Effects of Intrinsic Factors on the Clinical Pharmacokinetics of Vortioxetine

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Abstract

Vortioxetine is an antidepressant agent with multimodal activity that is approved for the treatment of major depressive disorder at doses of 5 to 20 mg once daily. Vortioxetine is a medium-clearance drug that undergoes extensive metabolism via several cytochrome P450 isozymes. A series of single- and multiple-dose pharmacokinetic studies were performed to evaluate the impact of intrinsic (ie, subject-related) factors, such as age, sex, race, and renal and hepatic function, on the pharmacokinetics of vortioxetine. The point estimates on the ratios and their 90% confidence intervals (CIs) for the central values of AUC (area under the concentration-time curve) and Cmax (maximum plasma concentration) were obtained by taking the antilog of the differences and 90%CIs in the log-transformed least-squares means. The results demonstrate that there were no clinically meaningful differences (defined as exposure difference between 50% and 2-fold change) in the exposure to vortioxetine (as assessed by AUC and Cmax) between elderly and younger subjects, men and women, and blacks and whites and among subjects with varying degrees of renal or hepatic impairment. These results suggest that no dosing adjustments of vortioxetine are required for the intrinsic factors investigated in these studies.

Keywords

vortioxetine, pharmacokinetics, age, sex, race, hepatic impairment, renal impairment, adverse events
CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8, and CYP2B6 and subsequent glucuronic acid conjugation.\textsuperscript{11,14} CYP2D6 is the primary enzyme catalyzing the metabolism of vortioxetine to its major metabolite (Lu AA34443), which is inactive. A second metabolite (Lu AA39835) is equipotent to vortioxetine as an inhibitor of human 5-HT transporter, but its concentration is much lower than that of the parent compound in plasma (ie, metabolic ratio \(\leq 0.04\)).\textsuperscript{15} and it is not expected to have effects on the central nervous system (CNS) based on a nonclinical pharmacology study.\textsuperscript{11,14} Therefore, the pharmacological activity of vortioxetine is assessed primarily on the basis of exposure to the parent drug. Following a single oral dose of \([14C]\)-labeled vortioxetine, approximately 59% and 26% of the administered radioactivity was recovered in urine and feces, respectively, as metabolites.\textsuperscript{16} Negligible amounts of unchanged vortioxetine were excreted in urine. Vortioxetine has been investigated in the multiple drug-drug interaction studies of coadministration with CNS-active agents (ie, ethanol, diazepam, and lithium)\textsuperscript{17} and drugs that interfere with hemostasis (ie, aspirin and warfarin),\textsuperscript{18} which found that vortioxetine had no meaningful effect on the PK of any of the evaluated agents in healthy subjects.\textsuperscript{19}

Because vortioxetine will be administered to a patient population with a wide range of demographic and disease characteristics, it is relevant to understand the specific intrinsic factors that might influence the clinical PK of the drug. Thus, a series of studies were undertaken to evaluate the PK of vortioxetine in various subpopulations and to provide guidance regarding recommended dosing in these subpopulations. This series of studies was designed to evaluate the effect of age, sex, and race, as well as renal and hepatic function, on the PK of vortioxetine.

**Methods**

**Study Design**

Study 111 was a single-blind, placebo-controlled, randomized, parallel-group trial that evaluated the effects of age, sex, and race. Studies 112 (on the effect of renal impairment) and 114 and 401 (on the effect of hepatic impairment) were open-label, nonrandomized, parallel-group studies. Study 111 evaluated both single and multiple doses of vortioxetine PK, whereas the other studies were single-dose studies. Additional details are included in Supplemental Table 1. These studies were conducted according to the World Medical Association Declaration of Helsinki, the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice, and all applicable regulations. The protocols were approved by the site-designated investigational review boards, and all subjects provided written informed consent.

