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Population Pharmacokinetic Modeling and Simulation to Guide Dose Selection for RBP-7000, A New Sustained-Release Formulation of Risperidone

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Abstract

RBP-7000 is a long-acting formulation of risperidone designed for once-monthly subcutaneous injection for the treatment of schizophrenia. The objective was to estimate clinically effective doses of RBP-7000 based on model simulations and on the comparison with other long-acting injectable antipsychotics. A population pharmacokinetic model of RBP-7000 was developed in 90 clinically stable schizophrenic patients having received single/repeated doses of 60, 90, or 120 mg. Model simulations were conducted to compare active moiety plasma exposure after repeated RBP-7000 administrations to the published data of long-acting risperidone injection (Risperdal® Consta®) at 25 and 50 mg, and of paliperidone palmitate (Invega® Sustenna®) at 50 and 100 mg equivalent paliperidone. Predictions of dopamine D2 receptor occupancy were derived from the simulated active moiety concentrations. Simulations showed similar active moiety plasma exposure at steady-state for 90 mg of RBP-7000 and 25 mg of long-acting risperidone. In comparison to risperidone, RBP-7000 reached effective concentrations immediately after the first administration. RBP-7000 at the doses of 60 and 90 mg provided similar active moiety plasma concentrations at steady-state compared to 50 and 100 mg equivalent paliperidone, respectively. These findings provide guidance for dose selection in Phase III clinical trials and suggest potential benefits for RBP-7000 over competitors.

Keywords

RBP-7000, long-acting risperidone, paliperidone palmitate, dopamine D2 receptor occupancy, dose switching simulation

RBP-7000 is a sustained-release formulation of risperidone currently being developed for the treatment of schizophrenia. RBP-7000 has been designed to be administered by once-monthly subcutaneous (SC) injection in order to address compliance issues associated with oral risperidone intake. Poor adherence to treatment is frequent in schizophrenic patients prescribed oral antipsychotic medications and has been identified as a major barrier to optimal outcomes as well as an important factor of relapse.[1–4]

RBP-7000 is injected subcutaneously using the ATRIGEL® delivery system. The ATRIGEL® delivery system is a sterile, polymeric solution of a biodegradable poly(DL-lactide-co-glycolide), or poly-L-lactic acid copolymer, dissolved in *N*-methyl-2-pyrrolidone, a water-miscible, biocompatible solvent.[5] The risperidone in RBP-7000 is both dissolved and suspended in that polymeric solution. After SC injection, the ATRIGEL® delivery system solidifies upon contact with body fluids and the resulting biodegradable implant delivers risperidone in a controlled fashion over an extended period of time. The tolerability and safety of RBP-7000 have been established for doses of 60, 90, and 120 mg in single and multiple ascending dose studies performed in clinically stable schizophrenic patients. The plasma concentration profiles of risperidone and 9-hydroxyrisperidone after administration of RBP-7000 exhibited complex kinetics, presenting a double peak of absorption with a prolonged terminal half-life. These profiles suggest a rapid delivery of risperidone from the SC injection site and a sustained release from the ATRIGEL® delivery system.

Pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation was integrated throughout the clinical development program of RBP-7000.[6,7] The objective of this initial modeling was to characterize the relationship between the administered doses, the active moiety exposure and efficacy/safety profiles, in order to guide dose selection for future Phase III trials. An important consideration for the selection of doses in Phase III trials

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is the comparison with other long-acting injectable antipsychotics at their clinically effective dosing regimens. Risperidone injection was the first approved long-acting injectable atypical antipsychotic with intramuscular injections every 2 weeks (Risperdal® Consta®; Janssen Pharmaceuticals, Inc.). The recommended dosage regimen is 25 mg but patients not responding to 25 mg may benefit from a higher dose (37.5 or 50 mg). Oral risperidone supplementation is recommended for the first 3 weeks of treatment in order to ensure adequate therapeutic plasma concentrations.[8] Well-designed clinical studies have demonstrated the efficacy of risperidone injection and confirmed that its safety and tolerability are comparable to those of oral risperidone.[9–13] Paliperidone palmitate, the palmitate ester of paliperidone, is a second generation long-acting injectable antipsychotic designed for the intramuscular route (Invega® Sustenna® Janssen Pharmaceuticals, Inc.). Paliperidone, the 9-hydroxy metabolite of risperidone, exhibits approximately equal pharmacologic activity to the parent compound.[14] As for RBP-7000, paliperidone palmitate is administered on a monthly basis, but the recommended clinical treatment requires two loading doses of 150 mg equivalent (mg eq.) paliperidone on day 1 and 100 mg equivalent paliperidone on day 8, each administered into the deltoid muscle.[15] The monthly maintenance dose is in the range of 25–150 mg equivalent paliperidone injected in either the gluteal or deltoid muscles, 75 mg equivalent paliperidone being the recommended dose.

The objective of the present analysis was to estimate the doses of RBP-7000 that are expected to provide similar active moiety exposure to long-acting risperidone injection and paliperidone palmitate during chronic treatment. A population PK model for RBP-7000 was developed from all available data collected in single and multiple ascending dose studies in order to refine our knowledge on the PK of this compound. The population PK model was further used to predict the active moiety plasma concentration–time profiles after repeated doses of RBP-7000 at 60, 90, and 120 mg and to compare these profiles with the published data of long-acting risperidone injection at the doses of 25 and 50 mg and paliperidone palmitate at the doses of 50 and 100 mg equivalent paliperidone. Predictions of dopamine (DA) D2 receptor occupancy were also derived from active moiety plasma concentrations using a previously published PK/PD model.[6]

Methods and Materials

Data

The population PK analysis of RBP-7000 was based on two clinical trials conducted in clinically stable schizophrenic patients. The first trial was a Phase I, randomized, open label, single ascending dose study where 45 subjects received a single dose of 60, 90, or 120 mg of RBP-7000. Each of the three dose levels included 15 subjects. Serial blood samples were collected prior to RBP-7000 SC injection on Day 1 (pre-dose sample) and at various times post-injection from Day 1 to Day 85 (28 samples) to provide full plasma concentration–time profiles of risperidone and 9-hydroxyrisperidone. All details on study design and blood sampling schedule are available in the reference.[6]

