Clinical Pharmacology in Drug Development
2020, 9(2) 224–234

DOI: 10.1002/cpdd.737

Population Pharmacokinetics of Paliperidone Palmitate (Once-Monthly Formulation) in Japanese, Korean, and Taiwanese Patients With Schizophrenia

Hiroko Shimizu[1], Martine Neyens[2], Marc De Meulder[2], Srihari Gopal[3], Yuko Tsukamoto[1], Mahesh N. Samtani[3], and Bart Remmerie[2]

Abstract

The paliperidone pharmacokinetics after intramuscular administration of once-monthly paliperidone palmitate in Japanese patients were studied in 3 phase 1 studies and in 2 phase 3 studies performed in Japan, Korea, and Taiwan. These data (Japanese, n = 509; Korean, n = 31; Taiwanese, n = 47) were used to describe the paliperidone palmitate pharmacokinetics in Japanese, to compare with non-Japanese, and to validate the historical population pharmacokinetic (Pop-PK) model for paliperidone palmitate, developed using data from studies in patients with schizophrenia outside Japan. The final historical Pop-PK model, including all significant patient covariates of Japanese studies, was used to simulate paliperidone plasma concentration–time data using nonlinear mixed effects, followed by comparison with actual data. Visual predictive checks displayed considerable overlap between predicted and actual plasma concentrations; the majority of observations were within the 90% prediction interval. Japanese, Korean, and Taiwanese patients had comparable plasma concentrations. Covariate distributions demonstrated comparatively lower median body mass index in Japanese, Korean, and Taiwanese patients versus rest-of-world population. Prediction errors for the data set used for external validation were within cutoff values, confirming accuracy/precision of the model. Paliperidone pharmacokinetics were adequately predicted for Japanese studies using the historical Pop-PK model, confirming its robustness. Pharmacokinetics in Japanese, Korean, and Taiwanese patients with schizophrenia were comparable with rest-of-world population.

Keywords

long-acting injectable, paliperidone palmitate, pharmacokinetics

Schizophrenia is a chronic and debilitating mental illness that affects millions worldwide.[1] Atypical antipsychotics are the mainstay of treatment for patients with schizophrenia. However, despite continued advancements in these medications during the past 50 years, poor medication adherence is high and presents the greatest obstacle to recovery and relapse prevention.[2,3] It is estimated that up to 75% of patients with schizophrenia have difficulty adhering to a daily oral treatment regimen[4], thereby increasing the risk of relapse. Relapse is disabling and distressing and is associated with a progressive functional deterioration and worsening treatment response and clinical prognosis, as well as slower and less complete recovery with each successive relapse.[5–7] Maintenance therapy is therefore an important aspect of the treatment of patients with schizophrenia.

Paliperidone, the active, 9-hydroxy metabolite of the atypical atipsychotic, risperidone, exhibits antagonism at both dopamine type 2 and serotonin 2A receptors. Being more hydrophilic than the parent, paliperidone has a different pharmacokinetic profile and is predominantly eliminated unchanged via the renal route.[8–10] Three formulations of paliperidone have been developed: an oral extended-release formulation, and a long-acting injectable (LAI) formulation (paliperidone palmitate) for intramuscular administration every 4 weeks (1-month formulation) and every

[1]Janssen Pharmaceutical K.K, Tokyo, Japan
[2]Janssen Research and Development, a division of Janssen Pharmaceuticals NV, Beerse, Belgium
[3]Janssen Research and Development LLC, Raritan, New Jersey, USA

Submitted for publication 1 March 2019; accepted 7 August 2019.

Corresponding Author:
Hiroko Shimizu, Janssen Pharmaceutical K.K, 5-2 Nishi-kanda-3-tyome, Chiyoda-ku, Tokyo, 101-0065 Japan
(e-mail: hshimizu@its.jnj.com)

3 months. These formulations are approved for the treatment of schizophrenia in numerous countries including the United States.

Following administration of paliperidone palmitate LAI (1-month formulation), drug release begins as early as the first day and can last for at least 4 months.[11] The median terminal half-life ($t_{1/2}$) ranges from 25 to 49 days over the dose range of 25 to 150 mg equivalent (eq.) paliperidone. The pharmacokinetics is dose-proportional in terms of total exposure (area under the plasma concentration–time curve [AUC]) and slightly less than dose-proportional for peak exposure (C_{max}) and the C_{max} is higher after deltoid injection compared with gluteal injection. After a single dose, the time to peak exposure (t_{max}) ranged from 13 to 14 days after deltoid and 13 to 17 days after gluteal injection.[12] In patients with mild renal impairment, dosage adjustment is necessary.[13] No dose adjustment is required in patients with mild or moderate hepatic impairment; no data currently exist regarding severe hepatic impairment. Elderly patients with normal renal function can receive the same dosage as younger adult patients with normal renal function.[11]

For adults, the recommended starting dose of paliperidone palmitate is 150 mg eq., followed by a second dose of 100 mg eq. 1 week later, both administered in the deltoid muscle. The recommended monthly maintenance dose (75 mg eq.) can be administered either in the deltoid or gluteal muscle. The maintenance dose can be adjusted within the range of 25 to 150 mg eq. based on individual patients' symptoms and/or tolerability without any oral supplementation. The injection can be administered either in the deltoid muscle (patients weighing ≤90 kg, 1-inch 23-gauge needle; >90 kg, 1.5-inch 22-gauge needle) or in the gluteal muscle (1.5-inch 22-gauge needle).[9,11–13]

