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Population pharmacokinetics of duloxetine in Japanese pediatric patients with major depressive disorder

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ABSTRACT

The objectives of this analysis were to characterize the pharmacokinetics of duloxetine in Japanese pediatric patients aged 9–17 years with major depressive disorder (MDD) and to explore potential intrinsic factors affecting its pharmacokinetics. A population pharmacokinetic (PK) model was developed with plasma steady-state duloxetine concentrations from Japanese pediatric patients with MDD in an open-label long-term extension trial in Japan (ClinicalTrials.gov Identifier: NCT03395353). Duloxetine pharmacokinetics in Japanese pediatric patients was well described by a one-compartment model with first-order absorption. The population mean estimates of CL/F and V/F of duloxetine were 81.4 L/h and 1170 L, respectively. Patient intrinsic factors were assessed for their potential influence on duloxetine apparent clearance (CL/F). Only sex was identified as a statistically significant covariate of duloxetine CL/F. Duloxetine pharmacokinetic parameters and model-predicted duloxetine concentrations at steady state in the Japanese pediatric population were compared with those in Japanese adults. The mean duloxetine CL/F in pediatrics is slightly higher than adults, it is, however, expected that comparable steady-state duloxetine exposure in pediatric patients can be achieved with the approved dose regimen for adults. The population PK model provides useful information to understand the pharmacokinetic characteristics of duloxetine for Japanese pediatric patients with MDD.

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1. Introduction

Duloxetine is an antidepressant classified as a serotonin-noradrenaline reuptake inhibitor (SNRI). Since 2010, it has been used in Japan for the treatment of depression and depressive state in adults, as well as pain associated with diabetic peripheral neuropathic pain (since 2012), fibromyalgia (since 2015), chronic low back pain (since 2016), and osteoarthritis (since 2016).

Duloxetine is currently not approved for use in pediatric patients (aged <18 years) with depression. Two Phase 3 trials have been conducted to examine duloxetine efficacy in pediatric patients with major depressive disorder (MDD) in the USA and other countries but failed to confirm the efficacy of both duloxetine as well as the positive control (fluoxetine) over the placebo [2,3].

We conducted an open-label long-term extension (OLE) trial in Japan to evaluate the safety and efficacy of duloxetine in pediatric patients with MDD as an extension of a 6-week randomized double-blind placebo-controlled clinical trial for the filing in Japan [1]. The blood samples for quantitation of plasma concentrations of duloxetine were collected from all subjects in the OLE study. The objectives of this analysis were to characterize the pharmacokinetics (PK) of oral duloxetine in Japanese pediatric patients aged 9–17 years and to identify potential intrinsic factors affecting the duloxetine PK.

2. Materials and methods

2.1. Data used in the population PK analysis

Population PK analysis was performed using the dataset from the OLE study. It was conducted at 36 medical institutions in Japan between January 2018 and July 2020 (ClinicalTrials.gov Identifier:

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NCT03395353). The study was a multicenter, open-label, uncontrolled, long-term treatment study of Japanese pediatric patients aged 9 to <18 years old with MDD. The planned dosing regimen in this study was either 40 mg/day or 60 mg/day of duloxetine for 50 weeks including initial dose adjustment time. Five PK samples were obtained from each subject from Visit 5 (Week 4) to the end of treatment period for analysis of steady-state duloxetine concentrations. If the duloxetine dose was changed before the PK assessment, PK samples were taken at least 2 weeks after the dose changes to evaluate the steady-state pharmacokinetics. And one or two of the five blood samples were scheduled to be drawn pre-dose for trough concentrations. The study protocols and informed consent forms were approved by the Institutional Review Board at each study site. The study was performed in accordance with Good Clinical Practice guidelines and in line with the principles set out in the Declaration of Helsinki.

2.2. Bioanalytical methods

Human plasma samples obtained in the study were analyzed by Sumika Chemical Analysis Service, Ltd. (Osaka Laboratory, Japan). The determination of duloxetine was conducted using 50 μ L of plasma by deproteinization with 210 μ L of methanol, and then separated and detected by liquid chromatography/tandem mass spectrometry (LC/MS/MS). The lower limit of quantification was 0.100 ng/mL. All test samples (512 samples) were measured under the conditions of validated stability (validated conditions: stored frozen at -80°C , for 13 months, up to six freeze/thaw cycles).

