

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210655Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA #	210655
Related Past IND	105623
Brand Name:	PERSERIS
Generic Name:	Risperidone, RBP-7000, Risperidone ATRIGEL
Dosage Form:	Extended release injectable suspension
Route of Administration:	Subcutaneous (SC) injection
Dosage Strength:	90 mg and 120 mg of risperidone powder in a syringe to be consituted with a liquid syringe of ATRIGEL
Indications:	Treatment of Schizophrenia in adults
Sponsor:	Indivior
Submission Type:	Standard
Submission Date:	9/28/2017
PDUFA Date:	7/28/2018
OCP Review Team:	Praveen Balimane, Kevin Krudys, Hao Zhu

Contents

1	EXECUTIVE SUMMARY.....	3
1.1.	Recommendation	5
1.2	Labeling Recommendations.....	5
1.3	Phase IV (PMR/PMC) Requirements/Commitments.....	5
2	Question Based Review	6
2.1	Are the proposed doses of 90 and 120 mg of PERSERIS supported by an efficacy and safety study? 6	
2.2	Was adequate PK bridging established between PERSERIS and the Listed Drug (LD), Risperdal?	7
2.3	Was the to-be-marketed formulation used in the pivotal efficacy and relative bioavailability study?	10

2.4	Was there any dose dumping observed with PERSERIS in the clinical trials? What studies were conducted to assess the effect of pressure, temperature or exercise on the release rate of drug from PERSERIS?.....	10
2.5	What were the clinical PK characteristics of single dose and multiple dose sub-cutaneous administration of PERSERIS?	11
2.6	Is PERSERIS suitable for use in patients who are known CYP2D6 poor metabolizers?	12
2.7	Is PERSERIS acceptable for use without any supplementation with oral risperidone?	13
2.8	What are the corresponding oral risperidone daily doses suitable for 90 mg PERSERIS and 120 mg PERSERIS?	13
3	Appendix: Population PK Analyses	15
4	Appendix: Individual study reviews	27

1 EXECUTIVE SUMMARY

Indivior has submitted an original New Drug Application (NDA) for PERSERIS (risperidone, RBP-7000) extended-release injectable suspension for subcutaneous administration. PERSERIS is an atypical antipsychotic product indicated for the treatment of schizophrenia.

Risperidone was first approved in 1993 and is currently available in several oral formulations (i.e., tablets, solution, and orally disintegrating tablets) and a long-acting intra-muscular injection (Risperdal Consta). PERSERIS is planned to be commercialized as an extended-release injectable suspension for subcutaneous use at two strengths- 90 mg and 120 mg. It is packaged as a powder of drug in a syringe and is to be constituted with a liquid syringe of ATRIGEL, which is a non-aqueous solution consisting of a (b) (4) polymer system, prior to injecting. RBP-7000 forms a solid depot when injected subcutaneously and releases risperidone for a minimum of 28 days (b) (4).

Risperdal (oral risperidone) serves as the Listed Drug (LD) for this NDA.

The NDA submission is supported by following key studies: 3 clinical pharmacology studies, 1 pivotal clinical efficacy & safety study, and 1 open-label, long-term safety study.

- Study RB-US-09-0007- Phase 1, single dose PK, safety, tolerability study at 60 mg in subjects with schizophrenia.
- Study RB-US-09-0008- Phase 1, single ascending dose study at 60 mg, 90 mg and 120 mg to assess the PK, safety and tolerability in subjects with schizophrenia.
- Study RB-US-09-0009 -Phase II-A, multiple ascending dose study over a dose range of 60 to 120 mg for safety/tolerability and PK in subjects with stable schizophrenia. This was the PK-bridging study conducted to provide the relative bioavailability to the Risperdal (oral risperidone), the Listed Drug
- Study RB-US-09-0010 - Phase III, double-blind, placebo-controlled efficacy and safety study of 2 doses of RBP-7000 (90 and 120 mg) in subjects with an acute exacerbation of schizophrenia
- Study RB-US-13-0005 - Phase III, open-label, long-term safety study with subjects from the Phase III study and de novo subjects with stable schizophrenia

Study RB-US-09-0009 provides the pivotal PK bridging data (i.e., relative bioavailability) to demonstrate that the average total risperidone concentrations with the long acting PERSERIS injection were generally similar to the levels obtained with oral risperidone. Overall, RBP-7000 (long acting SC injection) demonstrated linear PK from 60 mg to 120 mg dose level and reached steady state levels by the end of 2nd monthly dose. Similar average concentrations (C_{avg}) of risperidone and total active moiety were reached after daily administration of oral risperidone tablets and SC injection of RBP-7000 every 28 days under steady-state conditions. Additionally,

the Cmax values were generally higher after oral risperidone than after RBP-7000 SC Injections and the long acting injection had less fluctuation at steady state than oral risperidone.

Study RB-US-09-0010 was the pivotal efficacy/safety study and it showed that RBP-7000 at both 90 mg and 120 mg dose level is efficacious, with statistically significant improvements in PANSS and CGI-S scores compared with placebo. The changes from baseline in the PANSS total score and responder rates in the pivotal study were comparable with those reported previously for risperidone.