The pharmacokinetics of paliperidone after intramuscular administration of paliperidone palmitate have been evaluated in patients with schizophrenia in several global single- and multiple-dose phase 1, 2, and 3 studies.[9] Based on these studies outside of Japan, which included a small number of patients from other East Asian countries, a comprehensive population pharmacokinetic (Pop-PK) model for paliperidone palmitate was developed,[9,13] and used as the key evaluation tool in the present analysis. In this model, the plasma concentration–time profile for paliperidone following intramuscular administration of its palmitate ester was best described by a 1-compartment model with first-order elimination. The absorption of paliperidone was complex, and a dual input model was specified to best capture this complexity. The absorption component in this model allowed a fraction of the dose to enter relatively quickly into the central compartment following a zero-order process. After a lag time, the remaining fraction then entered the systemic circulation via a first-order process. This model facilitated understanding of the disposition of paliperidone and allowed an evaluation of the interindividual variability in the pharmacokinetics in the target patient population. The results suggested that the pharmacokinetics of paliperidone were mostly influenced by body mass index (BMI), creatinine clearance, injection site, injection volume, and needle length. The model was validated several times using external data sets from 2 phase 1 and 3 phase 3 studies.[14] Accuracy and precision of the external validations were consistently within the predefined criteria, that is, within the |15|% for median percent prediction error (PE%) and within the 30% for the median absolute PE% (|PE|%), respectively; thus, the model can be considered valid from an accuracy and precision standpoint.

The paliperidone pharmacokinetics after paliperidone palmitate intramuscular administration (1-month formulation) in Japanese, Korean, and Taiwanese patients was evaluated in 3 phase 1 and 2 phase 3 studies. In this post hoc analysis, the pharmacokinetic data obtained in these studies were described and compared with the rest-of-world (ROW) population. Additionally, the applicability of the historical Pop-PK model to Japanese, Korean, and Taiwanese patients was evaluated comparing the actual data obtained in the Japanese patients with the model-based predictions.

Methods

Data were obtained from 2 phase 1 studies in Japanese patients (studies JPN-1, and JPN-3 [NCT01942382]), a phase 2 (JPN-2 [NCT01606254]), 2 phase 3 studies (JPN-4 [NCT01299389] in Japanese, Korean, and Taiwanese patients and JPN-5 [NCT01258920] in Japanese patients). The protocols and amendments were reviewed and approved by independent institutional review boards. The studies were conducted in accordance with the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference on Harmonization, and local laws and regulations. All patients gave written informed consent before study entry, after full explanation of the study.

Study Population

Men and women patients were eligible for participation in the studies if they were between 20 and 65 years of age (20 years or older in JPN-4 and JPN-5), diagnosed with schizophrenia of any subtype according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, and clinically stable as per investigator judgment (JPN-1, JPN-2, and JPN-3) or had a Positive and Negative Syndrome Scale score of 60 to 120 (JPN-4 and JPN-5). Patients who had been

treated with an antipsychotic medication before study entry could continue using their medication throughout the study at the same dosage regimen in studies JPN-1 and JPN-3, excluding LAIs and risperidone. In the other studies, psychotropic drugs were not allowed. Epinephrine and carbamazepine were not allowed in any of the studies. Patients without documentation of previous treatment with risperidone or paliperidone received oral risperidone (or paliperidone extended release for studies JPN-4 and JPN-5) for at least 4 or 7 days at a dose appropriate for the study prior to the first paliperidone palmitate injection, to evaluate tolerability.

Study Designs

Doses of paliperidone palmitate can be expressed in terms of both milligram equivalents of the pharmacologically active fraction, paliperidone, and in milligrams of paliperidone palmitate; for example, 100 mg eq. equates to 156 mg paliperidone palmitate.

Studies JPN-1 and JPN-3 were phase 1 and JPN-2 phase 2, multicenter, open-label, randomized, parallel-group studies to evaluate the pharmacokinetics and safety of paliperidone palmitate in patients with schizophrenia. JPN-4 was a phase 3, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose, multicenter study in Japanese, Korean, and Taiwanese patients with schizophrenia to evaluate the efficacy of paliperidone palmitate. JPN-5 was a phase 3, open-label, flexible-dose, multicenter study in Japanese patients with schizophrenia to evaluate the long-term safety and tolerability of paliperidone palmitate. A summary of the dosage regimes and pharmacokinetic sampling is presented in Table 1.

Bioanalysis

Plasma concentrations of the paliperidone enantiomers (JPN-1, JPN-2, and JPN-3) were determined using a validated liquid chromatography coupled to tandem mass spectrometry method.[15] Plasma concentrations of racemic paliperidone (JPN-4 and 5) were determined using a validated liquid chromatography–tandem mass spectrometry method consisting of a protein precipitation step followed by high-performance liquid chromatography coupled to positive electrospray triple quadrupole mass spectrometry. In the protein precipitation step, 100-µL plasma aliquots were precipitated with 200-µL acetonitrile. After mixing and centrifugation, 5-µL of the supernatant was injected onto a Polaris C18-A 3-µm 4.6-mm ID × 30-mm analytical column. The mobile phase was a mixture of 0.01 mol/L ammonium formate (pH 4)/acetonitrile/methanol. Detection occurred by TurboIonSpray ionization (positive ion mode). Paliperidone was monitored at transition *m/z* 427.2 to 207.0 and the stable isotope labeled internal standard at transition *m/z* 431.2 to 209.0.

The performance of the assays was characterized by means of validation.[16] The accuracy of the methods was within the criteria of 80% to 120% at the level of the lower limit of quantitation (LLOQ) and 85% to 115% at the other levels. The interbatch precision (expressed as the coefficient of variation) did not exceed 20% at the LLOQ and 15% at the other levels. The analytical range was 0.200 to 100 ng/mL for paliperidone enantiomers and 0.1 to 250 ng/mL for racemic paliperidone. In cases where enantiomers of paliperidone were measured, paliperidone concentrations were calculated as the sum of the enantiomers and only total paliperidone concentrations were used for further interpretation. The total number of patients and pharmacokinetic samples for each study are summarized in Table 1.

Comparison of Pharmacokinetic Data From Different Populations

The paliperidone pharmacokinetic parameters obtained in the JPN-1 phase 1 study were compared to the ROW studies with similar design and dosing regimens.

