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ORIGINAL RESEARCH ARTICLE

Population Pharmacokinetics and Prediction of Dopamine D_2 Receptor Occupancy After Multiple Doses of RBP-7000, a New Sustained-Release Formulation of Risperidone, in Schizophrenia Patients on Stable Oral Risperidone Treatment

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Abstract

Background and Objectives RBP-7000 is a long-acting formulation of risperidone administered once monthly via subcutaneous (SC) injections for the treatment of schizophrenia. The objectives of the present study were to characterize the pharmacokinetics of RBP-7000 after multiple doses in schizophrenic patients on stable oral risperidone therapy and to evaluate the switch between oral risperidone and SC injections of RBP-7000.

Methods Data were collected in a phase IIa, open-label, multiple-ascending-dose study where 45 patients clinically stabilized on oral risperidone (2, 3 or 4 mg/day) were switched to receive 60, 90 or 120 mg/month SC injections of RBP-7000, respectively. Patients were thereafter switched back to oral risperidone. An integrated population pharmacokinetic model describing simultaneously risperidone and 9-hydroxyrisperidone after risperidone oral intake and RBP-7000 administration was developed in NONMEM using 5,232 quantifiable plasma concentrations. Predictions of dopamine D_2 receptor occupancy were derived using a previously published model.

Results A two-compartment model with first-order absorption was selected for oral risperidone, while a three-compartment model with first-order absorption and a transit compartment absorption model was selected for RBP-7000. Body mass index was identified as a significant covariate affecting the initial absorption of risperidone following RBP-7000 injection. Steady state was reached after the second or third RBP-7000 injection but plasma concentrations close to steady-state values were obtained right after the first injection when switching from oral risperidone therapy. Predicted dopamine D_2 receptor occupancy after repeated doses of 90 and 120 mg showed less fluctuation than after oral risperidone with acceptable ranges for clinical efficacy and a potentially safer profile with respect to extrapyramidal side effects.

Conclusion This analysis provided additional insight into the pharmacokinetics of RBP-7000 and for the comparison with oral risperidone treatment. The established model was used to support the design of a planned phase III study.

1 Introduction

The use of atypical antipsychotics for the treatment of schizophrenia has generally resulted in improved outcome, improved tolerability and/or reduced side effects compared with first-generation agents. However, these potential benefits have been greatly mitigated by patient non-adherence to daily oral medication such as risperidone. In clinical trials, non-compliance rates under oral antipsychotic medication are approximately 40–50 % [1] and these rates are obviously higher under routine treatment conditions. Non-compliance appears to have a counter-therapeutic effect on potential benefits of antipsychotic medications [2, 3] and has been identified as a major factor

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in relapse leading to re-hospitalization, poor clinical outcome and high economic costs [1, 4].

Long-acting injectable (LAI) antipsychotics have been developed to specifically address non-compliance issues. With LAI medications, the non-adherence rate dropped from 40–50 % under oral antipsychotic medication to less than 10 % [5]. LAI antipsychotics present additional advantages over oral therapy: they avoid the first-pass effect in the liver and achieve persistent drug exposure, requiring less frequent drug administrations and hence simplifying the treatment process. The first approved LAI atypical antipsychotic was long-acting risperidone (Risperdal® Consta®) administered twice monthly by intramuscular administration. An LAI formulation was further developed for paliperidone (Invega® Sustenna®) for monthly intramuscular injections. Paliperidone is also known as 9-hydroxyrisperidone, which is the main metabolite of risperidone and exhibits similar pharmacological activity [6].

RBP-7000 is a new LAI formulation of risperidone designed for once-monthly subcutaneous (SC) injection. While LAI risperidone uses drug-loaded microspheres to deliver the drug, RBP-7000 uses an in situ poly-DL-lactide-co-glycolide (PLGH) biodegradable implant, which delivers risperidone in a controlled fashion over an extended period of time. This PLGH implant is formed by SC injection of the ATRIGEL® Delivery System [7], a viscous liquid formulation, which solidifies upon contact with tissue fluids. The risperidone in RBP-7000 is both dissolved and suspended in the ATRIGEL® Delivery System. The pharmacokinetics of RBP-7000 were characterized in a phase I study following a single SC injection of 60, 90 or 120 mg [8]. Risperidone and 9-hydroxyrisperidone showed double peak plasma concentration–time profiles with a prolonged terminal half-life consistent with rapid delivery from the SC injection site and slow delivery from the ATRIGEL® Delivery System.

A multiple-ascending-dose (MAD) study was subsequently conducted for doses of 60, 90 and 120 mg of RBP-7000 in clinically stable schizophrenic patients previously stabilized on oral risperidone (2, 3 or 4 mg/day). The objective of the present work was to exploit these new data to characterize the pharmacokinetics of RBP-7000 after multiple doses and to evaluate the switch between oral risperidone and RBP-7000. An integrated population pharmacokinetic model simultaneously describing risperidone and 9-hydroxyrisperidone was developed, and dopamine D_2 receptor occupancy was used to predict efficacy and safety profiles. Finally, the pharmacokinetic time-course after multiple RBP-7000 doses was derived from the single-dose study and compared with model-predicted values from the MAD study to evaluate the predictive performance of the pharmacokinetic model.

2 Patients and Methods

2.1 Study Design

This was an open-label, phase IIa, MAD study designed to evaluate the safety, tolerability and pharmacokinetic profile of multiple SC injections of RBP-7000 (60, 90 or 120 mg) in 45 clinically stable schizophrenic patients on stable oral risperidone therapy (2, 3 or 4 mg once daily). All patients had a confirmed diagnosis of paranoid, residual or undifferentiated schizophrenia as defined by Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision (DSM-IV-TR) criteria. Clinically stable patients were defined as patients with no hospitalizations for acute exacerbations within 3 months of screening and a screening total Positive and Negative Syndrome Scale (PANSS) score $\leq$60.