In the calibration curve, the accuracy of the back-calculated concentration of each calibration standard sample must be within 20.0% at the lower limit of quantification (LLOQ) and within $\pm 15.0\%$.

2.3. Population PK analysis

2.3.1. Base model development

The PK profiles of duloxetine were examined using conventional compartment disposition models (one- or two-compartment models) with first order absorption. The dose proportionality of duloxetine PK in pediatrics has been investigated at previous studies in the United States [4], and dose-dependency in CL/F was apparently ignorable at dose range between 40 mg and 60 mg. A dose-proportional model was, therefore, introduced for the base model development in the analysis. The first-order rate constant of

absorption (K_a) was fixed at the reported value of 0.168 hr^{-1} in the previous study [4] due to insufficient data in the absorption phase available. The inter-individual variability for CL/F were assumed to follow a log-normal distribution. The proportional error model, the additive error model and the combined error model (the proportional error + the additive error model) were tested for intra-individual (residual) variability. Inter-occasion variability was not evaluated since it was difficult to distinguish from residual variability and inter-individual variability due to the limited PK samplings. An error model for intra-individual variability will be selected from the diagnostic plots and/or the objective function value (OBJ) at the statistical significance level of 0.05 ($p < 0.05$) based on the χ^2 test, that is, a difference in the objective function value (ΔOBJ) of less than -3.84 for one degree of freedom represents a statistically significant model improvement.

2.3.2. Covariate model development

A covariate model was constructed by combination of step-wise screening for covariates, forward selection, and backward deletion. The investigated covariates on CL/F were age, height, body weight, body mass index (BMI), body surface area (BSA), ideal body weight (IBW), lean body weight (LBW), and adjusted body weight (ABW) [5], sex, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (Tbil), creatinine clearance (CrCL), and age group (children [7–11 years old] and adolescents [12–17 years old]).

The significance level of 0.05 based on the χ^2 test ($p < 0.05$) was applied for the screening and the forward selection to construct a full model (decreased the value of OBJ less than -3.84 for one degree of freedom). The significance level of 0.01 based on the χ^2 test ($p < 0.01$) was applied for the backward deletion to construct a final model (increased the value of OBJ more than 6.64 for one degree of freedom).

2.3.3. Model evaluation

The base and final models were evaluated by using the point estimates of PK parameters and their 95% confidence intervals (CIs). The goodness of fit (GOF) plots were generated for model diagnostics. A prediction-corrected visual predictive check (pcVPC) [6] was performed and the final model was evaluated by comparing the observed plasma concentrations with the 95% prediction intervals (PIs) simulated from the final population PK parameters. A total of 200 data sets were simulated from the final population PK

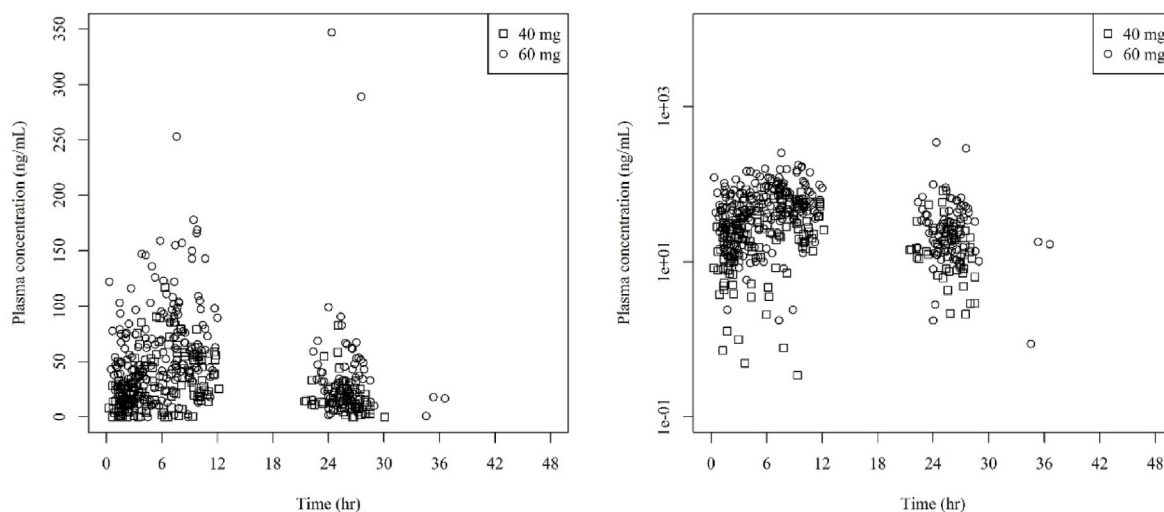


Fig. 1. Plasma duloxetine concentrations versus time after last dose (Left: linear scale, Right: semi-log scale).