The second trial was an open-label, Phase IIa, multiple ascending dose study conducted in 45 subjects who were on stable oral risperidone therapy (2, 3, or 4 mg once daily). Subjects on 2, 3, or 4 mg/day oral risperidone were switched to 60, 90, or 120 mg of RBP-7000, respectively. Each of the three dose levels included 15 subjects. RBP-7000 treatment consisted of three monthly SC injections administered on Day 1, Day 29, and Day 57. At the end of the third injection follow-up period, subjects were returned to their original doses of oral risperidone for a period of 3 days (Day 85–87). For those subjects who were not on a stable dose of 2, 3, or 4 mg of oral risperidone at the beginning of the study, the screening period was followed by a 7-day oral risperidone conversion and stabilization period starting at 2 mg/day. Subsequently, all subjects entered a 7-day pretreatment period, with once daily oral administration of risperidone at 2, 3, or 4 mg from Day-7 to Day-1 (the day preceding the first injection of RBP-7000). Serial blood samples for PK assessments of risperidone and 9-hydroxyrisperidone were collected prior to and after each injection of RBP-7000 throughout the dosing interval (19 samples after the first and third injections, 8 samples after the second injection) as well as during the initial pretreatment period and switch-back period under oral risperidone. Further details on study design and blood sampling schedule are available in the published paper.[7]

The preferred site for RBP-7000 SC injection was the abdomen, in a location with adequate amounts of SC tissue that did not have excessive pigment, nodules, lesions, or hair. When multiple doses were administered, the injection in the abdomen was done on the opposite side from the previous injection site. The clinical study protocol, informed consent forms, and all other appropriate study-related documents were reviewed and approved by an independent and appropriately constituted Institutional Review Board. The study was conducted in accordance with good clinical practice as required by US Food and Drug Administration (FDA) regulations, International Conference on Harmonization (ICH) guidelines, and standard operating procedures for clinical investigation and documentation in force at Reckitt Benckiser Pharmaceuticals Inc. (RBP). Compliance with these requirements also indicates conformity with the ethical principles that have their origins in the Declaration of Helsinki. Plasma concentrations of

risperidone and 9-hydroxyrisperidone were measured using a previously validated and published[6] method of liquid chromatography with tandem mass spectrometry (LC–MS/MS). The lower limit of quantitation (LLOQ) was 0.1 ng/mL for both analytes. The active moiety concentrations were calculated as the sum of risperidone and 9-hydroxyrisperidone plasma concentrations corrected by the molecular weight: [Active moiety] = [Risperidone] + [9-hydroxyrisperidone] × (410/426).

Population Pharmacokinetic Analysis

A population PK analysis was conducted to describe jointly risperidone and 9-hydroxyrisperidone plasma concentrations collected in the single and repeated dose studies of RBP-7000. As part of RBP-7000 development program, two population PK models sharing the same structure had been successively developed to describe the PK data in each study separately.[6,7] Thus, one objective of the present analysis was to refine the estimation of model parameters and to better characterize the effects of covariates by pooling the data of the two studies together and increasing sample size.

The multiple ascending dose study included a pretreatment period with oral risperidone. It was therefore necessary to account for this initial exposure by modeling risperidone and 9-hydroxyrisperidone data collected during that period. Oral risperidone pretreatment data had been previously analyzed in previous work[7] and the corresponding estimated population PK model was used in the present analysis with all parameters fixed. The structure of the oral risperidone model is displayed in the Supplemental Material (Figure S1) as well as model parameter estimates (Table S1). Any details on oral risperidone model building can be found in the previous publication.[7]

The population PK analysis of RBP-7000 was carried out in NONMEM software version 7.2 using the first-order conditional estimation with interaction (FOCE-I) method.[16] NONMEM was run in a Windows Vista operating system with the FORTRAN compiler *gfortran* version 4.6.0. Interindividual variability was estimated on all structural model parameters, assuming a log-normal distribution. The residual variability was modeled using additive, proportional, and combined error model structures. The appropriateness of the model was evaluated using various goodness-of-fit criteria, including standard diagnostic plots and the likelihood ratio test. The results for the likelihood ratio test were considered statistically significant when the difference in objective function value between two nested models was more than 3.84 ($P < 0.05$, one degree of freedom) throughout the base model building process. All data preparation, summary statistics, graphics, exploratory analyses, and post-processing of NONMEM outputs were performed in R software.[17]

Covariate Analysis

Body weight, body mass index (BMI), age, sex, race, cytochrome P450 2D6 (CYP2D6) phenotype, and RBP-7000 dose level were selected for the analysis. CYP2D6 phenotype was predicted from the CYP2D6 genotype according to the classification of ultrarapid, extensive, intermediate, and poor metabolizers as described in the literature.[18] The methodology for CYP2D6 genotype testing is detailed in Gomeni's paper.[6] A preliminary screening of covariates was performed based on the examination of the Empirical Bayes Estimates (EBEs) of individual PK parameters obtained from the base model (without covariates). Covariates showing a significant ($P < 0.05$) relationship with EBEs were further tested in NONMEM, as well as those for which a significant effect was reported in previous population PK analyses of RBP-7000.[6,7] Covariate model building in NONMEM was a stepwise process, consisting of a forward and a backward selection procedure. The likelihood ratio test was used to evaluate the significance of incorporating or removing fixed effects into the population model based on alpha levels that were set a priori (0.05 for the forward selection and 0.001 for the backward selection).

Model Evaluation

Model evaluation was based on standard diagnostic plots and visual predictive checks (VPC). VPC stratified by study and analyte were generated to evaluate the ability of the model to correctly predict risperidone and 9-hydroxyrisperidone plasma concentrations after single and multiple SC injections of RBP-7000. At each nominal time point, the observed plasma concentrations were summarized by their 10th, 50th, and 90th percentiles, and these percentiles were graphically compared to their 95% confidence intervals under the model. The 95% confidence intervals were computed by simulation from 500 replicates of the original dataset.