Patients on 2, 3 or 4 mg/day of oral risperidone received RBP-7000 SC injections of 60, 90 and 120 mg, respectively. Each of the three dose levels included 15 subjects. RBP-7000 treatment consisted of three monthly SC injections of RBP-7000 on day 1, day 29 and day 57. The preferred site for the SC injection was the abdomen, in a location with adequate amounts of SC tissue that did not have excessive pigment, nodules, lesions or hair. For the second and third RBP-7000 administrations, the injection in the abdomen was done on the opposite side from the previous injection site. 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 (days 85–87). After discharge on day 87, subjects returned to the Clinical Unit as outpatients for three weekly assessments.

For those subjects who were not on a previous 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. Then, all subjects entered a 7-day pretreatment period with once-daily oral doses of 2, 3 or 4 mg of risperidone from day -7 to day -1 (the day before the first RBP-7000 administration).

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. Written informed consent was obtained before a subject was enrolled in the study and prior to the commencement of any protocol-driven activities. A description of the trial protocol can be accessed at http://www.clinicaltrials.gov [NCT01677377].

2.2 Blood Sampling Schedule

Blood samples for risperidone and 9-hydroxyrisperidone pharmacokinetic assessments were collected after each SC injection of RBP-7000. For the first injection, blood

samples were collected on day 1 (pre-dose sample and at 1, 2, 3, 4, 6 and 12 h post-injection) as well as on days 2, 4, 6, 8, 9, 10, 11, 12, 15, 18, 22 and 25 at approximately the same time of day as dosing. For the second injection of RBP-7000, blood samples were collected on day 29 (pre-dose sample and at 4 h post-injection) as well as on days 30, 31, 36, 37, 38 and 39 at approximately the same time of day as dosing. For the third injection of RBP-7000, blood samples were collected on day 57 (pre-dose sample and at 1, 2, 3, 4, 6 and 12 h post-injection) as well as on days 58, 60, 62, 64, 65, 66, 67, 68, 71, 74, 78 and 81 at approximately the same time of day as dosing. Blood samples were also taken during the initial pretreatment period with oral risperidone on day −7 (pre-dose sample and at 1 h post-dose), days −3 and −2 (pre-dose samples) and day −1 (pre-dose sample and at 0.5, 1, 2, 4 and 8 h post-dose). During the switchback period, blood samples were collected on day 85 (pre-dose sample and at 0.5, 1, 2, 4 and 8 h post-dose) and on days 86 and 87 (pre-dose samples).

Plasma concentrations of risperidone and 9-hydroxyrisperidone were determined using a validated method of liquid chromatography with tandem mass spectrometry (LC–MS/MS). The analytical methodology was based on the following procedure: 0.05 mL of human plasma containing internal standards (d4-risperidone, d4-9-hydroxyrisperidone) was firstly acidified and then extracted using solid-phase extraction. Analysis requires evaporation of elute solvent before reconstitution. An aliquot of the extract was injected onto a Sciex API 5500 LC–MS/MS equipped with a high-performance liquid chromatography (HPLC) column. Quantitation was performed using weighted linear least-squares regression analysis generated from fortified plasma calibration standards prepared on the day of extraction or in bulk and frozen. This method was validated for a range from 0.1 to 100 ng/mL for both risperidone and 9-hydroxyrisperidone. The accuracy (overall bias) ranged from −4.4 to 0.4 % for risperidone and from −4.1 to 1.2 % for 9-hydroxyrisperidone. The precision (total coefficient of variation) ranged from 3.2 to 5.0 % for risperidone and from 4.3 to 11.7 % for 9-hydroxyrisperidone. The lower limit of quantitation was 0.1 ng/mL for both risperidone and 9-hydroxyrisperidone. The active-moiety concentration was calculated as the sum of risperidone and 9-hydroxyrisperidone corrected by the molecular weight [8].

2.3 Population Pharmacokinetic Analysis

An integrated population pharmacokinetic model was developed to simultaneously fit plasma concentrations of risperidone and 9-hydroxyrisperidone in the MAD study. The model included a joint model for risperidone and 9-hydroxyrisperidone to describe the pharmacokinetics after SC injection of RBP-7000 and a second joint model to describe the pharmacokinetics after risperidone oral intake. The second model was required to account for the initial exposure to risperidone and 9-hydroxyrisperidone during the oral risperidone pretreatment period.

Previously published models were selected as a starting point for model building. The population pharmacokinetic model developed from single-dose data (60, 90 and 120 mg) and published by Gomeni et al. [8] was selected for RBP-7000. The population pharmacokinetic model developed by Feng et al. [9] from sparse data matching our study conditions was selected for oral risperidone. The structures of these models are shown in Fig. 1. In the case of oral risperidone, the structural model for risperidone was a one-compartment model with first-order absorption (ka_{OR}) and two first-order elimination processes: one for the conversion to 9-hydroxyrisperidone ($k9_{el,OR}$) and one for the elimination of risperidone by other routes ($kr_{el,OR}$), i.e. renal excretion and biotransformation to other metabolites, in line with the literature [10]. A one-compartment model with first-order elimination ($k9_{el,OR}$) was used for 9-hydroxyrisperidone. In the case of RBP-7000, a dual absorption process was modelled to account for the double-peak plasma concentration–time profiles observed for risperidone and 9-hydroxyrisperidone. This dual absorption process was described by (1) a first-order rate constant (ka_1) associated with the first peak; and (2) a transit compartment absorption model [11], with absorption rate constant ka_2 and transit rate constant k_{tr}, associated with the second peak to mimic the slow delivery of risperidone from the ATRIGEL® Delivery System. Together with this absorption sub-model, the plasma disposition of risperidone was described by a two-compartment model with two first-order elimination processes: as for the oral risperidone model, systemically available risperidone was partly converted into 9-hydroxyrisperidone ($kr9$) and partly eliminated by other routes (kr_{el}). The plasma disposition of 9-hydroxyrisperidone following RBP-7000 administration was described by a one-compartment model with first-order elimination ($k9_{el}$). Since the volume of the 9-hydroxyrisperidone was not identifiable (no independent pharmacokinetic information after administration of the metabolite was available), it was set equal to the central volume of the parent compound up to a constant that was common to all subjects (fixed effect).