**Subjects**

Subjects in all studies included healthy men and women weighing \(\geq 50\) kg and with a body mass index of 19 to 38 kg/m\(^2\), inclusive. Subjects in study 111 (age, sex, and race) were aged 18 to 45 years ("young") or 65 to 85 years ("elderly"). Study 112 (renal impairment) subjects were aged 18 to 75 years and included both healthy subjects and those with varying degrees of renal impairment, stratified into 5 groups based on estimated serum creatinine clearance (CrCl) using the Cockcroft-Gault formula.\textsuperscript{20} Groups included healthy controls (CrCl > 80 mL/min), mild impairment (CrCl 51-80 mL/min), moderate impairment (CrCl 30-50 mL/min), severe impairment (CrCl < 30 mL/min), and end-stage renal disease (ESRD; on hemodialysis or with no or negligible urine output). Subjects in the hepatic impairment studies (studies 114 and 401) were aged 18 to 75 years and were classified as having no (studies 114 and 401), mild (study 114), moderate (study 114), or severe (study 401) hepatic impairment according to the Child-Pugh classification system.\textsuperscript{21} Healthy subjects enrolled in studies 112, 114, and 401 were individually matched with renally or hepatically impaired subjects on the basis of race, sex, age (±10 years), body weight (±30%), and smoking status.

**Dosing and Sampling**

In the single-dose phases, subjects received a single oral dose of vortioxetine on day 1 after an overnight fast of at least 8 hours. Vortioxetine 10 mg was used in all subjects except for those with severe hepatic impairment and their healthy matched controls (study 401), for whom vortioxetine 5 mg was used. Serial blood and urine samples for PK analyses of vortioxetine and its metabolites Lu AA34443 and Lu AA39835 were collected up to 120 hours after a single dose and up to 24 hours after the last once-daily doses in study 111, up to 120 hours postdose in study 112, up to 168 hours postdose in study 114, and up to 240 hours postdose in study 401. Blood samples for protein-binding determination were collected predose in studies 112, 114, and 401. In study 111 (healthy matched controls), subjects returned to the clinic after a 14-day washout period from the single-dose phase to begin the multiple-dose phase, in which they were randomized to receive vortioxetine 10 mg or placebo once daily for an additional 14 days.

**Pharmacokinetic Evaluations and Statistical Analysis**

Sample sizes for the hepatic impairment and renal impairment studies (112, 114, and 401) were determined in accordance with US Food and Drug Administration
Table 1. Subject Demographics and Baseline Characteristics

|                        | Study 111 (n = 63) | Study 112 (n = 66) | Study 114 (n = 33) | Study 401 (n = 12) |
|------------------------|--------------------|--------------------|--------------------|--------------------|
| Sex, n (%)             |                    |                    |                    |                    |
| Male                   | 31 (49)            | 38 (58)            | 19 (58)            | 10 (83)            |
| Female                 | 32 (51)            | 28 (42)            | 14 (42)            | 2 (17)             |
| Age (y), mean          | 51.3               | 58.7               | 53.6               | 52.6               |
| Ethnicity, n (%)       |                    |                    |                    |                    |
| Hispanic/Latino        | 49 (78)            | 43 (65)            | NR                 | 12 (100)           |
| Race, n (%)            |                    |                    |                    |                    |
| White                  | 32 (51)            | 34 (52)            | 33 (100)           | 12 (100)           |
| Black/African American | 31 (49)            | 26 (39)            | 0                  | 0                  |
| Asian                  | 0                  | 6 (9)              | 0                  | 0                  |
| BMI (kg/m²), mean      | 27.5               | 27.7               | 27.2               | 28.7               |

BMI, body mass index; NR, not reported.

(FDA) guidance. In the age, sex, and race study (111), sample size was calculated using a precision approach in which the analysis was assumed to be on log-transformed data. The sample-size calculation was based on an analysis of variance model with fixed main effects for age, sex, and race. For within-subject variability of CV% = 37% (estimated based on the median CV% of area under the concentration-time curve from time 0 extrapolated to infinity [AUC_{\infty}] from a previous single-dose study), to achieve ≥80% coverage probability that the 90% confidence intervals (CIs) on the ratio of reference to test was contained within 70% to 143% of the true ratio, a sample size of 64 subjects (8 subjects per group: 6 active and 2 placebo) was required.