Dose Assessment Simulation Studies

The ultimate objective of the analysis was to estimate the dose of RBP-7000 that would provide similar active moiety exposure to long-acting risperidone injection and paliperidone palmitate during chronic treatment. The reference active moiety plasma concentrations for long-acting risperidone and paliperidone palmitate were extracted from a previous publication[19] which reported simulations to evaluate the strategies for switching from long-acting risperidone to paliperidone palmitate. Two scenarios were simulated in this publication: (i) a low dose scenario, where 25 mg of long-acting risperidone was switched to 50 mg equivalent paliperidone, and (ii) a high dose scenario, where 50 mg of long-acting risperidone was switched to 100 mg equivalent paliperidone. These simulations were performed in a virtual population of 5,000 schizophrenic patients receiving five injections

of long-acting risperidone every 2 weeks, followed by 4 injections of paliperidone palmitate every 4 weeks starting 2 weeks after the last dose of long-acting risperidone. The medians and 90% prediction intervals of the simulated data were extracted from Samtani's paper[19] and compared to the expected active moiety plasma concentrations after multiple SC injections of RBP-7000. Three SC injections of RBP-7000 administered every 4 weeks were simulated for comparison with long-acting risperidone. These simulations were replicated under steady-state conditions for comparison with paliperidone palmitate. RBP-7000 simulations were performed using the final population PK model of RBP-7000 for more than 5,000 schizophrenic patients having the same covariate distribution as in the original dataset. Finally, a previously published PK/PD model[6] was applied to predict DA D2 receptor occupancy levels from the active moiety plasma concentrations. This was an E_{max} model characterized by the following equation:

$$RO = \frac{RO_{max} \times C}{K_d + C}$$

Where RO is the DA D2 receptor occupancy, RO_{max} is the maximal receptor occupancy, C is the active moiety plasma concentration, and K_d is the apparent equilibrium dissociation constant (i.e., the active moiety plasma concentration for which 50% of maximal receptor occupancy is achieved). As for most antipsychotics, RO_{max} was fixed to 100%.[20] The K_d parameter was reported to 10.1 ng/mL.[6]

Results

Data

PK data were obtained in 90 clinically stable schizophrenic patients including 65 males and 25 females. Descriptive statistics of the demographic characteristics are presented in Table 1. Overall, 7568 observations were used for the population PK analysis, corresponding to 3724 concentrations for risperidone and 3844 concentrations for 9-hydroxyrisperidone. Drug concentrations below the LLOQ (representing 3.5% of the data) were discarded from the analysis.

Table 1. Descriptive Statistics on the Demographic Data

Variable	Value
N	90
Age (years)	42.8 [9.8]
Weight (kg)	87.8 [14.3]
BMI (kg/m^2)	28.5 [3.9]
Sex (%)	
Female	27.8
Male	72.2
Race (%)	
Black or African American	78.9
White	18.9
Others	2.2
Phenotype (%)	
Poor metabolizers	3.3
Intermediate metabolizers	23.3
Extensive metabolizers	70.0
Ultrarapid metabolizers	3.3

Values are expressed as mean [standard deviation] unless stated otherwise. N: number of subjects. BMI: body mass index.

Final Population PK Model

As in previous PK analyses[6,7], risperidone plasma concentrations after SC injection of RBP-7000 were adequately described by a two-compartment model with first-order absorption and a transit compartment absorption model. This complex absorption sub-model was needed to describe the double peak plasma concentration profiles observed for risperidone and its metabolite after RBP-7000 administration. The first-order absorption rate constant, ka_1, accounts for the rapid absorption of risperidone from the SC injection site corresponding to the first peak. The transit compartment absorption model[21] mimics the slow delivery from the ATRIGEL® delivery system corresponding to the second peak. In agreement with the literature[22], systemically-available risperidone was partly converted into 9-hydroxyrisperidone and partly eliminated by other routes (biotransformation into other metabolites and renal excretion). A one-compartment model with first-order elimination was selected for 9-hydroxyrisperidone. Since there was no PK information available after administration of the metabolite, the apparent volume of distribution of the metabolite was not identifiable and was set equal to the apparent central volume of distribution of the parent compound up to a constant that was common to all subjects (fixed effect). The structure of the PK model is represented schematically in Figure 1. Model equations are provided in the Supplemental Material. Note that RBP-7000 exhibits flip-flop kinetics where the apparent terminal half-life is driven by the slow absorption of risperidone from the ATRIGEL® delivery system. This flip-flop kinetics increases the complexity of the model regarding the interpretation of PK parameters.

Parameter estimates of the final population PK model are shown in Table 2. A combined additive and proportional residual error model common to risperidone and 9-hydroxyrispridone was selected. Interindividual variability was estimated on all structural model parameters. BMI and race were the only significant covariates retained in the final model. BMI was found to have an impact on ka_1, the absorption rate constant associated with the first peak, with lower values of ka_1 in subjects having a higher BMI. This effect was