The population pharmacokinetic analysis was run in a stepwise manner. The first step was to develop the oral risperidone model based on the data collected during the initial pretreatment period, assuming steady-state conditions. This assumption was reasonable since the pretreatment period was preceded by a 7-day oral risperidone conversion and stabilization for those subjects who were

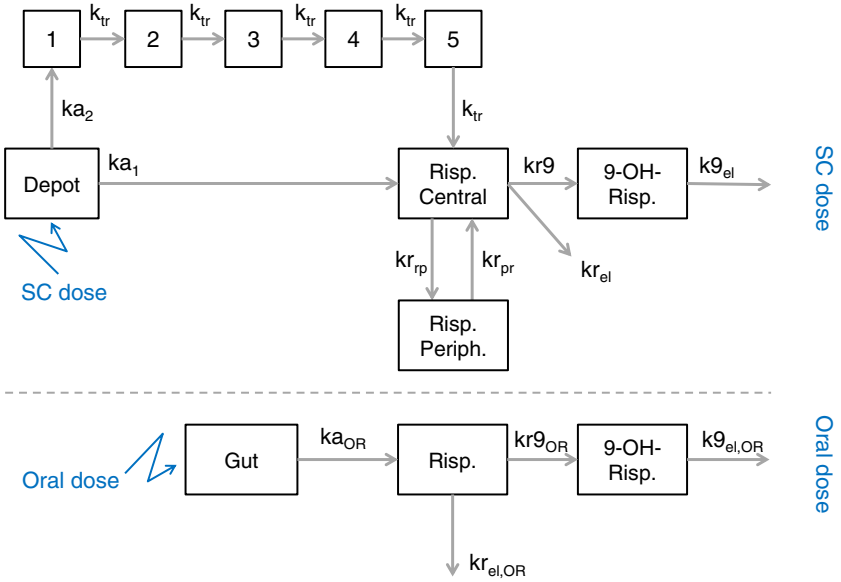

Fig. 1 Integrated population pharmacokinetic model for evaluating the switch between oral risperidone and RBP-7000. The model is a combination of two sub-models describing jointly risperidone (Risp.) and 9-hydroxyrisperidone (9-OH-Risp.) after subcutaneous (SC) injection of RBP-7000 and oral risperidone intake, respectively. Circulating concentrations were calculated as the results of oral risperidone and RBP-7000 administrations. RBP-7000 model: ka_1 is the rate constant for the rapid absorption of risperidone from the SC injection site; ka_2 and k_{tr} are the absorption and transit rate constants of the transit compartment absorption model used to mimic slow delivery from the ATRIGEL® Delivery System; kr_{rp} and kr_{pr} are the exchange rates between the central and the peripheral compartments of risperidone; $kr9$ is the rate constant for conversion of risperidone to 9-hydroxyrisperidone; kr_{el} is the rate constant for risperidone elimination by other processes; $k9_{el}$ is the elimination rate constant for 9-hydroxyrisperidone. Oral risperidone model: ka_{OR} is the rate constant for the oral absorption of risperidone; $kr9_{OR}$ is the rate constant for conversion of risperidone to 9-hydroxyrisperidone; $kr_{el,OR}$ is the rate constant for risperidone elimination by other processes; $k9_{el,OR}$ is the elimination rate constant for 9-hydroxyrisperidone

not on a stable dose of 2, 3 or 4 mg of oral risperidone at the start of the study. The second step was to fix the parameters of the oral risperidone model to the estimates obtained in the first step and to estimate RBP-7000 model parameters from the whole study data set.

Model estimation was performed using the first-order conditional estimation with interaction method (FOCE-I) in NONMEM software, version 7.2 (Icon Development Solutions, Ellicott City, MD, USA) [12]. Inter-individual variability (IIV) was estimated on all structural model parameters, assuming log-normal distributions. The residual variability was modelled using additive, proportional and combined error model structures. All data preparation, summary statistics, graphics, exploratory analyses and post-processing of NONMEM outputs were performed in R (version 3.0.1) [13].

2.4 Covariate Analysis

Covariate analysis was performed on the RBP-7000 model considering the following covariates: body weight, body mass index (BMI), age, sex, race, cytochrome P450 (CYP) 2D6 phenotype and dose. CYP2D6 phenotype was predicted from CYP2D6 genotype according to the classification of ultra-rapid, extensive, intermediate and poor metabolizers as previously described [14]. The methodology for CYP2D6 genotype testing was described by Gomeni et al. [8].

A preliminary screening of covariates was conducted based on the examination of empirical Bayes estimates (EBEs) of individual pharmacokinetic parameters obtained from the model without covariates. Covariates for which a significant ($p < 0.05$) relationship was evidenced in this preliminary analysis were further tested in NONMEM, as well as those for which a significant effect was reported in the previous population pharmacokinetic analysis of RBP-7000 [8]. Covariate model-building in NONMEM was a stepwise process, consisting of a forward and a backward selection procedure. A $p < 0.05$ (corresponding to a change in the objective function of 3.84 for one additional estimated parameter) was considered as significant in the forward procedure, while a more stringent criterion ($p < 0.001$, corresponding to a change in the objective function of 10.83 for one additional estimated parameter) was used in the backward procedure.