parameters using the original data set as a simulation template. For each simulation run, the median and the 5th and 95th percentiles of pharmacokinetic time course were calculated. Then, for each of those statistics, the 95% CIs were computed over the 200 runs for the simulated data sets and compared with the observations. A nonparametric bootstrap resampling procedure [7] was performed to assess the stability of the final parameter estimates and the robustness of the final model. The 1000 bootstrap sample sets were made by resampling from the original data set, and the parameter estimates for each of the 1000 sample sets were obtained using the final model. The medians and 95% CIs of the 1000 parameter estimates from bootstrap sample sets were compared with the mean

and 95% CIs calculated from the standard errors of the final parameters.

2.4. Software

Non-linear mixed effects modeling to build a population PK model was performed using the computer program NONMEM (version 7.4.4, ICON Development Solutions, US) with Gfortran (version 4.6.3), installed on a computer running under the Windows operating system. To support analyses and nonparametric bootstrap resampling by NONMEM, Perl-speaks-NONMEM (version 4.9.0) and Pirana (version 2.9.9) were used. For dataset creation, data summarization, and graphical presentation, Microsoft Excel for Office 365 MSO (16.0.12527.20612), R (version 3.6.3), and SAS (version 9.4, SAS Institute Inc., US) were used.

3. Results

3.1. Analysis dataset

A total of 512 plasma concentrations was obtained from the 141 subjects. Of them, 22 samples were excluded due to an overdose (2 samples), treatment discontinuation (8 samples), and/or below limit of quantitation (BLQ) records (14 samples). Consequently, 490 concentrations from 138 subjects were included in the analysis. Fig. 1 presents the plasma concentration versus time after the last dose.

Of a total of 138 patients, 8% (11 patients) were children aged 9–11 years and 92% (127 patients) were adolescents aged 12–17 years. The proportions of male and female patients were 30% (42 patients) and 70% (96 patients), respectively. The mean (range) of body weight were 36.9 (27.6–46.6) kg for the children and 52.5 (27.9–102.7) kg for the adolescents. The percentage of sex (male and female) were 54.5% and 45.5% for the children and 28.3% and 71.7% for the adolescents. The background data are summarized in Table 1 and Supplementary Table 1.

3.2. Population pharmacokinetic model

The model building process is shown in Supplementary Table 2. The one-compartment model with first-order absorption (Model 002) was selected as a structural PK model because a two-compartment model did not improve OBJ, and some parameters of the two-compartment model could not be estimated appropriately (Model 004). Absorption lag time was tested but was not accepted by inappropriate estimation in the structural PK model. The residual error was described with a proportional model which was chosen based on OBJ. We first tested a model that assumed a log-normal inter-individual variability both on CL/F and V/F with covariance between them based on previous studies [4]. However, the covariance was excluded from the model (Model 011) since random effects for CL/F and V/F were highly correlated (Model 002), suggesting that it was difficult to estimate both of them separately due to the limited PK samplings from each pediatric patient. The inter-individual variability on V/F was removed due to the high shrinkage (68%). Consequently, Model 012 were selected for the base model.

The covariates were tested with the base model as shown in Supplementary Table 2. Patient characteristics related to body size such as body weight, height, BMI, BSA, IBW, LBW, and ABW did not have a statistically significant effect on the duloxetine PK parameters. Only sex had an effect on CL/F in the final model with the CL/F of females being 70.7% relative to that of males. The estimated population PK parameters in the final model are shown in Table 2. The inter-individual variability for CL/F decreased from 51.6% (base