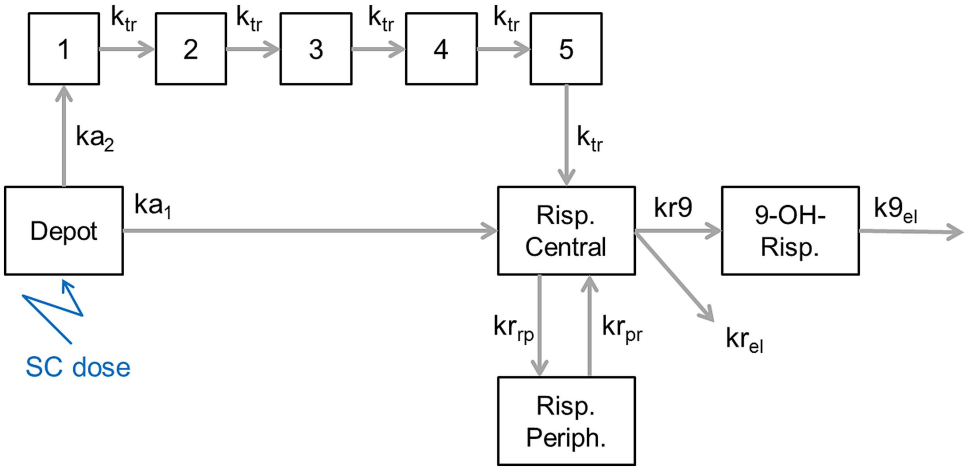

Figure 1. Population pharmacokinetic model for risperidone (Risp.) and 9-hydroxyrisperidone (9-OH-Risp.) after single/repeated subcutaneous (SC) injections of RBP-7000. ka_1 is the rate constant for the rapid absorption of risperidone from the SC injection site (depot compartment); ka_2 and k_{tr} are the absorption and transit rate constants of the transit compartment absorption model (compartments 1 to 5) used to mimic to slow delivery from the ATRIGEL® delivery system; kr_{rp} and kr_{pr} are the exchange rates between the central and peripheral compartments of risperidone; $kr9$ is the rate constant for risperidone conversion into 9-hydroxyrisperidone; kr_{el} is the rate constant for risperidone elimination by other processes; $k9_{el}$ is the elimination rate constant of 9-hydroxyrisperidone.

modeled using an exponential relationship: $\mathrm{ka}_{1\mathrm{tv}} = \theta_1 \exp(-\theta_2 \times (BMI - 29.2))$ where $\mathrm{ka}_{1\mathrm{tv}}$ is the typical value, θ_1 and θ_2 are fixed effect parameters, and 29.2 is the median BMI in the dataset. Race was found to have a significant effect on ka_2, the absorption rate constant of the transit compartment absorption model associated with the second peak. More specifically, a twofold higher ka_2 was estimated in Black subjects compared to the rest of the subjects (essentially composed of White subjects). Incorporating BMI in the model decreased interindividual variability on ka1 from 54 to 44%, while incorporating race in the model decreased interindividual variability on ka2 from 49% to 43%.

Table 2. Final Population PK Parameter Estimates (Relative Standard Errors of Estimates in %) for RBP-7000

Parameter	Fixed effect	Interindividual variability (%)
ka_1 (θ_1) (h^{-1})	0.0151 (11)	44 (12)
BMI on ka_1 (θ_2)	0.0803 (18)	
ka_2, *Blacks* (h^{-1})	0.0513 (11)	43 (13)
ka_2, *Others* (h^{-1})	0.0258 (16)	43 (13)
k_{tr} (h^{-1})	0.0283 (7.1)	46 (13)
V (L)	125 (12)	27 (17)
kr_{el} (h^{-1})	0.0092 (55)	91 (29)
$kr9$ (h^{-1})	0.0474 (23)	66 (8.7)
kr_{rp} (h^{-1})	0.537 (11)	57 (11)
kr_{pr} (h^{-1})	0.0226 (12)	59 (14)
$k9_{el}$ (h^{-1})	0.0620 (5.2)	27 (20)
Scaling factor *SF*	3.65 (17)	
Add. error (ng/mL)	0.0774 (2.0)	
Proportional error	0.335 (0.5)	

Interindividual variability was expressed as a coefficient of variation (calculated as the standard deviation × 100). The apparent central volume of distribution of risperidone and the apparent volume of distribution of 9-hydroxyrisperidone were equal $V \cdot SF$ and V, respectively.

$ka_{1tv} = \theta_1 \exp(-\theta_2 \times (BMI - 29.2))$, where ka_{1tv} is the typical value of ka_1, θ_1 and θ_2 are fixed-effect parameters, and 29.2 is the median value of BMI (body mass index) in the dataset.

VPC stratified by study and analyte are shown in Figure 2. In order to increase to number of data points per plot and to refine the evaluation of the model, drug plasma concentrations were normalized to the intermediate 90 mg dose (i.e., they were divided by the actual dose level and multiplied by 90). Overall, the model provided a good description of the data with respect to median concentrations and variability. The secondary peak of the metabolite was slightly underestimated in the single ascending dose study compared to the multiple ascending dose study. Also, variability was slightly underestimated for the metabolite, while it was well described for the parent compound. Standard diagnostic plots are displayed in the Supplemental Material (Figure S2) and do not show any apparent bias.

Dose Assessment Simulation Studies

The results of RBP-7000 simulations are shown in Figures 3 and 4 for the comparison with long-acting risperidone injection and paliperidone palmitate, respectively. The upper panel of Figure 3 shows the simulated active moiety plasma concentration–time profiles after 3 SC injections of RBP-7000 at 60, 90, or 120 mg administered every 4 weeks, compared with the active moiety plasma concentration–time profiles of long-acting risperidone at the dose of 25 mg administered every 2 weeks over 10 weeks. The simulations indicated that