The bioanalytical assay methodology has been described in previous studies of vortioxetine. Blood samples for the determination of plasma concentrations of vortioxetine and metabolites were collected in chilled Vacutainers containing ethylenediaminetetraacetic acid. Plasma and urine samples were stored at -20°C or lower prior to the analysis and were prepared by solid-phase extraction using Varian SPEC C8 cartridges in a 96-well plate format. Plasma and urine concentrations of vortioxetine and metabolites were measured by separate validated high-performance liquid chromatography with tandem mass spectrometry methods for each matrix. The internal standards were the 13C-labeled analogues of each of these 3 analytes. For the plasma assay, the linear ranges for vortioxetine, Lu AA34443, and Lu AA39835 were 0.08 to 80, 0.2 to 200, and 0.04 to 40 ng/mL, respectively. For the urine assay, the linear ranges were 10 to 2500 ng/mL for vortioxetine, 25 to 6250 ng/mL for Lu AA34443, and 10 to 2500 ng/mL for Lu AA39835. The accuracy and precision for these analytes were within 90.0% to 109.0% and 3.2% to 10.7%, respectively.

PK parameters were derived from the plasma and urine concentration-time data for all evaluable subjects using standard noncompartmental methods. The PK parameters included area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}) and from time 0 to 24 hours (AUC_{0-24}), C_{max}, time to reach C_{max} (t_{max}), and t½. Plasma and urine concentrations that were below the limit of quantification were set to zero in the computation of mean concentration values and in the derivation of individual-subject PK parameters. Subjects were also genotyped for common CYP2C9, CYP2C19, and CYP2D6 allelic variants associated with drug metabolism. Protein binding was assessed by equilibrium dialysis of the predose plasma sample spiked with radiolabeled parent drug (studies 112, 114, and 401). Unbound PK parameters were determined, including AUC_{last} and C_{max} for the unbound fraction (AUC_{last,u} and C_{max,u}), in the renal (study 112) and hepatic (studies 114 and 401) studies.

An analysis of covariance model for all studies was performed with body weight as a covariate and hepatic or renal function as a factor on the natural logarithms of AUCs and C_{max}. For study 111, the model also included fixed effects for age, sex, and race and interaction terms for age by race, age by sex, race by sex, and age by race by sex. For study 112 (renal impairment), study 114 (mild/moderate hepatic impairment), and study 401 (severe hepatic impairment), the renal or hepatic function group was used as a fixed factor to evaluate the effect of renal or hepatic impairment on vortioxetine and its metabolites. Within the framework of analysis of covariance, the point estimates on the ratios and their 90% CIs for the central values of AUC_{last} and C_{max} were obtained by taking the antilog of the differences and 90% CIs in the log-transformed least-squares (LS) means. In addition, the
relationship between renal function and PK variables was evaluated using regression methods, with estimated CrCl at check-in as an independent variable and the PK parameter as the dependent variable. Predictions (ie, estimates) and their precisions (90% CIs) for CrCl representative of the various renal function groups were obtained for each PK parameter. For hepatic impairment studies 114 and 401, the relationship between Child-Pugh score and dose-normalized $C_{\text{max}}$ and AUCs of vortioxetine, Lu AA34443, and Lu AA39835 was evaluated graphically by phenotype using the pooled data from these 2 studies.

**Safety Assessment**

Safety was monitored throughout the studies, including treatment-emergent adverse events (TEAEs), clinical laboratory test results (hematology, serum chemistry, and urinalysis), vital signs and weight measurements, 12-lead electrocardiogram assessments, and physical examination observations.

**Results**

**Subjects**

There were 63, 66, 33, and 12 subjects enrolled in studies 111 (age, sex, and race), 112 (mild, moderate, or severe renal impairment or ESRD), 114 (mild/moderate hepatic impairment), and 401 (severe hepatic impairment), respectively. Baseline demographics and patient characteristics are summarized in Table 1.