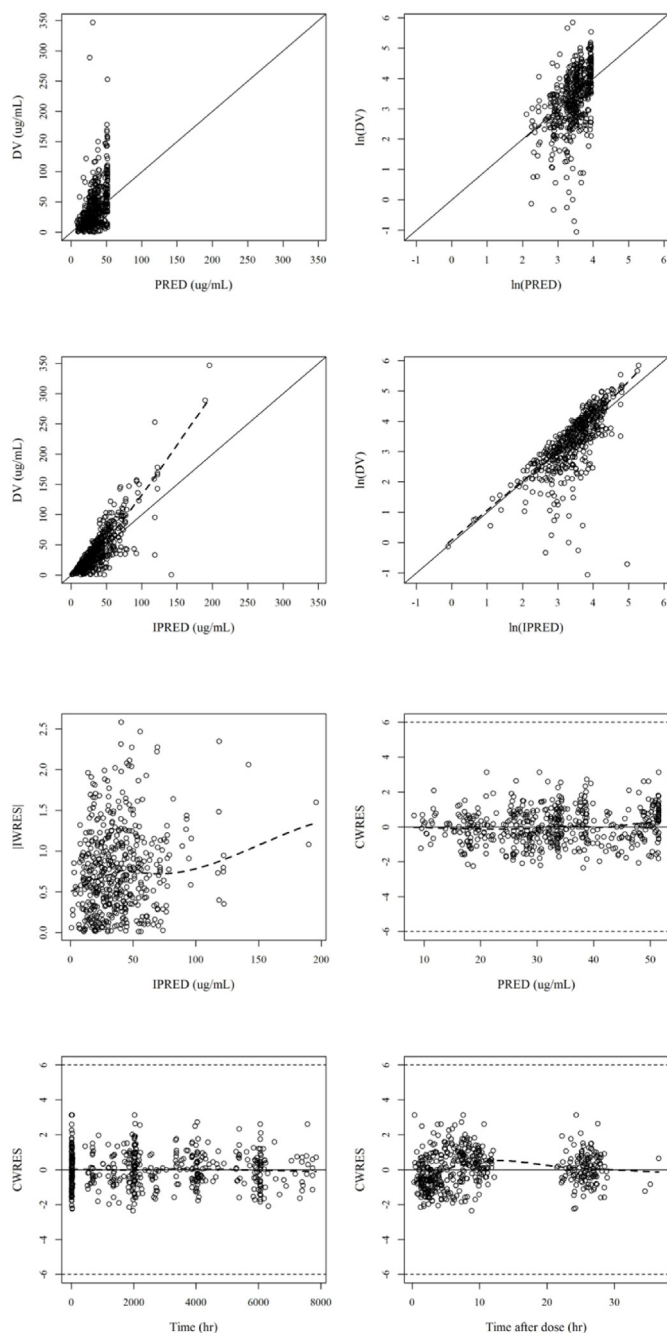


Fig. 2. Goodness-of-fit and QQ plots for the final model. Dashed lines show LOWESS curves. Solid line in the first four panels show $y = x$. Solid lines in the last three panels indicate CWRES levels of 0.

Table 1
Summary of the major patient background characteristics.

Age Groups [Number of Subjects]	Background Characteristics	Mean (SD)
Children (7–11 years) [N = 11]	Body weight (kg)	36.9 (6.9)
	Height (cm)	141.6 (10.4)
	Body mass index (kg/m ²)	18.3 (2.3)
	Body surface area (m ²)	1.21 (0.2)
	Age (years)	10.4 (0.7)
	Creatinine clearance (mL/min)	129 (32.3)
	Sex (Male: Female) ^a	6 (54.5%): 5 (45.5%)
Adolescents (12–17 years) [N = 127]	Body weight (kg)	52.5 (11.3)
	Height (cm)	159.6 (8.2)
	Body mass index (kg/m ²)	20.6 (4.3)
	Body surface area (m ²)	1.52 (0.2)
	Age (years)	15.0 (1.6)
	Creatinine clearance (mL/min)	143 (34.9)
	Sex (Male: Female) ^a	36 (28.3%): 91 (71.7%)

^a Number of subjects (percentage of all subjects).

model) to 48.0% (final model). The NONMEM run for the final model was completed successfully with ≥ 3 significant digits for all estimates.

The summary of post-hoc parameters (AUC and $C_{\max}$) for Japanese pediatric patients and the summary of PK parameters (AUC and $C_{\max}$) of healthy adults in a Japanese multiple-dose study are shown in Table 3 [8]. The model confirmed the studied dose for pediatrics with MDD to achieve sufficient exposure that is comparable or higher than that in adults.

3.3. Model evaluation

Using a non-parametric bootstrap resampling procedure, the 95% CIs of parameter estimates were calculated as shown in Table 2. The GOF plots for the base model and final model are shown

Table 2
Population PK parameter estimates for the final model.