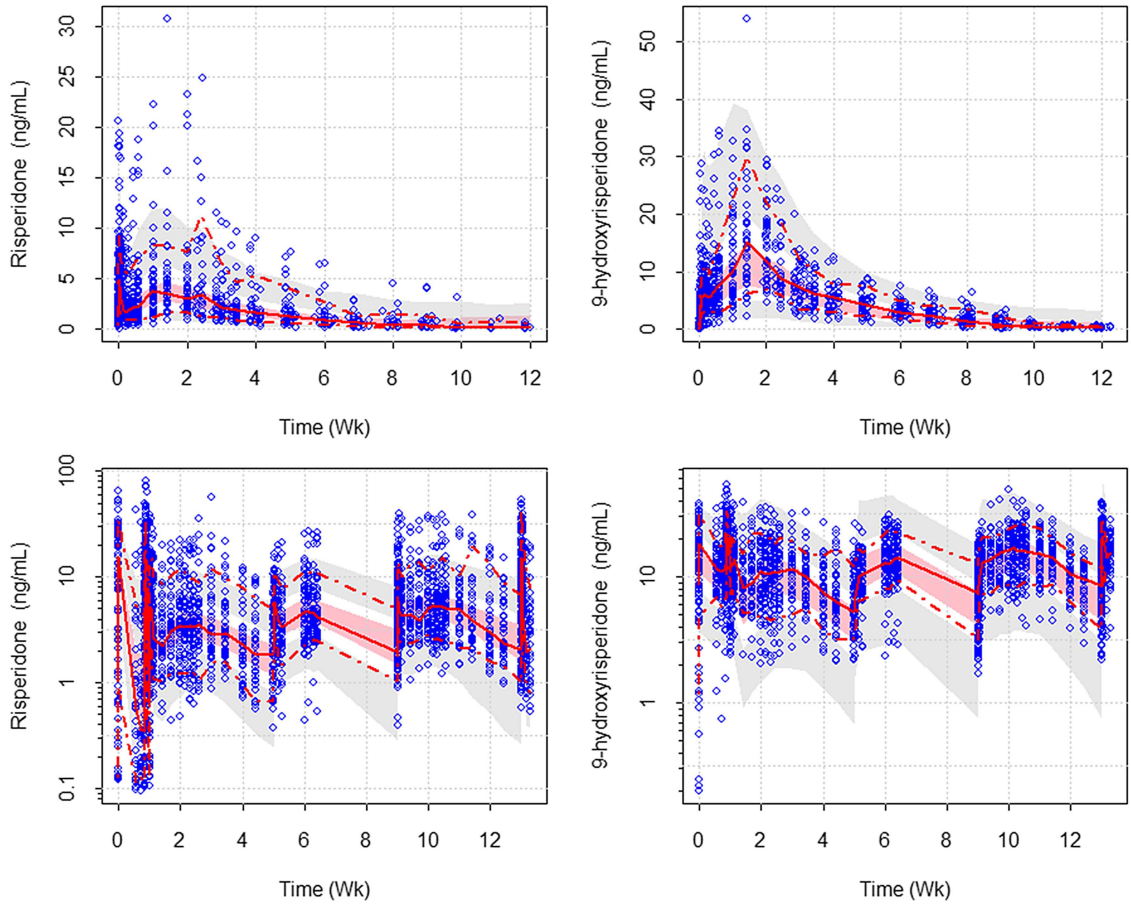

Figure 2. Visual predictive checks (VPC) for the final population pharmacokinetic model of RBP-7000. VPC plots stratified by study and analyte were generated after normalization of concentrations to the intermediate 90 mg dose. VPC were plotted in the normal scale for the single ascending dose study (upper panel), and in the semi-logarithmic scale for the multiple ascending dose study (lower panel). Left-hand side: risperidone. Right-hand side: 9-hydroxyrisperidone. The red lines represent the 10th, 50th, and 90th percentiles of the observed data (blue circles), the shaded gray areas are the 95% confidence intervals of the 10th and 90th percentiles of the simulated data, and the pink shaded areas are the 95% confidence intervals of the 50th percentiles of the simulated data.

RBP-7000 at the dose of 90 mg provided similar active moiety exposure to long-acting risperidone injection at the dose of 25 mg at steady-state, despite a higher degree of peak-trough fluctuations. While it took about 4–6 weeks to reach steady-state concentrations for long-acting risperidone, concentrations close to steady-state levels were attained right after the first SC injection of RBP-7000. Predictions of DA D2 receptor occupancy can be visualized in the lower panel of Figure 3. As expected from active moiety concentrations, RBP-7000 at the dose of 90 mg provided similar levels of receptor occupancy to long-acting risperidone injection at the dose of 25 mg at steady-state, despite higher fluctuations over 1 month. Exceeding the threshold of 80% has been associated with an increased risk of side effects, in particular extrapyramidal symptoms.[23] In the present simulations, the maximal levels for the 95th percentiles were 80% for 25 mg of long-acting risperidone and 82% for 90 mg of RBP-7000.

Figure 4 shows the simulated active moiety plasma concentration–time profiles at steady-state for monthly SC injections of RBP-7000 at 60, 90, and 120 mg, compared with those obtained after monthly intramuscular injections of paliperidone palmitate at 50 mg equivalent paliperidone. The simulations indicated that a dose of 60 mg of RBP-7000 would provide similar active moiety exposure to 50 mg equivalent paliperidone during chronic treatment. Overall, there was a good concordance in the expected DA D2 receptor occupancy levels for 60 mg RBP-7000 and 50 mg equivalent paliperidone. In both cases, the 95th percentile curve for DA D2 receptor occupancy was below the threshold of 80%.

Due to space limitation, the results of the comparison with the high doses of long-acting risperidone and paliperidone palmitate are displayed in the Supplemental Material (Figures S3 and S4). In the case of 50 mg of long-acting risperidone, none of the investigated doses of RBP-7000 (60, 90, or 120 mg) provided fully equivalent active