Population Pharmacokinetic Model-Based Simulations

The historical Pop-PK model was the key evaluation tool in this analysis.[9] Data set preparation, exploration, and visualization were performed using S-Plus 6.0 to 8.0 professional release 2 software (Insightful Corporation, Seattle, Washington) and R (version 2.14.1, 2012-02-29). Model-based simulations were performed using NONMEM Version V to VII,[17–19] and using the Intel FORTRAN 9.0 or 10 or GFORTRAN compilers for Windows. Measurements below the LLOQ and missing values were excluded from the analysis. The covariates included and the covariate effects implemented in the NONMEM code were only those factors that were found to be significant in the historical population model[13]: injection site (gluteal or deltoid), needle length, sex, age, creatinine clearance, BMI, and injection volume.

To verify the predictive value of the historical Pop-PK model, a visual predictive check (VPC) was performed; that is, the measured paliperidone concentrations in the Japanese, Korean, and Taiwanese patients were compared with the corresponding predicted values by the population model. Data sets were simulated based on the fixed- and random-effect estimates from the final historical model.[9] Simulated data sets had study design features and covariates (ie, dosing information and demographics) resampled from the JPN-1 through JPN-5 studies in Japanese, Korean, and

Table 1. Overview of Studies With Paliperidone Palmitate in Japanese, Korean, and Taiwanese Patients With Schizophrenia

	JPN-1	JPN-2	JPN-3	JPN-4	JPN-5
Dose regimen per treatment arm	Gluteal injections on day 1	Gluteal injections on days 1, 8, 36, and 64	Gluteal/deltoid injections on days 1, 8, 36, and 64	Gluteal/deltoid injections on days 1, 8, 36, and 64	Deltoid/gluteal injection on days 1 and 8, Q4W up to 11 injections
	A: 25 mg eq. on day 1 B: 50 mg eq. on day 1 C: 150 mg eq. on day 1	A: 50 mg eq. B: 100 mg eq. C: 150 mg eq. D: 150 (day 1), 50 (day 8), 50 (day 36), 50 mg eq. (day 64)	A: 150 mg eq. (deltoid) B: 75 mg eq. (deltoid) C: 75 mg eq. (gluteal)	A: 50 mg eq. (deltoid, day 1); 100 mg eq. (deltoid, day 8); 75 mg eq. (deltoid/gluteal on days 36 and 64) B: placebo	150 mg eq. (deltoid, day 1); 100 mg eq. (deltoid, day 8); Q4W up to 11 injections (flexible dose: 25 to 150 mg eq., deltoid/gluteal)
Number of patients randomized/ completed/analyzed	A: 25 mg eq.: 8/8/8 B: 50 mg eq.: 9/8/9 C: 150 mg eq.: 9/9/9 Total: 26/25/26	A: 50 mg eq.: 14/12/14 B: 100 mg eq.: 14/10/14 C: 14/14/14 D: 14/11/14 Total: 56/47/56	A: 24/21/24 B: 27/20/27 C: 25/22/25 Total: 76/63/76	A: 160/95/153 B: 164/55/0 (not included in analysis) Total: 324/150/153	201/119/198 Total: 201/119/198
Samples available/analyzed	545/482	963/905	1495/1401	1063/784	1674/1420
Time range of sampling	Days 1-127	Days 1-218	Days 1-190	Days 1-92	Days 1-344

eq., equivalent; JPN, study ID; Q4W, every 4 weeks.
Study JPN-4 also included Korean and Taiwanese patients.
The clinicaltrials.gov numbers (NCT numbers) for each of the studies JPN-2, JPN-3, JPN-4, and JPN-5 were NCT01606254, NCT01942382, NCT01299389 and NCT01258920, respectively. JPN-1 was not registered on ClinicalTrials.gov.

Table 2. Pharmacokinetic Parameters of Paliperidone After a Single Intramuscular Dose in the Gluteal Muscle of 25, 50, or 150 mg eq. Paliperidone Palmitate in Japanese Patients With Schizophrenia (Study JPN-1)

	25 mg eq.		50 mg eq.		150 mg eq.	
	N	Mean (SD)	n	Mean (SD)	n	Mean (SD)
C_{max} (ng/mL)	8	3.68 (2.26)	8	7.94 (6.64)	9	17.2 (9.95)
t_{max} (days)[a]	8	16.0 (4.0-25.0)	8	11.0 (4.00-42.2)	9	18.0 (4.0-28.0)
$AUC_{(0,t)}$ (ng • h/mL)	8	4634 (2386)	8	7353 (3751)	9	17764 (9538)
$AUC_{(0,\infty)}$ (ng • h/mL)	8	5713 (2829)	8	9198 (4764)	9	20861 (9960)
$t_{1/2}$ (days)[a]	8	30.2 (10.5-158.4)	8	45.2 (13.5-80.5)	9	45.0 (20.5-92.8)

$AUC_{(0,t)}$, area under the plasma concentration–time curve up to the time of the last quantifiable concentration; $AUC_{(0,\infty)}$, area under the plasma concentration–time curve extrapolated to infinity; C_{max}, maximum plasma concentration; $t_{1/2}$, apparent terminal half-life; t_{max}, time to maximum plasma concentration.
[a]Median (range).

Taiwanese patients. A VPC was performed after the 5th, 50th, and 95th percentiles were calculated from the simulated profiles. These percentiles were superimposed on the raw data to allow visual assessment of model predictability. In addition, model accuracy and precision were evaluated; PE% was computed for each concentration value. For JPN-4 and JPN-5, summary statistics of PE% and |PE|% were calculated to assess accuracy and precision, and the model was considered acceptable if the median PE% and the median |PE|% were within |15|% and 30%, respectively.[15]

Results

Pharmacokinetic Results From Phase 1 Studies in Japanese Patients

After a single intramuscular injection, C_{max} was reached 16, 11, and 18 days after the injection, for 25, 50, and 150 mg eq., respectively, in the JPN-1 study (Table 2). Thereafter, concentrations decreased gradually, but still exceeded the LLOQ on the last evaluation day (126 days after injection). C_{max} and AUC appeared to increase in a dose-proportional manner between 25 and 50 mg eq. and less than proportional with doses between 50 and 150 mg eq., while $t_{1/2}$ was shorter for the 25-mg eq. dose (30.2 days) compared to the 50 and 150 mg eq. doses (45.2 and 45.0 days, respectively) (Table 2).