**Pharmacokinetics**

_Age, Sex, Race (Study 111)._ Mean plasma concentration-time profiles of vortioxetine on day 28 following once-daily dosing for 14 days (end of multiple-dose phase) for age, sex, and race are displayed in Figure 1. Statistical analyses of the plasma PK of multiple-dose vortioxetine by age, sex, and race are summarized in Table 2. AUC$_{0-24}$ and $C_{\text{max}}$ were 27% and 23% lower, respectively, in elderly subjects compared with younger subjects. When evaluated by sex and race, the respective vortioxetine AUC$_{0-24}$ and $C_{\text{max}}$ values were 27% and 24% higher in women than in men and 25% and 33% higher in black subjects than in white subjects (Table 2 and Figure 2). The effects of age, sex, and race were generally consistent between the single-dose phase and multiple-dose phase of this study (Supplemental Table 2).

_Renal Function (Study 112)._ The percentage of unbound vortioxetine ranged from 0.88% to 1.04% in the renal impairment groups and from 1.02% to 1.10% in the healthy matched control groups (ie, approximately 99% protein bound for all groups). Because there was no apparent difference in plasma protein binding of vortioxetine between subjects with hepatic impairment and their healthy controls, only the PK parameters based on total plasma vortioxetine concentrations are presented in this article.

LS means analyses of vortioxetine PK parameters in the 4 renally impaired groups (mild, moderate, severe, ESRD) and their healthy matches are summarized in Table 3. No statistically significant differences were observed for AUC$_{\text{last}}$ or $C_{\text{max}}$ between any of the renal impairment groups and their healthy matches (Figure 2). AUC$_{\text{last}}$ was 9%, 16%, and 11% higher in
**Table 2. Effects of Age, Sex, and Race on the Multiple-Dose Pharmacokinetics of Vortioxetine 10 mg (Study 111)**

| LS Mean | Reference | Test | Ratio of LS Means (%) | 90% CI for Ratio of LS Means (%) |
|---------|-----------|------|------------------------|----------------------------------|
| **Age** |           |      |                        |                                  |
| Young   | (n = 20) | Elderly | (n = 20) |                        |                                  |
| $AUC_{0-24}$ (ng·h/mL) | 370.47 | 470.67 | 127.05 | (102.25–157.86) | 123.48 | (101.13–150.77) |
| $C_{max}$ (ng/mL) | 19.80 | 24.45 | 128.46 | (101.13–150.77) | 123.56 | (101.09–151.03) |
| **Sex** |           |      |                        |                                  |
| Male    | (n = 22) | Female | (n = 18) |                        |                                  |
| $AUC_{0-24}$ (ng·h/mL) | 369.87 | 471.44 | 127.46 | (102.46–158.56) | 123.56 | (101.09–151.03) |
| $C_{max}$ (ng/mL) | 19.80 | 24.46 | 123.56 | (101.09–151.03) | 123.56 | (101.09–151.03) |
| **Race** |           |      |                        |                                  |
| White   | (n = 21) | Black | (n = 19) |                        |                                  |
| $AUC_{0-24}$ (ng·h/mL) | 373.36 | 467.03 | 125.09 | (100.72–155.35) | 132.96 | (108.94–162.27) |
| $C_{max}$ (ng/mL) | 19.08 | 25.38 | 132.96 | (108.94–162.27) | 132.96 | (108.94–162.27) |

$AUC_{0-24}$, area under the plasma concentration-time curve from time 0 to 24 hours; CI, confidence interval; $C_{max}$, maximum observed plasma concentration; LS, least squares.

Subjects with mild, moderate, or severe renal impairment, respectively, than in their healthy controls. Slight differences (<11%) were observed for $C_{max}$ in subjects with mild, moderate, or severe renal impairment compared with their healthy controls. Vortioxetine $AUC_{last}$ and $C_{max}$ were 13% and 27% lower, respectively, in subjects with ESRD than in healthy controls.