2.5 Model Evaluation

The final population pharmacokinetic model was evaluated using standard diagnostic plots and visual predictive

checks (VPC). VPC evaluate whether the model is able to produce simulated data that are similar to the original observed data. Here, 500 replicates of the study design were simulated using the final model. These simulations were used to compute 95 % confidence intervals for the 10th, 50th (median) and 90th percentiles of the concentrations at each time point. These 95 % confidence intervals were then compared graphically with the 10th, 50th and 90th percentiles derived from the observed data. If the model performs well, it is expected that most of the 'observed' percentiles lie within the 95 % confidence intervals derived from the simulations.

2.6 Prediction of Dopamine D_2 Receptor Occupancy

Dopamine D_2 receptor occupancy was predicted using a published pharmacokinetic/pharmacodynamic model [8] described by Eq. 1:

$$\mathrm{RO} = \frac{\mathrm{RO}_{\max} \times C}{K_{\mathrm{diss}} + C} \quad (1)$$

where RO is the dopamine D_2 receptor occupancy, $\mathrm{RO}_{\max}$ is the maximal receptor occupancy that can be achieved, C is the active-moiety plasma concentration and K_{diss} is the apparent equilibrium dissociation constant (i.e. the active-moiety plasma concentration for which 50 % of maximal receptor occupancy is achieved). This model has been shown to apply for most antipsychotics with an $\mathrm{RO}_{\max}$ equal to 100 % [15]. $\mathrm{RO}_{\max}$ was thus fixed to 100 % and the K_{diss} parameter was estimated to 10.1 ng/mL with a standard error of 0.31 [8].

Monte Carlo simulations (500 replicates of the study design) were performed with the final population pharmacokinetic model, and the above pharmacokinetic/pharmacodynamic model was used to simulate dopamine D_2 receptor occupancy–time profiles from the simulated active-moiety concentrations. Simulated dopamine D_2 receptor occupancy data were summarized at each time point by the 5th and 95th percentiles. Additionally, the pharmacokinetic/pharmacodynamic model was used to derive individual predictions of dopamine D_2 receptor occupancy for subjects in the MAD study based on their individual pharmacokinetic predictions.

2.7 Prediction of Multiple Doses from Single Dose

The last objective of the analysis was to evaluate the ability to predict the pharmacokinetic profile of RBP-7000 after multiple doses given single-dose data. Monte Carlo simulations were conducted using the current model (developed from repeated-dose data) and a previous population pharmacokinetic model developed from single-dose data [8]. The simulation scenarios duplicated the design of the MAD study (500 replicates). In each case, the oral risperidone model estimated from the MAD study (Table 2) was applied to simulate oral risperidone data during the initial pretreatment period. The predictions for the active-moiety plasma concentration were summarized for each model by the 5th, 50th and 95th percentiles at each time point. These percentiles were plotted over time for model comparison.

3 Results

3.1 Subject Characteristics

Descriptive statistics of the demographic data of the 45 subjects included in the trial are shown in Table 1. The overall age range was 20–54 years with a mean age of 42.6 years. The overall range of body weights was 50–120 kg with a mean body weight of 86.8 kg. There were 12 female and 33 male participants. The majority of the subjects were Black or African American (62 %), 33 % were White, and there were one Hispanic and one Cambodian.

3.2 Final Population Pharmacokinetic Model

Following inspection of the raw data and data cleaning, 5,232 observations were included in the analysis (risperidone: 2,585; 9-hydroxyrisperidone: 2,647). Drug concentrations below the lower limit of quantification (BLQ) were considered as missing. BLQ data were all obtained during the initial pretreatment with oral risperidone and

Table 1 Descriptive statistics on the demographic data

Variable	Value
N	45
Age (years)	42.6 [9.2]
Weight (kg)	86.8 [15.0]
BMI (kg/m^2)	28.6 [4.3]
Sex (%)	
Female	26.7
Male	73.3
Race (%)	
Black or African American	62.2
White	33.3
Others	4.4
Phenotype (%)	
Poor metabolizers	4.4
Intermediate metabolizers	8.9
Extensive metabolizers	86.7

Values are expressed as mean [SD] unless stated otherwise

BMI body mass index, *N* number of subjects, *SD* standard deviation

Table 2 Final population pharmacokinetic parameter estimates for oral risperidone (OR) and RBP-7000

Parameter	Fixed effects (RSE %)	Interindividual variability [CV % (RSE %)]
First step—Oral risperidone		
ka_{OR} (h^{-1})	3.64 (17)	
V_{OR} (L)	63.8 (13)	37 (17)
$kr_{el,OR}$ (h^{-1})	0.0344 (34)	64 (21)
$kr9_{OR}$ (h^{-1})	0.0990 (18)	87 (14)
$k9_{el,OR}$ (h^{-1})	0.0782 (5.5)	15 (44)
Scaling factor SF_{OR}	3.18 (14)	
Proportional error	0.41 (5.2)	
Second step—RBP-7000		
ka_1 (h^{-1})	0.0266 (63)	31 (23)
ka_2 (h^{-1})	0.0185 (14)	58 (21)
k_{tr} (h^{-1})	0.0247 (8.3)	40 (18)
V (L)	171 (18)	35 (35)
kr_{el} (h^{-1})	0.011 (124)	
$kr9$ (h^{-1})	0.102 (32)	63 (16)
kr_{rp} (h^{-1})	0.572 (15)	49 (24)
kr_{pr} (h^{-1})	0.0114 (23)	89 (27)
$k9_{el}$ (h^{-1})	0.0484 (9.1)	14 (68)
Scaling factor SF	1.34 (20)	
BMI on ka_1	−0.0425 (51)	
Additive error (ng/mL)	0.089 (11)	
Proportional error	0.33 (0.7)	