After repeated intramuscular injections of 50, 100, and 150 mg eq. in the gluteal muscle (on days 1, 8, 36, and 64), the plasma paliperidone concentrations varied widely among the patients in the JPN-2 study. However, paliperidone exposure after the fourth dose increased with the dose within the dose range of 50 mg to 150 mg eq. paliperidone (Table 3). The $t_{1/2}$ ranged from 58.5 days for the 100 mg eq. dose to 95.5 days for the 150 mg eq. dose. These $t_{1/2}$ appear to have large variability likely due to the small sample size.

After repeated administration of 75 mg eq. paliperidone palmitate in the deltoid muscle in the JPN-3 study, paliperidone exposure was about 25% higher for the fourth injection and t_{max} was reached earlier than with gluteal administration (Table 3). After the second injection, paliperidone exposure was about 45% higher for deltoid injection than gluteal injection. The distributions of individual plasma concentrations after deltoid and gluteal injection overlapped, even more so at the fourth compared with the second injection. There were only 6 quantifiable plasma concentrations of paliperidone palmitate, namely, in 6 patients in the JPN-3 study. In Japanese patients, single and repeated intramuscular injections (25 to 150 mg eq.) were generally safe and well tolerated. No new safety signals were detected in these phase 1 studies.

Comparison of Pharmacokinetic Data From Different Populations

Pharmacokinetic parameters in the JPN-1 and JPN-2 studies were compared with the ROW studies having a design similar to these Japanese studies. The median values of dose-normalized AUC and C_{max} were used for this comparison. Paliperidone exposure in Japanese patients remained generally within the distribution of the ROW population (Figure 1). Repeated paliperidone palmitate administrations displayed a similar pattern, with the actual plasma concentrations obtained in Japanese patients within the range of those in the ROW studies having a similar dosing regimen (data not shown).

Population Pharmacokinetic Database Description

In total, 5740 nonplacebo samples from 518 patients were available (Table 1). Following data cleanup, 4992 pharmacokinetic samples with valid concentration-time points were available from 509 patients. Samples were excluded because the concentrations were below LLOQ or not assessable (47 samples) or if initial

Table 3. Pharmacokinetic Parameters of Paliperidone in Japanese Patients With Schizophrenia After the Fourth Intramuscular Dose in the Gluteal Muscle of 50, 100, or 150 mg eq. Paliperidone Palmitate (Study JPN-2) and in the Gluteal or Deltoid Muscle of 75 or 150 mg eq. Paliperidone Palmitate (Study JPN-3)

	50 mg eq. gluteal		100 mg eq. gluteal		150 mg eq. gluteal	
Study JPN-2	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
C_{max} (ng/mL)	13	13.7 (7.52)	12	33.5 (19.8)	14	43.1 (30.3)
t_{max} (days)	13	11.05 (4.82)	12	9.70 (4.59)	14	9.60 (6.98)
Median (range)	13	10.99 (1.99-21.01)	12	7.89 (5.97-21.81)	14	7.50 (2.93-27.01)
$AUC_{(0,\tau)}$ (ng •h/mL)	13	7081 (3581)	12	15 898 (7535)	14	21 853 (15 534)
$C_{ss,av}$ (ng/mL)	13	10.7 (5.42)	12	23.9 (11.4)	14	32.8 (23.1)
$t_{1/2}$ (days)	10	68.1 (48.0)	10	58.5 (29.1)	9	95.5 (98.8)
	75 mg eq. deltoid		75 mg eq. gluteal		150 mg eq. deltoid	
Study JPN-3	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
C_{max} (ng/mL)	19	22.2 (12.9)	22	19.0 (15.2)	20	44.0 (20.8)
t_{max} (days)	19	6.51 (2.94)	22	9.69 (5.02)	20	7.59 (5.18)
Median (range)	19	6.97 (1.97-13.99)	22	7.96 (3.87-20.98)	20	6.38 (1.98-21.93)
$AUC_{(0,\tau)}$ (ng • h/mL)	19	10 927 (5944)	22	9139 (7250)	20	22 821 (11 218)
$t_{1/2}$ (days)	15	129.4 (139.8)	9	79.0 (45.4)	14	67.3 (25.8)

$AUC_{(0,\tau)}$, area under the plasma concentration–time curve over the dosing interval; C_{max}, maximum plasma concentration; $C_{ss,av}$, average plasma concentration; $t_{1/2}$, apparent terminal half-life; t_{max}, time to maximum plasma concentration.