Parameter	Units	Final model			Bootstrap estimates	
		Estimate	%RSE	95% CI	Median	95% CI
Pharmacokinetic parameters						
CL/F	L/hr	81.4	10.1	64.8–98.0	80.6	68.1–97.0
V/F	L	1170	15.0	919.0–1420	1150	937.0–1540
Ka	1/hr	1.68 ^a	—	—	—	—
Effect of Sex on CL/F		0.707	10.7	0.566–0.848	0.712	0.591–0.861
% CV for IIV for CL/F (sh _{ηp})	%	48.0 (8.3)	18.3	47.9–48.1	47.2	38.8–56.7
% CV for proportional residual error (sh _ε)	%	48.3 (8.0)	5.1	48.3–48.3	48.1	44.6–51.7

IIV = interindividual variability.

^a Fixed parameter.**Table 3**
Summary of Steady-state $C_{\max}$ and AUC in Japanese children and adolescents (simulated based on the individual post-hoc parameters from the final model, and the dosage used for the simulation were 40 and 60 mg) and healthy adults (observation).

Dose (mg)	Age Group	Number of subjects	$C_{\max}$ (ng/mL)	AUC (ng·hr/mL) ^a
40	children (9–11 years)	7	30.0 (16.8)	591.6 (404.6)
	adolescents (12–17 years)	71	34.8 (18.3)	707.6 (441.3)
	adults	6	31.5 (16.8)	426.8 (263.6)
60	children (9–11 years)	8	49.5 (24.9)	995.0 (598.9)
	adolescents (12–17 years)	87	54.0 (26.3)	1103 (633.5)
	adults	6	68.1 (20.8)	895.8 (344.3)

Mean (SD).

^a AUC_{0-tau} for children and adolescents, and AUC₀₋₂₄ for adults.

in Supplementary Fig. 1 and Fig. 2. The final model well captures the sex effect on CL/F as demonstrated by no significant difference both in empirical Bayes prediction of η of CL/F between males and females (Supplementary Fig. 2 (a) and Supplementary Fig. 3). Also, the final model was evaluated by a pcVPC, and the concentration profiles of the observed median, 5th, and 95th percentiles for the duloxetine concentrations were captured by the 95% PIs of the corresponding estimated percentiles as shown in Fig. 3 and Supplementary Fig. 4 (a). These findings supported the conclusion that the final model well described the observed steady-state plasma duloxetine concentrations in pediatric patients. Consequently, we concluded the population PK model of duloxetine was appropriately constructed for the obtained data from Japanese pediatric patients with MDD Fig. 2

4. Discussion

This study reports the population PK model and exposure information of duloxetine for Japanese children. Although duloxetine has not been approved for pediatric use in Japan, they would be useful to consider an appropriate dose regimen of duloxetine for Japanese children. We investigated the effects of intrinsic factors on Japanese pediatric PK. Duloxetine plasma concentrations were adequately described by the one-compartment model with first-order absorption. Although the inter-individual variability on V/F and the covariance between CL/F and V/F was incorporated in a model reported previously [4], the final model included the inter-individual variability only on CL/F because the inter-individual variability on CL/F and V/F were highly correlated and the inter-individual variability on V/F was not appropriately estimated without the covariance. The population PK model suggested that CL/F was affected by sex. Similarly, a previous study has reported that a population PK model of duloxetine for adult patients has the effect of sex as a covariate of F [9]. One possible explanation is that duloxetine is mainly metabolized by CYP1A2 and CYP2D6, and a gender difference is known for CYP1A2. A gender difference is known for CYP1A2 [10]. The stronger activity of CYP1A2 in males