BMI body mass index, *CV* coefficient of variation, *RSE* relative standard error of estimates, *SC* subcutaneous; Oral risperidone model: ka_{OR} rate constant for the absorption of risperidone; $kr9_{OR}$ rate constant for conversion of risperidone to 9-hydroxyrisperidone; $kr_{el,OR}$ rate constant for risperidone elimination by other processes; $k9_{el,OR}$ elimination rate constant for 9-hydroxyrisperidone, V_{OR} volume of distribution of the central compartment; RBP-7000 model: ka_1 rate constant for the rapid absorption, ka_2 rate constant for the slow absorption, k_{tr} transit rate constant, kr_{el} rate constant for risperidone elimination by other processes, $kr9$ rate constant for conversion of risperidone to 9-hydroxyrisperidone, kr_{rp} and kr_{pr} exchange rates between the central and the peripheral compartments of risperidone, V volume of distribution of the central compartment. The apparent central volume of distribution of risperidone and the apparent volume of distribution of 9-hydroxyrisperidone equal $V{\cdot}SF$ and V, respectively

represented 7.9 % of the data collected during that period. Accounting for these data in the oral risperidone model using an appropriate methodology (method M3 in Ahn et al. [16]) did not change the model parameter estimates and it was thus decided to discard them from the analysis.

Parameter estimates of the final population pharmacokinetic model of oral risperidone are displayed in Table 2. Between-subject variability was estimated on all structural model parameters, with the exception of the absorption rate constant, which was set equal for all subjects. The inclusion of a scaling factor (fixed effect) between the apparent volumes of distribution of risperidone and 9-hydroxyrisperidone led to a significant drop in the objective function value (63 units). Such a scaling factor was used in the previous population pharmacokinetic model of RBP-7000 [8] and supports a greater volume of distribution for risperidone, consistent with the fivefold lower lipophilicity of the metabolite [17]. A proportional residual error model common to risperidone and 9-hydroxyrisperidone was retained. The model provided a reasonable description of the data collected during the oral risperidone pretreatment period, as illustrated in the diagnostic plots (see Electronic Supplementary Material). VPC stratified by analyte are shown for the oral risperidone model in Fig. 2. In order to increase the number of data points per plot and to refine the evaluation of the model, concentrations were normalized to the intermediate 3 mg dose given the linearity of the pharmacokinetics (i.e. they were divided by the actual dose level and multiplied by 3). The VPC plots indicated that the oral risperidone model predicted the data reasonably well, even though more complex models with two compartments for risperidone and a first-pass effect as proposed by Vermeulen et al. [18] would have been certainly more appropriate. Unfortunately, such models could not be estimated from our data.

In a second step, the parameters of the oral risperidone model were fixed to their previous estimates (Table 2) and the integrated population pharmacokinetic model shown on Fig. 1 was run on the whole data set to estimate RBP-7000 model parameters. Model equations, consisting of 12 differential equations, are provided in the Electronic Supplementary Material. A combined additive and proportional residual error model common to risperidone and 9-hydroxyrisperidone was used. The model provided a reasonable fit of the data and was thus retained for subsequent covariate model development. The exploratory analysis on individual pharmacokinetic parameter predictions (EBEs) identified BMI, weight and race as significant covariates: BMI and weight had an impact on the absorption rate constant for the first peak (ka_1), while race had an impact on the absorption and transit rate constants associated with the second peak (ka_2 and k_{tr}). Between BMI and weight, only BMI was kept for further analysis since the two covariates were highly correlated and BMI was slightly more significant than weight. It is noteworthy that BMI was also a significant covariate in the population pharmacokinetic analysis of Invega® Sustenna®, affecting the absorption of paliperidone palmitate ester following intramuscular administration [19]. Regarding CYP2D6 phenotype, the majority of the subjects were classified as extensive metabolizers (86.7 %) with only four intermediate metabolizers and two poor metabolizers. Although a major difference was seen on $kr9$ (the rate constant for