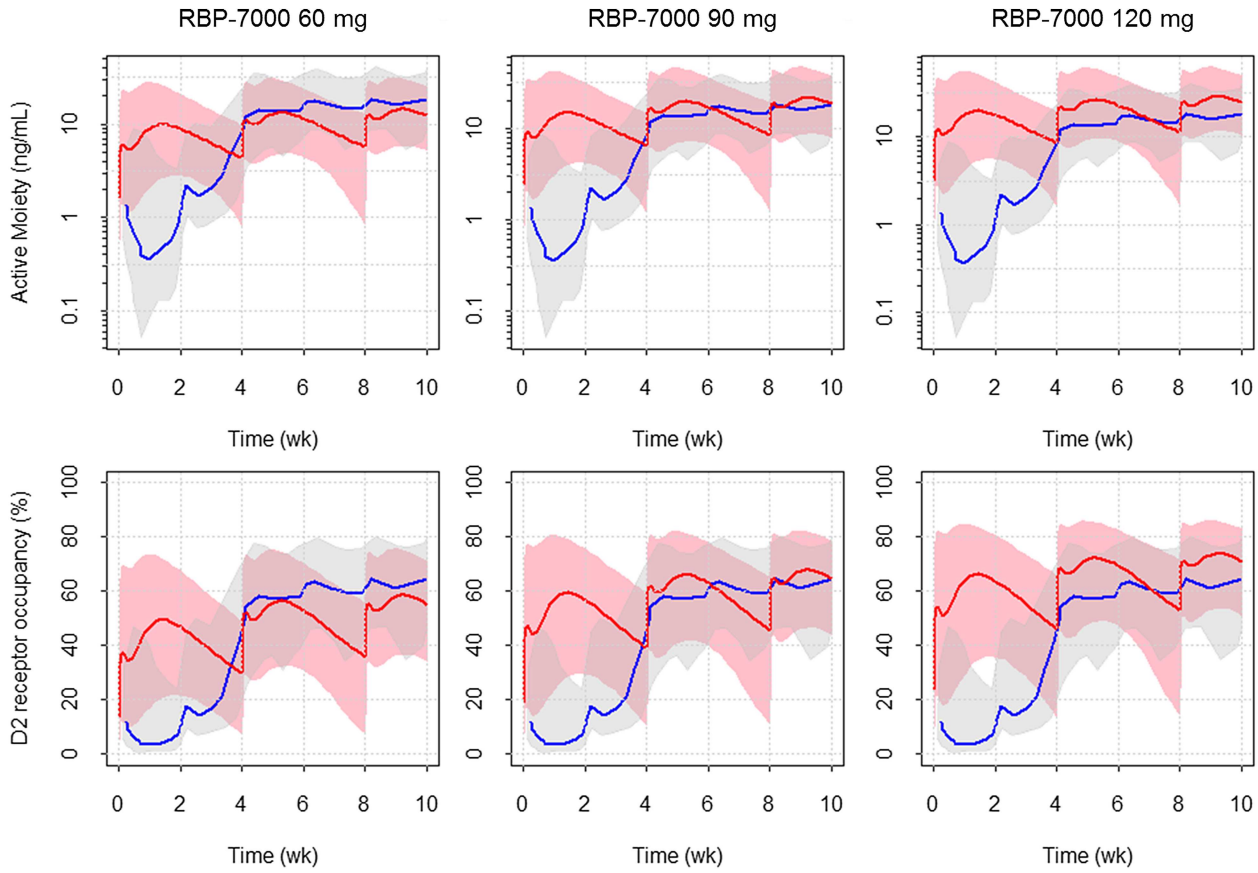

Figure 3. Simulation studies to compare active moiety plasma concentrations (upper panel) and dopamine D2 receptor occupancy (lower panel) after repeated doses of RBP-7000 (60, 90, 120 mg) administered once per month and repeated doses of risperidone long-acting injectable formulation (25 mg) administered every 2 weeks. Active moiety concentration data after long-acting risperidone injection were extracted from a published simulation study[19] where subjects received five injections of long-acting risperidone before switching to paliperidone palmitate on week 10. Long-acting risperidone data before week 10 were presented against RPB-7000 simulated data. Dopamine D2 receptor occupancy levels were simulated from active moiety plasma concentrations using a previously published pharmacokinetic/pharmacodynamic model.[6] The red curve and shaded pink area represent respectively the medians and 90% prediction intervals of RBP-7000 simulated data. The blue curve and shaded gray area represent respectively the medians and 90% prediction intervals of long-acting risperidone data.

moiety plasma exposure. The closest plasma concentration levels were achieved with the 120 mg dose of RBP-7000. Additional model simulations showed that a higher dose of RBP-7000 would be required to achieve similar active moiety plasma exposure to 50 mg of long-acting risperidone. These aspects are further addressed in the discussion section. Regarding paliperidone palmitate, RBP-7000 at the dose of 90 mg provided active moiety levels comparable to those obtained with 100 mg equivalent paliperidone.

Discussion

The population PK analysis, based on two clinical studies, confirmed previous findings obtained by analyzing each study separately.[6,7] Especially, BMI was identified as a significant covariate affecting the first peak of risperidone and 9-hydroxyrisperidone. The first peak of risperidone occurred at a median time of 4–6 hours post-injection, indicating that a fraction of the dose was not trapped in the biodegradable implant formed by solidification of the ATRIGEL® delivery system but was readily available for absorption. The impact of BMI on the first peak suggests that the adipose composition at the injection site (in the abdomen) influences the early absorption of risperidone which is a lipophilic drug. It is noteworthy that BMI was also identified as a significant covariate for the absorption of paliperidone, also lipophilic, by the intramuscular route.[24]

In contrast to previous population PK analyses (the single dose study contained almost exclusively Black subjects), race was identified as a statistically significant covariate in the present analysis. Race was found to affect the absorption rate constant for the second peak (ka_2) whose estimate was twice higher in Black subjects than in the rest of the subjects (essentially White subjects). Despite this difference, race had a limited impact on active moiety plasma concentration profiles: at