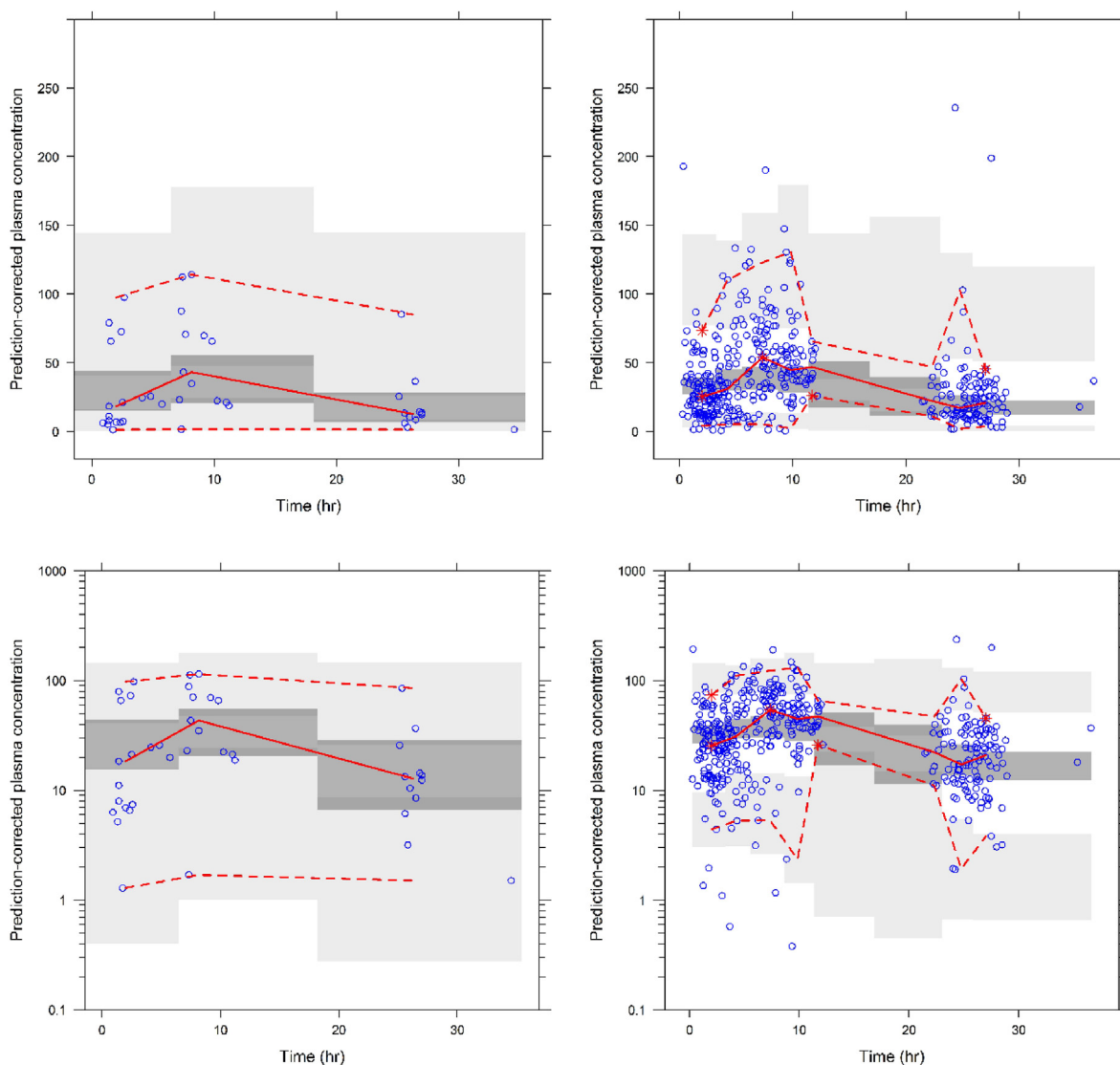


Fig. 3. Prediction-corrected visual predictive check for the final model stratified by Children (Left) and Adolescents (Right)

Red solid line: observed median. Red dashed line: observed 5th and 95th percentiles. Dark grey shaded area: model predicted 95% CI of median. Grey shaded area: model predicted 95% CIs of 5th and 95th percentiles. Time: time after the reference dose. 200 simulations.

(Upper: Linear scale, Lower: Semilog scale). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

than that in females may be related to the generally lower plasma concentration of duloxetine in males.