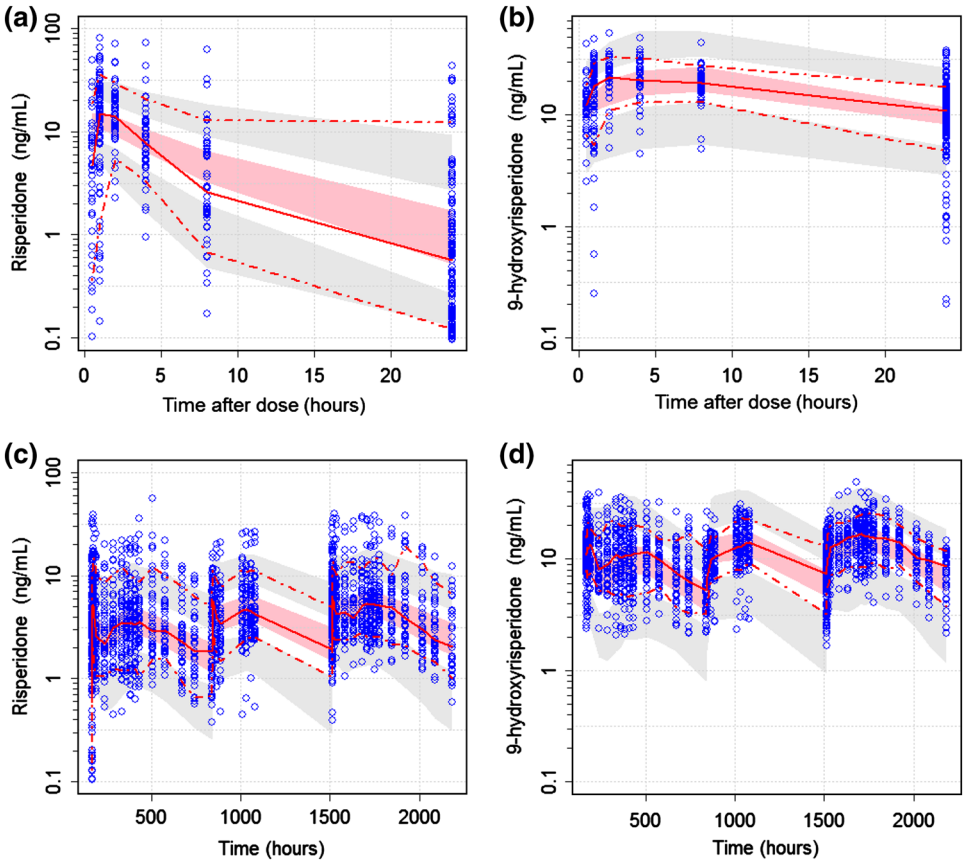

Fig. 2 Visual predictive checks (VPC) for the final population pharmacokinetic model. VPC were plotted in a semi-logarithmic scale for each formulation. **a** Risperidone and **b** 9-hydroxyrisperidone after oral risperidone administration (pretreatment data). **c** Risperidone and **d** 9-hydroxyrisperidone after RBP-7000 administration. In order to increase the number of data points per plot, plasma concentrations were normalized to the intermediate dose (3 mg for oral risperidone, 90 mg for RBP-7000). The *red lines* represent the 10th, 50th and 90th percentiles of the observed data (*blue circles*), the *shaded grey 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. For oral risperidone, time after dose was used instead of time for the *x* axis

conversion of risperidone to 9-hydroxyrisperidone), *kr*9 being much lower in poor-metabolizer subjects, this effect could not be tested in NONMEM given the small number of poor metabolizers in the study. Finally, two additional covariates identified in the previous population pharmacokinetic analysis of RBP-7000 on single-dose data [8] were tested in NONMEM: dose on *V* (apparent volume of distribution of 9-hydroxyrisperidone, equal to the apparent central volume of distribution of risperidone up to a constant) and BMI on ka_2.

The relationship between parameter (P_{tv}) and covariates (Cov) was tested using Eq. 2:

$$P_{tv} = P_1 \cdot e^{(P_2 \cdot \mathrm{Cov})} \quad (2)$$

where P_1 and P_2 are fixed-effect parameters. After application of the forward and backward selection procedures, only BMI was retained in the model with an effect on ka_1: patients with smaller BMI showed a higher initial peak following RBP-7000 SC administration. Population pharmacokinetic parameter estimates for the RBP-7000 model are shown in Table 2. Relative standard errors were of acceptable size, with the exception of kr_{el}, which was poorly estimated. However, as it was not physiologically plausible to set kr_{el} to zero, it was decided to keep this parameter in the model. Standard diagnostic plots (see Electronic Supplementary Material) and VPC (Fig. 2) showed that the model adequately described the observed RBP-7000 data. As for the oral risperidone model, concentrations were normalized to the intermediate dose (90 mg) for the construction of VPC. The dispersion in data (quantified by 10th and 90th percentiles in VPC plots) was well predicted by the model, despite a slight overestimation for the metabolite.

3.3 Prediction of Dopamine D_2 Receptor Occupancy

Predictions of dopamine D_2 receptor occupancy are shown in Fig. 3 for each treatment group. Globally, there was