Based on the regression analysis, a statistically significant linear relationship between the $AUC_{last}$ of vortioxetine and CrCl was observed; however, the predicted $AUC_{last}$ values for each renal impairment group did not differ from those for the corresponding healthy control group by more than 30%. No relationship between vortioxetine $C_{max}$ values and CrCl was identified.

**Hepatic Function (Studies 114 and 401).** The percent of unbound vortioxetine ranged from 0.88% to 1.00% for those with mild, moderate, and severe hepatic impairment and from 0.91% to 1.06% for their healthy matched controls (i.e., approximately 99% protein bound for all groups). As with the renal impairment study (112), this article presents only the PK parameters based on total plasma vortioxetine concentrations.

LS mean analyses of PK parameters for each hepatic subgroup are summarized in Table 3. $AUC_{last}$ and $C_{max}$ values were lower in subjects with mild hepatic impairment (9% and 14%, respectively) and those with moderate hepatic impairment (2% and 16%, respectively) than in their healthy matched controls; however, these differences were not statistically significant (Figure 2). For subjects with severe hepatic impairment, $AUC_{last}$ was 10% higher and $C_{max}$ was 24% lower for those with severe hepatic impairment compared with their healthy controls. There also was no clear relationship between Child-Pugh score and exposure to vortioxetine, as measured by $AUC_{last}$ or $C_{max}$ by graphic evaluations.

**Safety**

Twenty-eight of 48 vortioxetine-treated subjects (58%) in study 111 (age, sex, race study) experienced a TEAE; the most common events were nausea (15%), headache (15%), abdominal pain (6%), blood pressure increased (6%), and dizziness (6%), the majority of which were mild in intensity and self-limiting. The incidence of TEAEs was higher among elderly subjects (16 of 24 [67%] versus younger subjects (12 of 24 [50%]). TEAEs were higher in women than in men (18 of 24 [75%] vs 10 of 24 [42%]) and in blacks compared with whites (16 of 24 [67%] vs 12 of 24 [50%]). In study 112 (renal impairment study), 6 of the 33 subjects with renal impairment (mild, 4 of 8 [50%]; moderate, 0 of 8 [0%]; severe, 1 of 9 [11%]; and ESRD, 1 of 8 [13%]) experienced a TEAE, with all TEAEs considered mild in intensity and self-limiting. Diarrhea occurred in 2 subjects with renal impairment, with all other events occurring in no more than 1 subject. Between studies 114 and 401, there were no TEAEs reported among subjects with mild hepatic impairment, 3 of 8 (37%) reported among subjects with moderate hepatic impairment, and 2 of 6 (33%) reported among subjects with severe hepatic impairment, all of which were considered mild and self-limiting. Four events (nausea [n = 2] and vomiting [n = 1] in the moderate hepatic group and vomiting [n = 1] in the severe hepatic group) were the only TEAEs considered to be related to study treatment.

**Discussion**

Vortioxetine is an antidepressant with a multimodal mechanism of action that has demonstrated beneficial activity in the treatment of MDD. The recommended starting dose of vortioxetine is 10 mg once daily.
Figure 2. Impact of intrinsic factors on the multiple-dose pharmacokinetics of vortioxetine. Values are ratios of geometric means and 90% CIs. AUC_{0-24}, area under the plasma concentration-time curve from time 0 to 24 hours; AUC_{last}, AUC from time 0 to the time of the last quantifiable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; ESRD, end-stage renal disease; PK, pharmacokinetics (parameter).

(administered without regard to meals) with an increase to 20 mg once daily as tolerated, because higher doses have been associated with better treatment effects. Vortioxetine 5 mg once daily can be considered for those who do not tolerate the higher doses.