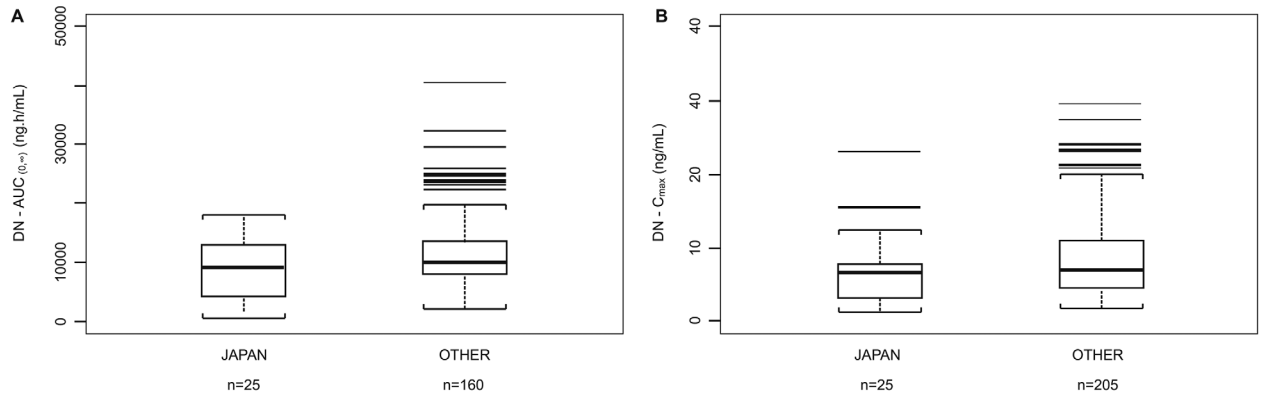

Figure 1. Dose-normalized (A) area under the plasma concentration–time curve (AUC; Japanese/JAPAN: JPN-1 study; rest-of-world: phase 1 studies INT-12, PSY-1002, and PSY-1004); (B) maximum plasma concentration (C_{max}; Japanese/JAPAN: JPN-1 study, rest-of-world: phase 1 studies INT-12, PSY-1002, and PSY-1004) following single intramuscular injections of paliperidone palmitate. DN - $AUC_{(0,\infty)}$, dose-normalized area under the plasma concentration-time curve extrapolated to infinity; DN - C_{max}, dose-normalized maximum plasma concentration.

paliperidone concentrations were affected by prior oral risperidone or paliperidone (criterion: >10 ng/mL on day 4, 90 samples). In addition, samples were excluded for disallowed concomitant medications (61 samples), needle length deviating from protocol (28 samples), or other (3 samples). Pretreatment samples (519 samples) were excluded as well.

All studies included Japanese patients only, with the exception of JPN-4, which included 75 Japanese, 31 Korean, and 47 Taiwanese patients. Patients' demographics, which were statistically significant covariates from the historical Pop-PK model, are described in Table 4. For comparison, the distribution of covariates of the ROW population is provided as well.

Comparison of the covariate distributions between the Japanese (including Korean and Taiwanese) and the ROW populations suggests that most important covariates are similar (Table 4). Gender was more equally distributed in the JPN-5 study compared to the other studies and the ROW population. The median BMI was lower for Japanese, Korean, and Taiwanese patients, ranging from 21.8 to 24.7 kg/m^2, compared to the ROW population (26.8 kg/m^2). The distribution of

Table 4. Demographic Characteristics of the Studies in Japanese, Korean, and Taiwanese Patients Compared With the Rest-of-World Population

	JPN-1	JPN-2	JPN-3	JPN-4		JPN-5	ROW[12]
Number of patients, n	26	56	76	153[a]	75[b]	198	1795
Sex, n (%)							
Men	16	40	49	96	46	102	1152
	(62)	(71)	(64)	(63)	(61)	(52)	(64)
Age (y)							
Median (range)	46	49	48	44	49	43	42
	(20-57)	(25-64)	(27-64)	(20-78)	(22-78)	(20-79)	(18-76)
Mean (SD)	42.4	47.4	46.2	45.8	50.7	45.5	41.0
	(10.1)	(12.0)	(11.2)	(13.5)	(14.62)	(12.56)	(11.1)
Weight (kg)							
Median (range)	64	64	65	62	58	65	79.5
	(45-87)	(39-94)	(42; 99)	(35-120)	(35-120)	(33-103)	(39.5-236.8)
Mean (SD)	67.32	64.7	64.2	63.0	60.7	66.3	82.1
	(10.62)	(10.10)	(13.64)	(14.27)	(16.02)	(14.01)	(19.8)
Height (cm)							
Median (range)	164	166	165	164	162	163	172
	(150-179)	(144-186)	(143-179)	(140-187)	(140-180)	(141-191)	(122-201)
Mean (SD)	164.10	165.0	164.0	163.3	161.4	162.9	171.8
	(8.08)	(9.44)	(8.76)	(9.55)	(9.39)	(9.27)	(9.62)
Body mass index (kg/m^2)							
Median (range)	24.7	23.5	23.1	22.5	21.8	24.6	26.8
	(17.8-34.5)	(17.7-32.9)	(17.2-35.6)	(15.9-39.1)	(15.9-39.1)	(14.3-37.2)	(16-69)
Mean (SD)	25.01	23.7	23.8	23.5	23.0	24.9	27.8
	(3.77)	(2.8)	(4.36)	(4.44)	(4.70)	(4.50)	(6.23)
Creatinine clearance (mL/min)							
Median (range)	115	110	100	103	99.7	116	111
	(51.0-154)	(47.5-184)	(60.6-202)	(40.7-227)	(40.7-227)	(45.5-228)	(30.9-477)
Mean (SD)	116	111	105.4	105.9	104.1	119	116
	(26.13)	(32.41)	(30.97)	(34.51)	(39.65)	(36.00)	(35.1)

JPN, study ID; ROW, rest-of-world.

[a]Population consisted of 75 Japanese, 31 Korean, and 47 Taiwanese patients.

[b]Japanese patients only; except for JPN-4, other Japanese studies included only Japanese; all patients were included in the pharmacokinetic analysis set except for JPN-4 and JPN-5 studies wherein pharmacokinetic analysis was performed only in pharmacokinetic analysis set. The clinicaltrials.gov numbers (NCT numbers) for each of the studies JPN-2, JPN-3, JPN-4 and JPN-5 were NCT01606254, NCT01942382, NCT01299389 and NCT01258920, respectively. JPN-1 was not registered on ClinicalTrials.gov.

the key covariates in the Japanese trials was largely overlapping with the distribution for the ROW population.

Overlay plots comparing results from the Pop-PK model-based simulations to the actual observed plasma concentrations are presented in Figure 2A, 2B, 2C (JPN-1 study), Figure 2D (JPN-4 study), and Figure 2E (JPN-5 study). The VPCs for JPN-2 and JPN-3 studies are presented in supplementary online material (Figure S1). The majority of the observations were within the 90% prediction interval. For JPN-4 and JPN-5 studies, 91.8% and 94.7% of the observations, respectively, were within the 90% prediction interval. However, there was a tendency toward overprediction for the 75 mg eq. gluteal treatment group from study JPN-3 likely due to the small sample size (Figure S1), which is not observed for the gluteal injections at other doses (50 to 150 mg eq. from study JPN-2; Figure S1). In addition, actual plasma concentrations among Japanese, Korean, and Taiwanese patients were comparable (Figure 2D).