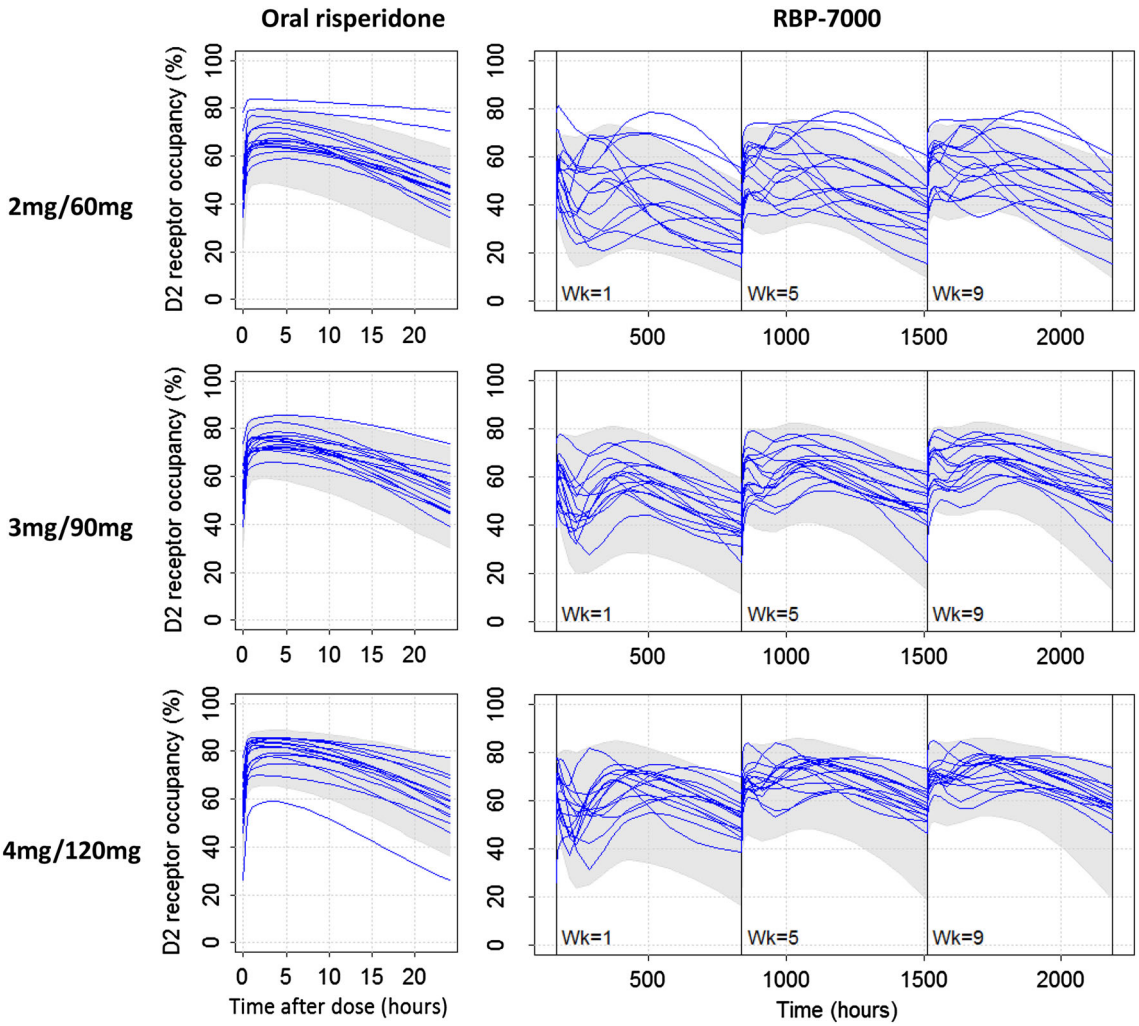

Fig. 3 Predictions of dopamine D_2 receptor occupancy for patients under a stable oral risperidone dose (2, 3 or 4 mg/day) and after switching from oral risperidone to RBP-7000 (3 consecutive administrations of 60, 90 or 120 mg every month). The *shaded grey areas* represent the 90 % prediction intervals for the model predictions in a virtual group of patients having the same covariate distribution as in the original data set. The *blue lines* represent the individual predictions for the patients in the study. For oral risperidone, time after dose was used instead of time for the *x* axis. *Wk* week

good concordance between the individual predictions of the subjects and the variability in dopamine D_2 receptor occupancy predicted by the model in a virtual group of patients having the same covariate distribution as in the original data set. The levels of dopamine D_2 receptor occupancy following the first RBP-7000 SC injection were close to steady-state levels obtained with the second and third SC injections. Repeated doses of RBP-7000 at 90 mg and 120 mg provided dopamine D_2 receptor occupancy in the range of potentially efficacious values. Also, dopamine D_2 receptor occupancy fluctuated less after SC injections compared with oral administrations at the corresponding dose level, with lower maximal occupancy, which supports a potentially safer profile for RBP-7000 with respect to extrapyramidal symptoms.

3.4 Prediction of Multiple Doses from Single Dose

The prediction of active-moiety concentrations after repeated doses was compared with the repeated-dose profiles predicted from single-dose data [8] (Fig. 4). There was globally a good consistency between the predictions of the two models as judged by the overlap of the 90 % prediction regions. The median active-moiety concentration profile from single-dose data was slightly below the current model predictions in the lowest dose group and slightly above the current model predictions in the highest dose group. This small discrepancy was due to the fact that the previous model, built from single-dose data, included a dose effect on the apparent volume of distribution, leading to higher concentrations at higher doses. Such effect was not

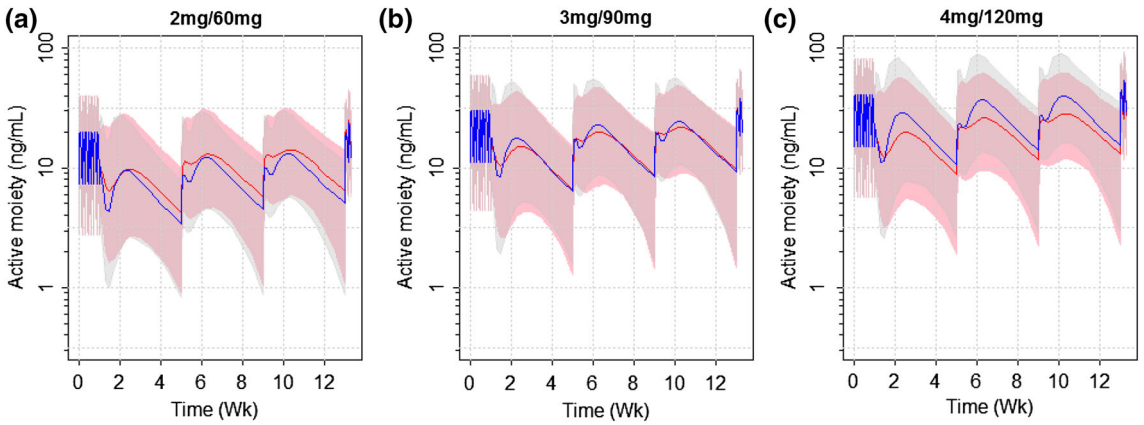

Fig. 4 Comparison of active-moiety plasma concentrations predicted by the current model developed from multiple-ascending-dose (MAD) study data and the previously published RBP-7000 model developed from single-dose data [8] for **a** the 2 mg/60 mg group, **b** the 3 mg/90 mg group and **c** the 4 mg/120 mg group. The *shaded pink areas* represent the 90 % prediction intervals for the predictions obtained with the current model. The *shaded gray areas* represent the 90 % prediction intervals for the predictions obtained with the previous model. The median active-moiety plasma concentration profiles correspond to the *red curves* for the current model and to the *blue curves* for the previous model. *Wk* week

evidenced in the MAD study. Overall, the large overlap between model predictions shows that multiples doses of RBP-7000 can be predicted reasonably well from single-dose data.