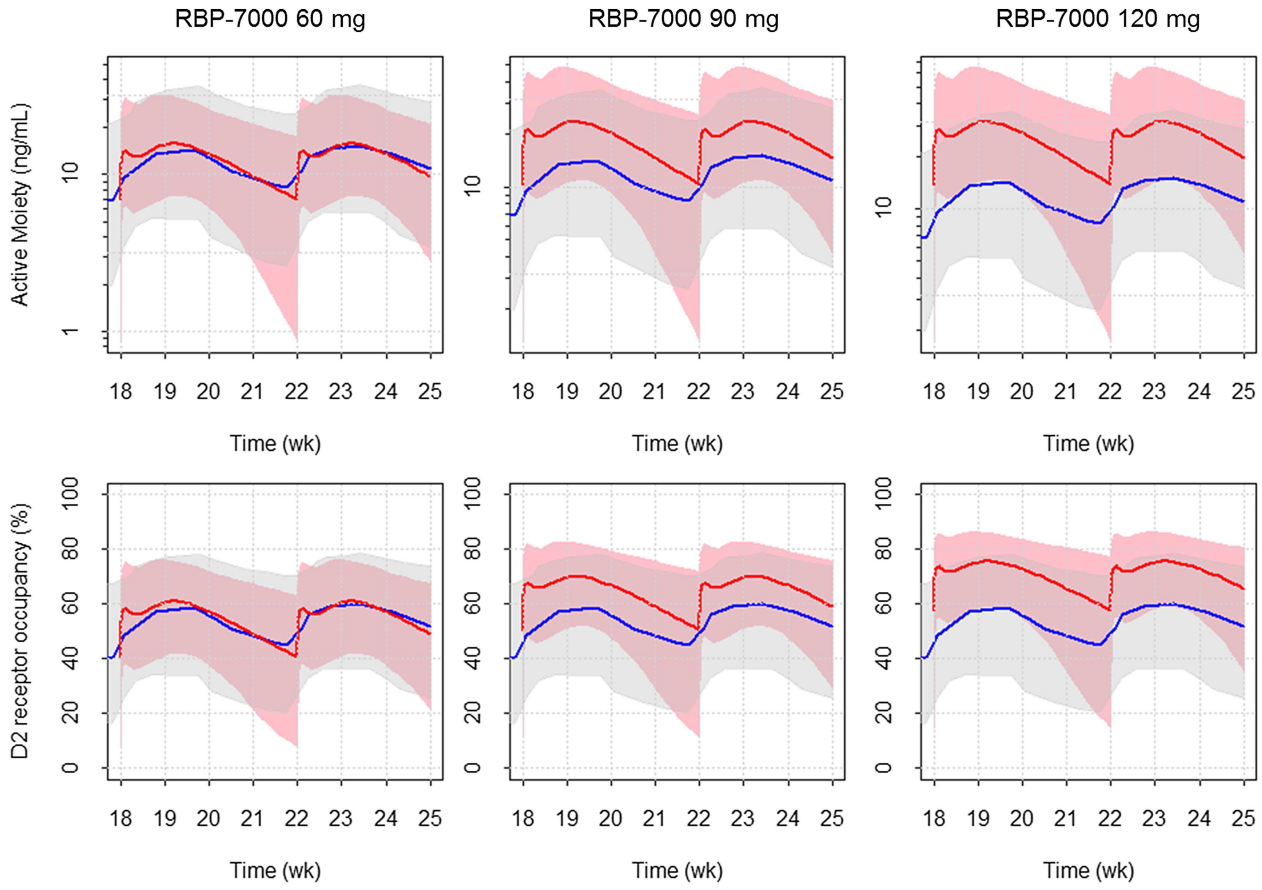

Figure 4. Simulation studies to compare active moiety plasma concentrations (upper panel) and dopamine D2 receptor occupancy (lower panel) at steady-state after once monthly injections of RBP-7000 (60, 90, 120 mg) and once-monthly injections of paliperidone palmitate (50 mg equivalent paliperidone). Active moiety concentration data after paliperidone palmitate injection were extracted from a published simulation study[19] where subjects received five injections of long-acting risperidone before switching to paliperidone palmitate on week 10. Steady-state data after week 18 are presented against RPB-7000 simulated data. Dopamine D2 receptor occupancy levels were simulated from active moiety plasma concentrations using a previously published pharmacokinetic/pharmacodynamic model.[6] The red curve and shaded pink area represent respectively the medians and 90% prediction intervals of RBP-7000 simulated data. The blue curve and shaded gray area represent respectively the medians and 90% prediction intervals of paliperidone palmitate data.

steady-state, the maximal plasma concentration (C_{max}) was only 3.5% higher for the second peak in typical Black subjects than in typical White subjects having a median BMI of 29 kg/m^2, and 11% lower for the first peak. BMI had a more pronounced effect than race on active moiety plasma concentrations: in typical White subjects, the C_{max} of the active moiety for the first peak was reduced by approximately 38% as BMI increased from 19 to 35 kg/m^2 under steady-state conditions. The secondary peak was only marginally affected by an increase in BMI. Since the second peak is related to the sustained release of risperidone from the ATRIGEL® delivery system resulting in prolonged plasma concentrations and shows higher or similar plasma levels compared to the first peak, no BMI-base dose adjustments are expected. Further information from the Phase III studies will be useful to address the BMI effect on the pharmacokinetics of RBP-7000.

Since the conversion of risperidone into 9-hydroxyrisperidone is mainly driven by CYP2D6 polymorphic enzyme, CYP2D6 phenotype was expected to be an influential covariate on the PK of RBP-7000. The CYP2D6 poor metabolizer phenotype has been shown to be associated with adverse drug reactions and discontinuation following risperidone treatment[25] but also with greater clinical improvement in total positive and negative syndrome scale (PANSS) scores.[26] In the present study, the preliminary analysis on EBEs supported lower rates of conversion of risperidone to 9-hydroxyrisperidone (kr_9) in CYP2D6 poor metabolizers, and higher rates of conversion in CYP2D6 ultrarapid metabolizers, compared to intermediate or extensive metabolizers in line with previous PK studies.[27,28] No significant difference was seen between CYP2D6 intermediate and extensive metabolizers. Due to size limitations (only 3 poor metabolizers and 3 ultrarapid

metabolizers were included in the analysis), these differences could not be reasonably tested in NONMEM. Thus, the present findings need to be re-evaluated when data from larger clinical trials become available.

Overall, model parameter estimates were consistent with previous parameter estimates obtained from the analysis of repeated dose study data only.[7] Small differences were found with the parameter estimates obtained from the analysis of single dose study data.[6] These differences were mostly attributed to a different covariate model structure (no normalization to median BMI) and to the inclusion of a dose-dependence on the volume of distribution of risperidone and 9-hydroxyrisperidone, leading to higher concentration–time profiles at higher doses. Such dose-dependence was not evidenced in the repeated dose study or in the present meta-analysis.

The population PK model of RBP-7000 was used to simulate active moiety plasma concentrations after repeated doses of 60, 90, and 120 mg of RBP-7000 and to compare these concentrations with those expected after repeated administrations of long-acting risperidone (25 or 50 mg) and paliperidone palmitate (50 or 100 mg equivalent paliperidone. Active moiety concentrations were calculated to account for the activity of both risperidone and 9-hydroxyrisperidone. The pharmacological properties of the 9-hydroxy metabolite appear to be comparable to those of risperidone itself, both in respect of the profile of interactions with various neurotransmitters and its potency, activity, and onset and duration of action.[33,34] And 9-hydroxyrisperidone has been approved as paliperidone for the treatment of schizophrenia. Although the two compounds do not necessarily have the same tissue distribution (especially, the brain-to-plasma concentration ratio is higher for risperidone than for its metabolite[33]), the combined risperidone and 9-hydroxyrisperidone plasma concentration is commonly used to reflect overall body exposure. Furthermore, the active moiety concentration has been shown to contribute the overall antipsychotic effects in the treatment and to correlate well with efficacy/safety endpoints.[35,36]

Reference competitor data were extracted from a previous publication[19] which reported the results of a PK simulation study evaluating the strategies for switching from long-acting risperidone (25 or 50 mg) to paliperidone palmitate (50 or 100 mg equivalent paliperidone, respectively) in schizophrenic patients. This simulation study, in combination with others, was used to support the current dosing recommendations of paliperidone palmitate and their approval by the US Food and Drug Administration (FDA) and other regulatory agencies around the world.