External Validation

The goodness-of-fit plots for the external validation data sets from phase 3 studies JPN-4 and JPN-5 showed appropriate agreement between predicted and observed plasma concentrations. The conditional weighted residuals were randomly scattered across the predicted concentration range and across time. A density plot of conditional weighted residuals indicated that the residuals are normally distributed, with a mean of approximately zero. Overall, the diagnostic plots for conditional weighted residuals indicate that the historical model predicted the external data set adequately (data not shown). The median %PE and

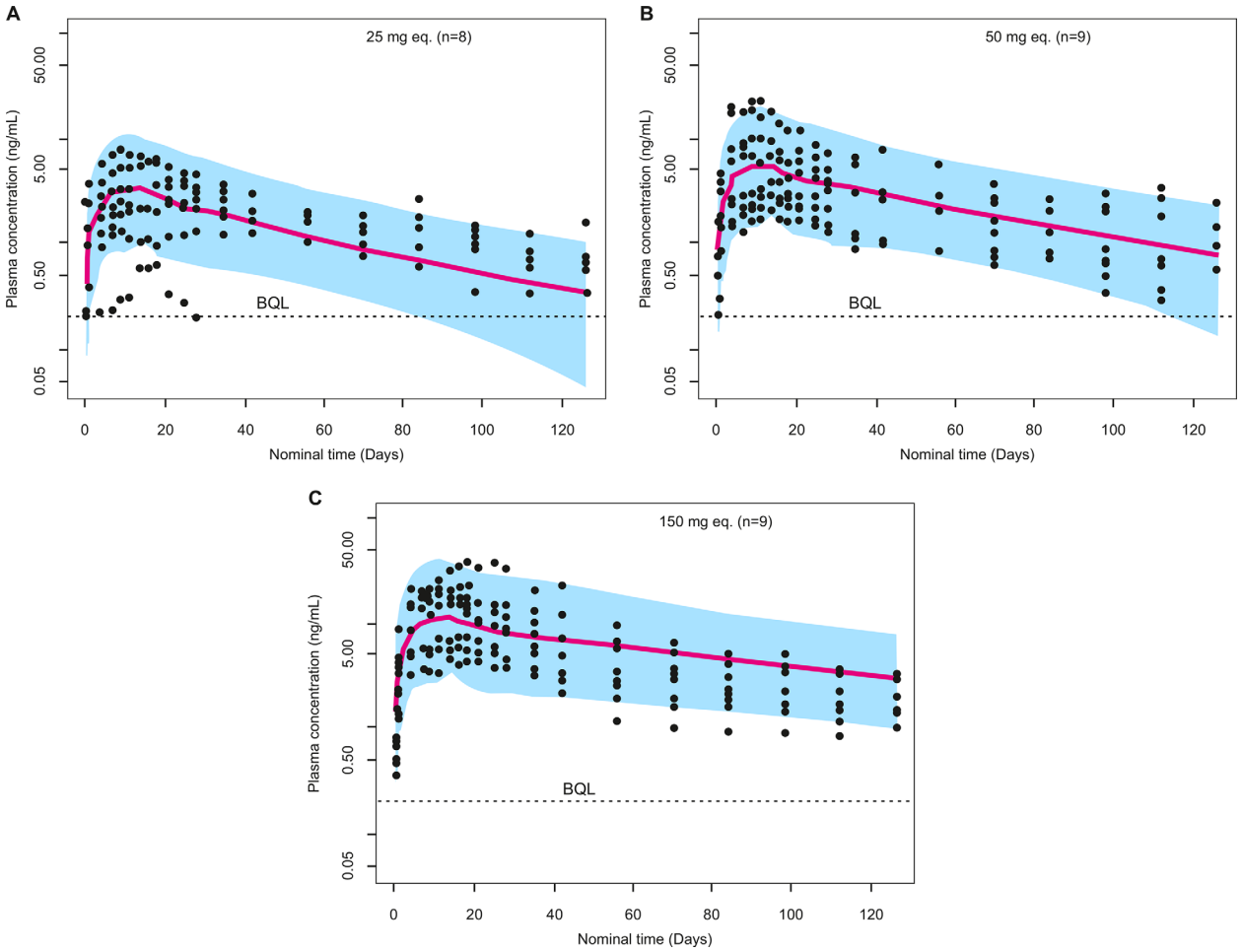

Figure 2. Visual predictive checks for single and multiple doses of paliperidone palmitate across the entire dose range (25 to 150 mg eq.). Study JPN-1: gluteal single doses of (A) 25 mg eq., (B) 50 mg eq., and (C) 150 mg eq. Study JPN-4 (D): deltoid injections of 150 mg eq. on day 1 and of 100 mg eq. on day 8, 75 mg eq. deltoid or gluteal injections on days 36 and 64. Study JPN-5 (E): deltoid injections of 150 mg eq. on day 1 and of 100 mg eq. on day 8, thereafter deltoid or gluteal injections every 4 weeks for up to 11 injections with flexible dose of 25 to 150 mg eq. BQL, below quantification limit; eq., equivalent.

|%PE| (25th, 75th percentile) were 3.66 (–9.42, 15.73) and 13.03 (6.07, 21.27) for JPN-4 and 2.39 (–9.38, 13.25) and 11.47 (5.64, 20.00) for the JPN-5 study, respectively. The external validation statistics were not computed for the JPN-1 to JPN-3 studies due to the small sample sizes in these phase 1/2 studies (only VPCs were done; data not shown).

Discussion

This article presents for the first time detailed pharmacokinetic data for paliperidone following doses of paliperidone palmitate in the Japanese population. Moreover, the applicability of the historical Pop-PK model for the data from Japanese, Korean, and Taiwanese patients with schizophrenia is described.

