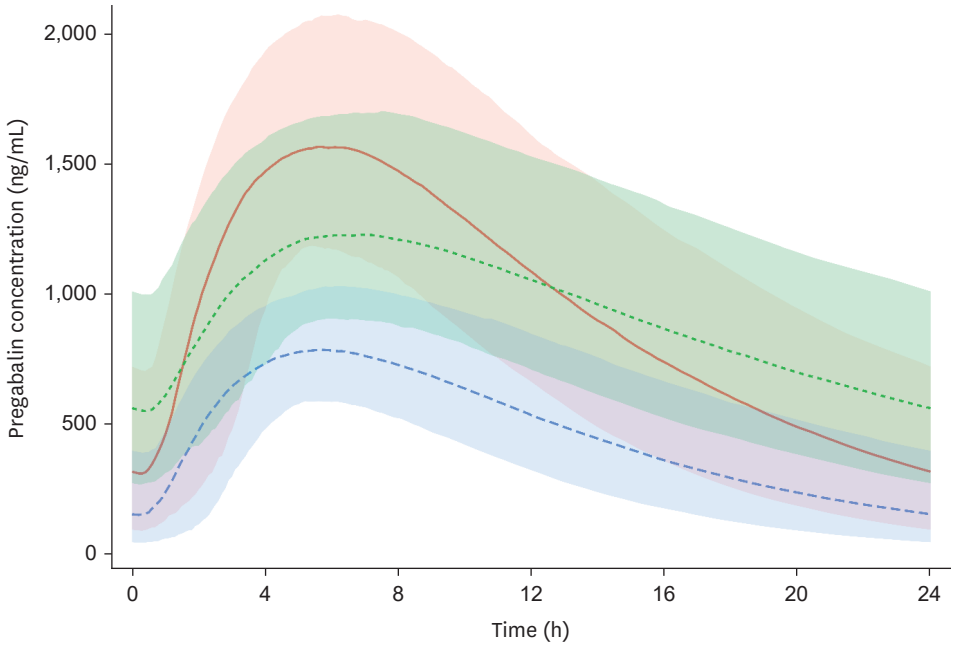

Figure 4. Simulated median plasma concentration-time curves at steady-state of pregabalin when administered YHD1119 tablet once daily in subjects with representative eGFR values of 45 and 90 mL/min/1.73 m^2. Blue: Once-daily dosing of YHD1119 tablet 75 mg tablet in subjects with an eGFR of 90 mL/min/1.73 m^2; Red: Once-daily dosing of YHD1119 tablet 150 mg tablet in subjects with an eGFR of 90 mL/min/1.73 m^2; Green: Once-daily dosing of the YHD1119 75 mg tablet in subjects with an eGFR of 45 mL/min/1.73 m^2; Shades are between 5 quantiles and 95 quantiles.
eGFR, estimated glomerular filtration rate.

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Furthermore, pre-dose concentrations in Period 2 of Cohort A were undetectable across all subjects, indicating a sufficient wash-out interval. Given that the percentage of post-dose BQL data exceeded 10% of the total dataset, the M4 method was considered appropriate [20]. Accordingly, NCA and population PK analyses are well-supported.

The results from the NCA and BE statistics provided substantial evidence for dose proportionality, linear kinetics, and the impact of renal function on the clearance of YHD1119 tablets. The administration of a double dose in Cohort A resulted in an approximately two-fold increase in both C_{max} and AUC, with nearly similar values for CL/F, V_z/F, and T_{max}. Considering Cohort B, the PK profile demonstrated the characteristic patterns associated with reduced clearance. The C_{max} slightly increased at a slightly delayed T_{max}, and AUC and $t_{1/2}$ significantly increased with a corresponding decrease in CL/F, resulting in comparable total exposure between Cohorts B (Y75T) and A (Y150T). These results align with those of previous studies assessing the pregabalin PK profile, indicating that the dosing regimen of the new pregabalin formulation, i.e., the YHD1119 tablet, can be adopted in a manner consistent with available formulations [5,22,23].

The adoption of a one-compartment model with first-order elimination and absorption with a lag effectively characterized the underlying PK properties. Considering NCA results and the well-established correlation between renal function and pregabalin clearance, the inclusion of eGFR as a linear covariate with a breakpoint on clearance was rationalized [13,24]. The final population PK model was confirmed to adequately describe the dataset according to the goodness-of-fit plot, and parameter estimates were accurate and precise according to the relative standard error and bootstrap results and physiologically plausible. The VPC result demonstrated good model predictability across all cohorts and formulations. Bockbrader et al. [18] and Shoji et al. [19] have reported lower estimates of CL/F and V_z/F and a higher breakpoint estimate of pregabalin than those determined in the current study. These differences may be attributed to methods used to estimate renal function, with creatinine clearance (CL_{cr}) estimated in previous reports and MDRD-eGFR determined in the current study. In the present study, CL_{cr} values were higher than MDRD-eGFR values. In addition, the smaller k_a and the larger T_{lag} observed in this study are consistent with the slow absorption of the current SR formulation. Although variability was introduced through IOV on T_{lag}, a difference in the absorption of the two formulations, i.e., Y75T and Y150T could not be established, as the dose was not a meaningful covariate on T_{lag}. Overall, the population PK evaluation was consistent with existing knowledge and satisfactorily explained the current dataset.

The limitations of the current need to be addressed, including the small sample size and homogeneity of subject characteristics, potentially hindering the widespread applicability of the results and limiting the strength of the statistical conclusions [25]. Furthermore, age, which differed significantly between the two cohorts, served as a confounding factor. Previous studies showed that pregabalin clearance is significantly affected by renal clearance, not age [18,19,26]. In addition, this study revealed that the clearance (CL/F) did not exhibit a linear relationship with age in each cohort using NCA, and age did not emerge as a significant covariate in the modeling process. It should be noted that the current study elicited essential PK insights in Korean subjects despite these limitations; however, further research evaluating YHD1119 tablet PK and pharmacodynamics in diverse patient populations with varying degrees of renal function is warranted.

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In conclusion, the findings of our study revealed that the PK profile of the YHD1119 tablet in Korean patients with impaired renal function was consistent with that of the existing pregabalin formulations: The total pregabalin exposure of Y75T in patients with moderate renal impairment was comparable with that of Y150T in subjects with near-normal renal function. Thus, it is recommended to reduce the YHD1119 tablet doses by approximately 50% for patients with moderate renal impairment compared to those with near-normal renal function.

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