The US FDA has provided guidance to pharmaceutical companies regarding the need to study the effect of patient-related factors (eg, age, sex, race, liver impairment, and kidney impairment) on the PK of drugs under development.\textsuperscript{22–24} This guidance is aimed toward providing the best possible recommendations with respect to specific dosages for these patient subpopulations. The current single-dose and multiple-dose PK studies were conducted in accordance with the regulatory guidance to provide recommendations regarding the dosing of vortioxetine in various patient subpopulations. In all studies, an adequate number of subjects were enrolled to have a sufficient number for analysis,
Table 3. Effects of Hepatic and Renal Impairment on the Single-Dose Pharmacokinetics of Vortioxetine 10 mg (Mild or Moderate Hepatic Impairment, All Degrees of Renal Impairment) or 5 mg (Severe Hepatic Impairment) — Studies 112, 114, and 401

| LS Mean | HMC | Test | Ratio of LS Means (%) | 90%CI for Ratio of LS Means (%) |
|---------|-----|------|------------------------|---------------------------------|
| Hepatic impairment                          |     |      |                        |                                 |
| Mild (10 mg)                                |     |      |                        |                                 |
| AUC_{last} (ng·h/mL)                        | 329.89 | 299.96 | 90.93                  | (70.71–116.93)                  |
| C_{max} (ng/mL)                             | 4.65  | 3.98  | 85.55                  | (72.52–100.93)                  |
| Moderate (10 mg)                            |     |      |                        |                                 |
| AUC_{last} (ng·h/mL)                        | 274.48 | 269.17 | 98.07                  | (74.29–129.46)                  |
| C_{max} (ng/mL)                             | 4.07  | 3.41  | 83.88                  | (66.54–105.76)                  |
| Severe (5 mg)                               |     |      |                        |                                 |
| AUC_{last} (ng·h/mL)                        | 160.98 | 177.70 | 110.39                 | (76.73–158.81)                  |
| C_{max} (ng/mL)                             | 2.04  | 1.54  | 75.52                  | (49.41–115.46)                  |
| Renal impairment                            |     |      |                        |                                 |
| Mild (10 mg)                                |     |      |                        |                                 |
| AUC_{last} (ng·h/mL)                        | 229.60 | 250.56 | 109.13                 | (91.42–130.27)                  |
| C_{max} (ng/mL)                             | 4.56  | 4.08  | 89.50                  | (75.05–106.74)                  |
| Moderate (10 mg)                            |     |      |                        |                                 |
| AUC_{last} (ng·h/mL)                        | 250.48 | 290.62 | 116.03                 | (95.70–140.68)                  |
| C_{max} (ng/mL)                             | 4.20  | 4.23  | 100.59                 | (84.60–119.59)                  |
| Severe (10 mg)                               |     |      |                        |                                 |
| AUC_{last} (ng·h/mL)                        | 259.17 | 286.43 | 110.52                 | (92.56–131.96)                  |
| C_{max} (ng/mL)                             | 4.33  | 4.69  | 108.18                 | (93.13–125.65)                  |
| ESRD (10 mg)                                |     |      |                        |                                 |
| AUC_{last} (ng·h/mL)                        | 232.23 | 202.38 | 87.15                  | (64.38–117.97)                  |
| C_{max} (ng/mL)                             | 4.72  | 3.47  | 73.42                  | (54.18–99.48)                   |

AUC_{last}, area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; CI, confidence interval; C_{max}, maximum observed plasma concentration; ESRD, end-stage renal disease; HMC, healthy matched control; LS, least squares.

and matched controls were selected to participate based on predetermined criteria, as specified in the protocols. In addition, the conclusion that there is no clinically meaningful effect of the intrinsic factors on the PK of vortioxetine was based on a thorough understanding of the vortioxetine exposure-response relationships for efficacy and safety and on the study results that the changes relative to matched controls were between 50% and the 2-fold boundary for both AUC and C_{max}.