4 Discussion

The objectives of this population pharmacokinetic analysis were to (1) characterize the pharmacokinetic profile of RBP-7000 after multiple doses of 60, 90 and 120 mg in clinically stable schizophrenic patients on previous stable oral risperidone therapy (2, 3 or 4 mg/day); and (2) assess the potential risk of extrapyramidal symptoms associated with the switch between oral risperidone and RBP-7000 treatments based on estimated dopamine D_2 receptor occupancy.

The integrated population pharmacokinetic model was a combination of two models: (1) a model for oral risperidone; and (2) a model for RBP-7000. The model adequately described the data, as judged from the diagnostic plots and VPC. BMI was the only covariate retained in the final model of RBP-7000. BMI had a significant impact on the initial rate of absorption of risperidone from the SC injection site, i.e. patients with a smaller BMI exhibited a higher initial peak, which is in line with previous findings [8]. Simulation of typical individuals showed that increasing BMI from 19 to 35 kg/m^2 reduced the first peak by a factor of approximately 30 % for risperidone and approximately 20 % for 9-hydroxyrisperidone. Since the majority of the subjects were extensive metabolizers (with only two poor metabolizers and four intermediate metabolizers), CYP2D6 phenotype could not reasonably be tested as a covariate in the model. Although CYP2D6 phenotype appears to slightly affect the active-moiety plasma concentration [18], the poor-metabolizer phenotype seems to be associated with adverse drug reactions and treatment discontinuation [20]. This last point deserves further investigation in phase III studies.

An important issue in drug development is the linearity of the pharmacokinetics and the ability to predict repeated doses from single-dose data. The predictions of active-moiety plasma concentrations after repeated doses of RBP-7000 were generated using the final model and compared with the repeated-dose profiles predicted from single-dose data [8]. Overall, the concordance between the predictions was good. Only small differences were found, which were attributed to the inclusion of dose dependence on the volume of distribution of risperidone and 9-hydroxyrisperidone in the previous model of RBP-7000 developed from single-dose data, leading to higher concentration–time profiles at higher doses [8]. Such dose dependence was not evidenced in the repeated-dose study. Overall, the results of the simulations indicated that multiple doses of RBP-7000 could be reasonably well predicted from single-dose data, supporting no time dependency of the pharmacokinetics.

When switching from 2/3/4 mg of oral risperidone to 60/90/120 mg of RBP-7000, respectively, plasma concentrations of risperidone and 9-hydroxyrisperidone were not very different between the first, second and third SC injections of RBP-7000. These results show that steady state was nearly reached after the first SC injection, which is important when considering the switch between two treatments. The plasma concentrations of risperidone and 9-hydroxyrisperidone declined slowly after RBP-7000

administration, in line with the sustained release nature of the RBP-7000 formulation. These persistent concentrations resulted in less variable plasma concentrations over time compared with daily administrations of oral risperidone.

A pharmacokinetic/pharmacodynamic model was applied to predict dopamine D_2 receptor occupancy levels. Dopamine D_2 receptor occupancy levels are recognized to be a key driver for clinical efficacy and safety response to antipsychotic drugs. The currently accepted hypothesis is that dopamine D_2 receptor occupancy should range from $\sim$65 to $\sim$80 % for an optimal antipsychotic effect and minimal side effects [21]. Exceeding the threshold of 80 % was associated with an increased risk of side effects, in particular extrapyramidal symptoms. The predicted dopamine D_2 receptor occupancy after repeated doses of 90 and 120 mg of RBP-7000 was in the range of potentially efficacious values, with lower maximal occupancy levels compared with daily oral administrations of risperidone. These results support a potentially safer profile for RBP-7000 than for oral risperidone with respect to extrapyramidal side effects. The comparison of the individual predicted dopamine D_2 receptor occupancy between oral risperidone and RBP-7000 indicates that only 2 of 15 subjects at the dose of 120 mg exceeded the threshold of 80 % while 9 of 15 subjects treated with oral risperidone at the dose of 4 mg/day exceeded this value. These findings indicated that RBP-7000 is expected to have a substantially better safety profile for extrapyramidal symptoms than oral risperidone.

Overall, the results of the clinical study indicated that RBP-7000 was safe and well tolerated. Treatment with RBP-7000 maintained the neurological and clinical symptom assessments after the oral risperidone stabilization period (baseline). The PANSS total scores, PANSS positive scale scores and PANSS general psychopathology scale scores demonstrated similar levels to baseline over the RBP-7000 treatment period for the 60 and 90 mg groups and a slight improvement in the 120 mg group. The maximum improvement, a −2.5 mean change from baseline in the 120 mg group, was observed for the PANSS total scores. Abnormal Involuntary Movement Scale (AIMS) mean total scores, Clinical Global Impression (CGI) mean scores, Simpson–Angus Scale (SAS) mean total scores and Barnes Akathisia Scale (BAS) mean total scores were maintained at similar levels compared with baseline over the RBP-7000 treatment period, with no obvious differences between the three RBP-7000 treatment groups. Three subjects (one per treatment group) reported suicidal ideation during the RBP-7000 treatment period. All three subjects had a previous history of suicidal ideation and there were no suicide attempts during the study.

5 Conclusion

An integrated population pharmacokinetic model was developed to describe the population pharmacokinetics of RBP-7000, a new once-monthly SC formulation of risperidone, in clinically stable schizophrenic patients who were previously on a stable dose of oral risperidone. The analysis provided additional insight into the pharmacokinetics of RBP-7000, refining previous knowledge and supporting RBP-7000 clinical development by addressing key questions through Monte Carlo simulations. Specifically, the results of the analysis suggested a potentially safer profile for RBP-7000 than for oral risperidone with respect to extrapyramidal symptoms. Although promising, these results need to be validated in larger clinical studies.

Conflict of interest 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 consultants for Reckitt Benckiser Pharmaceuticals, Inc. This project was funded by Reckitt Benckiser Pharmaceuticals, Inc., and there was no external funding.

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