The results of the present study indicated that a dose of 60 mg of RBP-7000 should provide similar steady-state active moiety plasma levels to chronic administration of 50 mg equivalent paliperidone, and that a dose of 90 mg of RBP-7000 should provide similar steady-state active moiety plasma levels to chronic administration of 25 mg of long-acting risperidone. Given the linearity of the kinetics of long-acting risperidone over the dose range of 12.5–50 mg[8,29] and assuming that RBP-7000 kinetics is linear up to 180 mg, it can be extrapolated that 180 mg of RBP-7000 would give equivalent active moiety plasma exposure to 50 mg of long-acting risperidone, which was confirmed by additional PK simulations (not shown). In the case of paliperidone palmitate, previous studies showed that paliperidone exposure increased dose proportionally over the dose-range of 25–150 mg, but that the peak concentrations were somewhat less than dose proportional for the higher doses due to slower absorption.[24] More precisely, there was a decrease in the absorption rate constant with an increase in the injection volume (0.5 mL for 50 mg equivalent paliperidone, and 1 mL for 100 mg equivalent paliperidone). This could explain our findings of comparable active moiety concentration levels between 90 mg RBP-7000 and 100 mg equivalent paliperidone in our simulations, while 60 mg RBP-7000 and 50 mg equivalent paliperidone provided similar active moiety concentrations.

RBP-7000 and paliperidone palmitate are administered once per month and seem therefore more convenient for long-term treatment than long-acting risperidone administered twice monthly. The results of the simulations showed that RBP-7000 and paliperidone palmitate provided sustained concentration levels over 1 month of treatment (i.e., median active moiety concentration profiles at steady-state were very close for doses of 60 mg RBP-7000 and 50 mg equivalent paliperidone). However, while the initiation of paliperidone palmitate treatment requires two loading doses at Day 1 and at Day 8,[15] active moiety concentrations close to steady-state levels were attained right after the first SC injection of RBP-7000. For long-acting risperidone, it took approximately 6 weeks from the start of the therapy to reach steady-state concentrations. Thus, RBP-7000 would present an advantage over the competitors in the sense that it does not seem to require any loading dose or supplementation with oral risperidone as required for paliperidone palmitate and long-acting risperidone injection, respectively.

Our simulations also showed that the active moiety plasma concentrations fluctuated less after administration of long-acting risperidone than after administration of RBP-7000. The consequences on drug efficacy and safety (extrapyramidal side effects) were evaluated based on the predictions of brain DA D2 receptor occupancy using a previously published PK/PD model.[6] DA D2 receptor occupancy is recognized to be a key driver of clinical efficacy and safety response to antipsychotic drugs. The currently accepted hypothesis is that DA D2 receptor occupancy should range from ~65% to ~80% for optimal antipsychotic effect and minimal extrapyramidal side

effects.[23] Available positron emission tomography (PET) data suggest that dosing long-acting risperidone at 25–50 mg every 2 weeks is sufficient in attaining clinical response with minimal risk of extrapyramidal symptoms.[30,31] In our simulations, the predicted 95th percentiles of DA D2 receptor occupancy were below 80%–82% for 90 mg of RBP-7000 and 25 mg of long-acting risperidone, hence supporting safety. The predicted 5th percentiles were lower for 90 mg of RBP-7000 than for 25 mg of long-acting risperidone over the second half of the monthly dosing interval for RBP-7000 and the clinical relevance of this difference needs to be evaluated. It is noteworthy that in the multiple ascending dose study evaluating the switch from oral risperidone to RBP-7000, treatment with RBP-7000 led to similar and stable PANSS scores compared to oral risperidone.[7] Thus, it appears that the fluctuations seen on RO predictions for RBP-7000 would have no noticeable impact on clinical endpoints as assessed from PANSS scores measurements.

Concerning paliperidone palmitate, a recent post-hoc analysis of seven randomized controlled studies showed that the incidence rates of spontaneously reported extrapyramidal symptoms were generally lower for paliperidone palmitate following approximately 90 days of exposure compared to oral paliperidone following approximately 40 days of exposure at comparable doses.[32] Also, the use of medications for the treatment of emergent extrapyramidal adverse events was significantly lower in paliperidone palmitate-treated patients (12%) than in oral paliperidone-treated patients (17%, $P = 0.0035$). In these studies, paliperidone palmitate was administered at doses ranging from 25 to 150 mg equivalent paliperidone. Since our simulations showed comparable DA D2 receptor occupancy between 60 mg RBP-7000 and 50 mg equivalent paliperidone on one hand and between 90 mg RBP-7000 and 100 mg equivalent paliperidone on the other hand, one may reasonably assume that the incidence rates of extrapyramidal side effects will also be low for RBP-7000 at these doses.

In conclusion, the population PK analysis of RBP-7000 confirmed previous knowledge and identified race as an additional covariate. BMI and race were found to have a statistically significant effect on the absorption of RBP-7000, with race having only limited impact on active moiety plasma concentrations. Although these findings needs to be validated in larger PK studies, the present simulations suggest potential benefits of RBP-7000 compared to other long-acting antipsychotics and provide further guidance for dose selection in future Phase III clinical trials.

Declaration of Conflicting Interests

At the time this manuscript was submitted for publication, B. Zheng, C. Heidbreder, P.J. Fudala, and A.F. Nasser were full-time employees of Reckitt Benckiser Pharmaceuticals Inc. C.M. Laffont and R. Gomeni were paid consultants for Reckitt Benckiser Pharmaceuticals Inc.

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