The current studies evaluated the effect of various intrinsic factors on the PK of the parent drug. Metabolites were analyzed in these studies but are not presented in this article because they are either inactive or considered minor with limited CNS penetration. All the studies evaluated the effect of vortioxetine 10 mg (the recommended initial starting dose) except for study 401 (severe hepatic impairment), in which vortioxetine 5 mg was used. A lower dose was chosen for this patient subpopulation because vortioxetine is primarily eliminated via hepatic metabolism. Subjects with severe hepatic impairment typically have significantly lower liver metabolic enzyme levels/activities and therefore are likely to be exposed to higher plasma drug levels and, possibly, more pronounced adverse events. Although subjects in the hepatic and renal impairment studies were genotyped to explore the relationship between predicted CYP phenotypes and vortioxetine exposure, the numbers of subjects classified as CYP2D6, CYP2C9, and CYP2C19 poor metabolizers (PMs) were too low to make definitive conclusions. A potential effect of inferred metabolic status for CYP2D6, CYP2C19, and CYP2C9 was assessed in the phase 1 population PK analysis using data from 887 subjects (70% male and 30% female) from 26 clinical pharmacology studies. The results from this population PK analysis indicated that oral clearance was approximately 2-fold higher in CYP2D6 extensive metabolizers (EMs; n = 540) than in PMs (n = 38); however, the approximately 2-fold higher vortioxetine exposure in CYP2D6 PMs did not translate into significant changes in the safety and tolerability profile of vortioxetine, as no significant differences in the adverse event profile between the CYP2D6 PMs and the non-PMs were observed. No CYP2C9 PMs were identified in the phase 1 population PK analysis, and no relationship between vortioxetine CL/F and the CYP2C9 inferred metabolic status was observed. CYP2C19 PMs were shown to have a 31% lower CL/F compared with CYP2C19 EMs; however, this higher
vortioxetine exposure was not considered clinically meaningful.

Age was also found to impact the oral clearance to a statistically significant degree in this analysis. Consistent with the results from study 111 (age, sex, and race), the effect of age on vortioxetine exposure was not considered clinically meaningful based on simulations from the population PK analysis, as a 75-year-old subject is expected to have approximately 40% higher exposure compared with the population mean of 44 years. Sex, race, and ethnicity were not identified as statistically significant covariates for vortioxetine PK based on the population PK analysis for healthy subjects.

Results from these studies demonstrated that the PK profiles of vortioxetine were generally similar in elderly and younger subjects, men and women, black and white subjects, and in subjects with varying degrees of renal and hepatic impairment. These results suggest that no dosing adjustments are required on the basis of age, sex, race, ethnicity, or renal function. In addition, no dosage adjustment is required for those with mild or moderate hepatic impairment. The results of study 401 presented here, which showed that severe hepatic impairment did not significantly alter the PK of vortioxetine, support the administration of the drug to patients with severe hepatic impairment without dose adjustment.

A potential limitation of the current study is that only single doses of vortioxetine were evaluated in studies 112 (renal impairment), 114 (hepatic impairment), and 401 (hepatic impairment), with patients in clinical practice generally started at a lower dose and titrated to the highest effective dose over multiple weeks. However, FDA guidance states that a single-dose study may be sufficient for cases for whom there is evidence that multiple-dose PK is accurately predicted by single-dose data (ie, when the drug displays linear and time-independent PK at the concentrations anticipated).22,23 Vortioxetine showed similar oral clearance following single and multiple doses, and the population PK analysis for healthy subjects indicated no apparent time dependence or nonlinearity.11

Conclusion

The results of these studies support a recommendation that dosing adjustments not be required based on age, sex, race, hepatic function (mild, moderate, or severe impairment), or renal function (mild, moderate, or severe impairment or ESRD).

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Declaration of Conflicting Interests

Dr. Grace Chen, Dr. John Affinito, and Dr. Shining Wang are current employees of Takeda Pharmaceutical Company, Ltd. Dr. George G. Nomikos, Dr. William Jacobson, Ms. Zhen Zhao, and Ms. Jinhui Xie are former employees of Takeda Pharmaceutical Company, Ltd.

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**Supporting Information**

Additional supporting information may be found online in the Supporting Information section at the end of the article.