The comparison of pharmacokinetic parameters after single and multiple intramuscular administration in Japanese (JPN-1 and JPN-2) and non-Japanese patients shows that paliperidone exposure in Japanese patients was within the distribution of the ROW population. In addition, plasma concentrations from Japanese (studies JPN-3, JPN-4, and JPN-5) and non-Japanese studies having a similar dosing regimen were largely overlapping. After the fourth injection, paliperidone exposure was about 25% higher and t_{max} was reached earlier with deltoid compared to gluteal administration. After the second injection, paliperidone exposure was about 45% higher for deltoid injection than gluteal injection (JPN-3). This difference was also observed in the ROW population, where the deltoid over gluteal ratios of C_{max} and AUC were 1.26 at the fourth injection and around 1.45 at the second injection; that is, the difference in exposure between the 2 injection sites is smaller upon multiple dosing.[12] The comparability of actual plasma concentrations among Japanese, Korean, and Taiwanese patients from the JPN-4 study (Figure 2D) supports the appropriateness

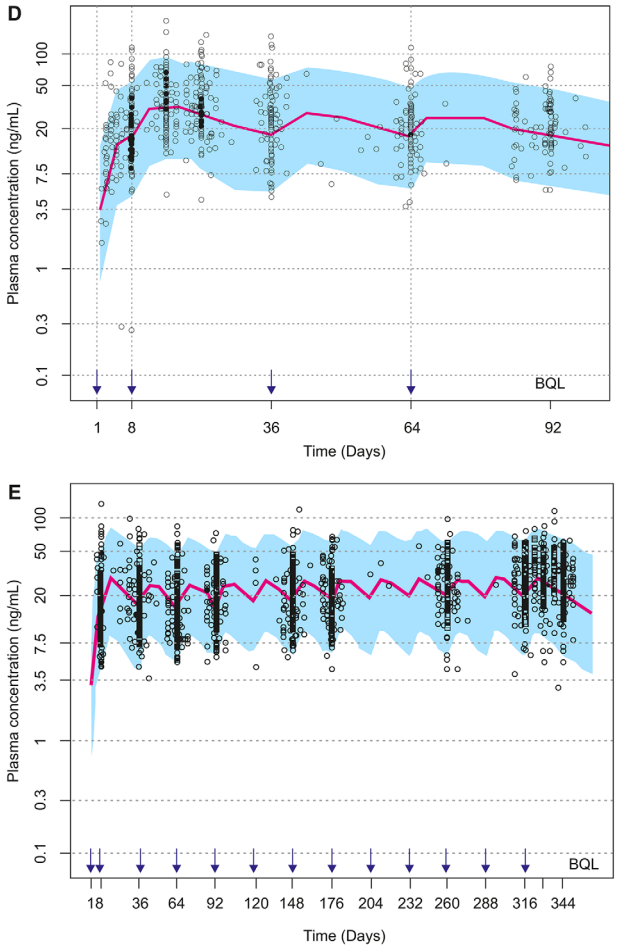

Figure 2. *Continued.*

of combining data from Korea and Taiwan with those from Japan, along with Pop-PK analysis results, which indicated the absence of a race effect on the pharmacokinetics of paliperidone palmitate. This is comparable with oral paliperidone, which displays comparable pharmacokinetics among Chinese, Japanese, and white patients.[20]

Ethnic or racial differences in pharmacokinetics are commonly observed with psychotropic drugs. For instance, several studies indicate that Asians have higher plasma concentrations of haloperidol and its metabolite, and thus a reduced haloperidol dose is required than whites receiving the same dose.[21–23] The metabolism of haloperidol is mediated by cytochrome P450 2D6, which is known to be polymorphic and a number of distinct alleles have been found to exhibit ethnic variation in their distribution. However, such polymorphisms are not relevant for paliperidone because it is mainly excreted unchanged by the kidneys.

The VPCs can be considered as being adequate because the overlay plots comparing results from the Pop-PK simulation to the actual observed plasma concentrations show considerable similarity, and the majority of the observations were within the 90% prediction interval. The model was considered valid from an accuracy and precision standpoint, as the observed median %PE and |%PE| (25th, 75th percentile) were well within the predefined cutoff values of within the |15|% for median PE% and within the 30% for median |PE|% based on the results of external validations for the JPN-4 and JPN-5 studies. The distributions further illustrate the suitability of the structural and covariate components of the historical model.[9] The historical Pop-PK model predicted the pharmacokinetics in Japanese, Korean, and Taiwanese patients adequately, and the paliperidone pharmacokinetics after paliperidone palmitate intramuscular administration in these patients were comparable with those in the ROW population.

The covariates included in the analysis were injection site (gluteal or deltoid), needle length, sex, age, creatinine clearance, BMI, and injection volume. The Pop-PK analysis previously confirmed that patients

with a higher BMI show slightly lower initial exposure to paliperidone. To mitigate this effect the initiation regimen is started with deltoid doses, and patients with a higher BMI are administered the dose with a longer 1.5-inch needle.[13] More than half of the patients with schizophrenia included in the ROW Pop-PK data set were overweight, obese, or morbidly obese.[9] However, the Asian population generally had a lower median BMI than the population in the ROW, and these patients may therefore get the initiation doses with a 1-inch needle. The VPCs, together with the calculated accuracy and precision, suggests that the Pop-PK model, taking into account the BMI effect as a covariate, is predictive for Japanese patients. However, as an inherent limitation of VPC, differences between model-predicted percentiles based on simulated (usually based on large data sets) and observed data can occur with small data sets included in the predictive check. For example, there was underprediction for the 25 mg eq. dose group that could be a result of the small data set ($n \geq 8$). In addition, the concentrations in the terminal profile were censored due to samples being below the LLOQ, and therefore there were very few observations at the lowest predicted concentrations. By contrast, the 75 mg eq. gluteal treatment group from the JPN-3 study showed a trend toward overprediction, which was not observed for the gluteal injections at other doses (25 to 150 mg eq.).