Anomalous high concentrations (>250 ng/mL) were observed in two subjects. A sensitivity analysis, in which eight samples from them were excluded, was conducted by using the final model to assess the effect of the outliers on the results. The differences in the population mean parameters estimated using the remaining 482 concentrations and all 490 concentrations were $<3\%$. Another sensitivity analysis was done without 7 low concentrations ($DV/IPRED <5\%$). The population mean parameters were comparable with those in final model (the difference $<2\%$). These results suggest a minimal effect of the outliers on the final parameter estimate. The duloxetine PK parameters for the reference population of US pediatric patients ($BSA = 1.55$ m², Dose = 60 mg, and non-American Indian race) were estimated to be 79.7 L/h for CL/F and 1200 L for V/F [4], and the parameters for the reference population of Japanese pediatric patients (Sex = male) were estimated to be 81.4 L/h for CL/F and 1170 L for V/F as shown in Table 2. Although the

number of Japanese children subjects in this study has an imbalanced age distribution and also the final population PK model is not the same, the estimated population mean parameters in Japanese and US pediatric patients were comparable. This is probably because the population PK models were constructed mainly based on the data in pediatric patients aged 9 years old or older for both the Japanese and US pediatric patients since more than half of the data for the US pediatric model were also from adolescents. In the US pediatric model, the effect of BSA was included in CL/F, while the effect of sex was included in CL/F in the Japanese pediatric model. We examined the effect on the model of body size descriptors such as body weight, height, BMI, BSA, IBW, LBW, and ABW; none of them were included in the model. The patient numbers of males/females were imbalanced in adolescents. However, the BSA for male and female adolescents was comparable with mean (SD) values of 1.53 (0.2) m² and 1.48 (0.2) m², respectively, and no clear trend between BSA and CL/F was not identified in males, females, or overall patients in Supplementary Fig. 2 (base model). Therefore,

the imbalance of male/female in adolescents was not considered to affect the model construction regarding the selection of BSA as a covariate. Since the range of body size in this study was limited with the mean (range) body weight of 36.9 (27.6–46.6) kg, patients with a broad range of body size (especially smaller body size) should be included in the analysis to further identify effects of these descriptors.

Comparisons of duloxetine PK parameters in Japanese pediatric patients with Japanese adult patients are shown in Table 3, the pcVPC stratified by sex is shown in Supplementary Fig. 4 (a), and the individual observed plasma concentration data for Japanese adult males is shown in Supplementary Fig. 4 (b). The mean CL/F values at 40 mg for Japanese children, adolescents and adults were 97.9 L/hr, 82.6 L/h and 93.7 L/h, respectively, and at 60 mg are 71.3 L/h, 68.5 L/h and 67.0 L/h, respectively. The mean duloxetine CL/F in pediatrics was slightly higher than adults at each dose level, however, as shown in Table 3 and Supplementary Fig. 4, the plasma exposures in pediatrics (even in males) are higher than or comparable to those in adults, indicating that in terms of drug exposure, the dose in this clinical trial yielded adequate exposure to pediatric subjects from the PK perspective.

The final model well captured the duloxetine concentration regardless of the age and weight as shown in Supplementary Fig. 1 (b). However, the range of age and body size in this analysis were limited. Therefore, further investigations are necessary to develop the population PK model for the pediatrics less than 9 years old and/or less than 30 kg.

5. Conclusion

We developed the population PK model sufficiently describes duloxetine steady-state PK after oral administration to Japanese pediatric patients aged 9–17 years with MDD for the first time. Duloxetine plasma concentrations were adequately described by the one-compartment model with first-order absorption. The exposure of pediatric patients was comparable or higher than that of adults when duloxetine was administered using the same dosage regimen. Therefore, the expected exposure was achieved in the pediatric subjects in this clinical trial. This population PK model provides useful information to understand the pharmacokinetic characteristics of duloxetine for Japanese pediatric patients with MDD.

Author disclosure statements

Risa Y. Shibata and Ryuji Kubota are employees of Shionogi & Co., Ltd. Osaka Japan; Toshihiro Wajima was an employee of Shionogi & Co., Ltd. (present affiliation: Clinical Pharmacology, IDEC Inc., Tokyo, Japan); Kazunori Uenaka and Atsunori Kaibara are employees and shareholder of Eli Lilly Japan, Kobe, Japan.

Author's contributions

R. Kubota and T. Wajima designed the analysis. R.Y. Shibata analyzed the data and wrote the manuscript. K. Uenaka, A. Kaibara, and reviewed the analyses and the manuscript.

Declaration of competing interest

The authors are employees of Shionogi & Co., Ltd or Eli Lilly Japan, which sponsored this research. The authors have indicated that they have no other conflict of interest regarding the content of this article.

The sponsor was involved in the study design, collection/analysis/interpretation of data, writing of the report, or the decision to submit the article for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.dmpk.2023.100496>.

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