In summary, the paliperidone pharmacokinetics after single and multiple dose of paliperidone palmitate in Japanese, Korean, and Taiwanese patients with schizophrenia were comparable with those in the ROW population. The historical Pop-PK model predicted the external data sets from the Japanese studies adequately, confirming the robustness of the Pop-PK model. It can be concluded that, from a pharmacokinetic perspective, Japanese patients can be administered with the same initiation and maintenance doses as the ROW population.

Acknowledgments

The authors thank the study participants, without whom this study would not have been accomplished, and all the investigators for their participation. The authors thank Anita van den Oetelaar (Author et al., the Netherlands) for assistance in preparing the manuscript. The authors also thank Rohit Bhandari, PhD and Priya Ganpathy, MPharm CMPP (SIRO Clinpharm Pvt. Ltd., India), for providing writing/editorial assistance during the development of this paper.

Conflicts of Interest

HS, MN, MDM, SG, YT, MS, and BR were employees of Janssen Research and Development in the previous 3 years. MDM, SG, YT, MNS, and BR are stockholders of Janssen Research and Development.

References

1. Green MF. Impact of cognitive and social cognitive impairment on functional outcomes in patients with schizophrenia. *J Clin Psychiatry*. 2016;77(suppl 2): 8-11.
2. Keith SJ, Kane JM. Partial compliance and patient consequences in schizophrenia: our patients can do better. *J Clin Psychiatry*. 2003;64(11):1308-1315.
3. Wiersma D, Nienhuis FJ, Slooff CJ, Giel R. Natural course of schizophrenic disorders: a 15-year followup of a Dutch incidence cohort. *Schizophr Bull*. 1998;24(1): 75-85.
4. Bhanji NH, Chouinard G, Margolese HC. A review of compliance, depot intramuscular antipsychotics and the new long-acting injectable atypical antipsychotic risperidone in schizophrenia. *Eur Neuropsychopharmacol*. 2004;14(2):87-92.
5. Chen EY, Hui CL, Dunn EL, et al. A prospective 3-year longitudinal study of cognitive predictors of relapse in first-episode schizophrenic patients. *Schizophr Res*. 2005;77(1):99-104.
6. McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiol Rev*. 2008;30:67-76.
7. Weiden PJ, Olfson M. Cost of relapse in schizophrenia. *Schizophr Bull*. 1995;21(3):419-429.
8. Corena-McLeod M. Comparative pharmacology of risperidone and paliperidone. *Drugs R D*. 2015;15(2):163-174.
9. Samtani MN, Vermeulen A, Stuyckens K. Population pharmacokinetics of intramuscular paliperidone palmitate in patients with schizophrenia: a novel once-monthly, long-acting formulation of an atypical antipsychotic. *Clin Pharmacokinet*. 2009;48(9):585-600.
10. Vermeir M, Naessens I, Remmerie B, et al. Absorption, metabolism, and excretion of paliperidone, a new monoaminergic antagonist, in humans. *Drug Metab Dispos*. 2008;36(4):769-779.
11. Gopal S, Gassmann-Mayer C, Palumbo J, Samtani MN, Shiwach R, Alphs L. Practical guidance for dosing and switching paliperidone palmitate treatment in patients with schizophrenia. *Curr Med Res Opin*. 2010;26(2):377-387.
12. Cleton A, Rossenu S, Crauwels H, et al. A single-dose, open-label, parallel, randomized, dose-proportionality study of paliperidone after intramuscular injections of paliperidone palmitate in the deltoid or gluteal muscle in patients with schizophrenia. *J Clin Pharmacol*. 2014;54(9):1048-1057.
13. Samtani MN, Gopal S, Gassmann-Mayer C, Alphs L, Palumbo JM. Dosing and switching strategies

for paliperidone palmitate: based on population pharmacokinetic modelling and clinical trial data. *CNS Drugs*. 2011;25(10):829-845.
14. Coppola D, Liu Y, Gopal S, et al. A one-year prospective study of the safety, tolerability and pharmacokinetics of the highest available dose of paliperidone palmitate in patients with schizophrenia. *BMC Psychiatry*. 2012; 12:26. https://doi.org/10.1186/1471-244X-12-26
15. De Meulder M, Remmerie BM, de Vries R, et al. Validated LC-MS/MS methods for the determination of risperidone and the enantiomers of 9-hydroxyrisperidone in human plasma and urine. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2008;870(1):8-16.
16. Viswanathan CT, Bansal S, Booth B, et al. Quantitative bioanalytical methods validation and implementation: best practices for chromatographic and ligand binding assays. *Pharm Res*. 2007;24(10):1962-1973.
17. Beal SL, Sheiner LB. *NONMEM Users Guides*. Ellicott City, MD: Icon Development Solutions; 1989-1998.
18. Boeckman A, Sheiner L, Beal, S. *NONMEM VI*. Ellicott City, MD: GloboMax, ICON Development Solutions; 2007.
19. Hough D, Lindenmayer JP, Gopal S, et al. Safety and tolerability of deltoid and gluteal injections of paliperidone palmitate in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;33(6):1022-1031.
20. Si T, Shu L, Liu Y, Su YA, Guo C, Zhang H. Single-dose pharmacokinetics of paliperidone extended-release tablets in healthy Chinese subjects. *Hum Psychopharmacol*. 2010;25(5):404-409.
21. Chang WH, Jann MW, Hwu HG, et al. Ethnic comparison of haloperidol and reduced haloperidol plasma levels: Taiwan Chinese versus American non-Chinese. *J Formos Med Assoc*. 1991;90(6):572-578.
22. Potkin SG, Shen Y, Pardes H, et al. Haloperidol concentrations elevated in Chinese patients. *Psychiatry Res*. 1984;12(2):167-172.
23. Zhang-Wong J, Beiser M, Zipursky RB, Bean G. An investigation of ethnic and gender differences in the pharmacodynamics of haloperidol. *Psychiatry Res*. 1998;81(3):333-339.

Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.