Our findings are summarized below:

- PERSERIS is a long-acting, sub-cutaneous injection of Risperidone. After a single injection, the concentration of the total active moiety (i.e., risperidone + active metabolite: 9-hydroxyrisperidone) rises rapidly reaching the 1st Tmax (due to the burst effect of the formulation) at around 8 hour on day 1 followed by a 2nd Tmax later on approximately day 11. The 1st Cmax is approximately 50% of the 2nd Cmax. The mean terminal T1/2 of total active moiety was approximately 8 days and steady state concentrations were reached by the end of 2nd monthly injection with minimal accumulation. The PK was dose-proportional from 60 mg to 120 mg dose range.
- The proposed doses of 90 mg and 120 mg of PERSERIS are acceptable since:
 - A pivotal Phase 3 efficacy/safety study (RB-US-09-0010) showed that RBP-7000 at both 90 mg and 120 mg dose level was efficacious with statistically significant improvements in PANSS and CGI-S scores compared with placebo.
 - Circulating levels of total active moiety were comparable between the approved oral risperidone vs. PERSERIS injection. The average concentrations (Cavg) of total active moiety at steady-state after daily administration of oral risperidone tablets and SC injection of RBP-7000 (every 28 days) were similar i.e., oral at 3 mg/day similar to 90 mg PERSERIS and oral at 4 mg/day similar to 120 mg PERSERIS. There was less fluctuation at steady state for PERSERIS injection compared with oral risperidone.
- A relative bioavailability study was conducted to bridge the PK of PERSERIS to approved generic oral risperidone (ANDA 78871 by Workhardt) but not the Listed Drug, Risperdal. It was determined to be acceptable by the agency's 505(B)(2) committee.
- PERSERIS does not require either a loading dose or supplemental oral risperidone for efficacy.
- No evidence of dose dumping was observed in pharmacokinetic data collected for PERSERIS from around 100 individual subjects across several clinical trials.

Note: The product is listed as either PERSERIS, RBP-7000 or Risperidone ATRIGEL throughout the review

1.1. Recommendation

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology information provided in the NDA package to support a recommendation of approval of PERSERIS. The acceptability of specific drug information is provided below.

Decision	Acceptable to OCP	Comment
Overall	Yes	Pending labeling agreement with the sponsor
Evidence of effectiveness and safety	Yes	Based on Study US-09-0010 (Efficacy/Safety study)
Proposed dose for adult patients	Yes	Based on Study US-09-0010 and PK-bridging study (Study RB-US-09-0009)
Labeling	Changes suggested	Pending satisfactory agreement with the sponsor

1.2 Labeling Recommendations

The final labeling language is subject to change pending satisfactory agreement with the sponsor.

1.3 Phase IV (PMR/PMC) Requirements/Commitments

No Phase IV studies are recommended.

2 QUESTION BASED REVIEW

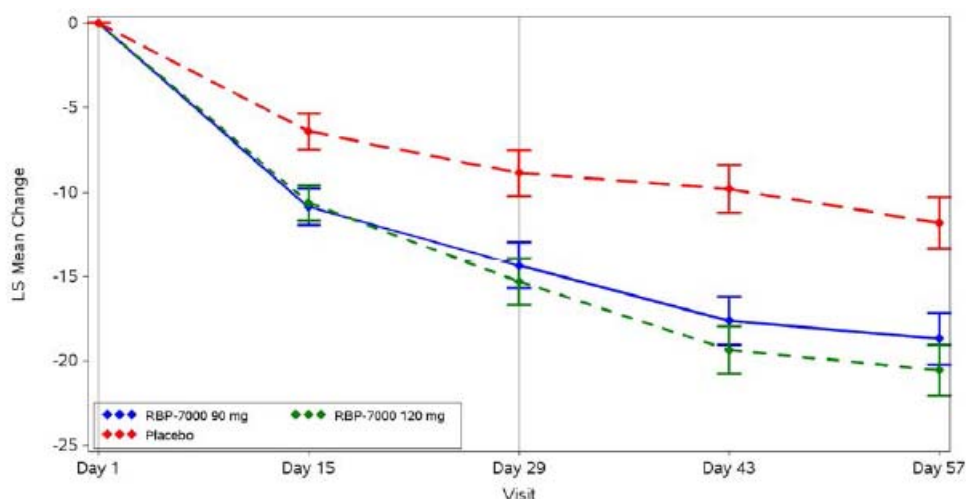
2.1 Are the proposed doses of 90 and 120 mg of PERSERIS supported by an efficacy and safety study?

Yes.

A pivotal Phase 3 efficacy/safety study (RB-US-09-0010) showed that RBP-7000 at both 90 mg and 120 mg dose level was efficacious with statistically significant improvements in PANSS and CGI-S scores compared with placebo. The changes from baseline in the PANSS total score and responder rates in the pivotal study were comparable with those reported previously for risperidone.

The primary objective of this efficacy study was to assess the efficacy of RBP-7000 (90 and 120 mg) compared with placebo on the symptoms of acute schizophrenia over an 8-week treatment period using the change from baseline (defined as the last non-missing value before the first dose of RBP-7000 or placebo on Day 1) to end of treatment in the PANSS total score, which is the sum of all 30 PANSS items. In summary, the primary objective of Study 09-0010 was met. In this 8-week, placebo controlled study, RBP-7000 90- and 120-mg doses were both superior to placebo as demonstrated based on the MMRM analysis of change from baseline in PANSS total scores for the ITT population. RBP-7000 90 and 120 mg were also significantly superior to placebo based on the MMRM analysis of the change from baseline in CGI-S score using the ITT population. Both RBP-7000 dose groups also had higher percentages of responders at the 20%, 30%, 40% and 50% level at all time points compared with placebo with respect to PANSS total score and PANSS positive subscale score.

Figure 1 Study 09-0010: Change From Baseline by Treatment Group in PANSS Total Score for Baseline and Visit 5/Day 15, Visit 6/Day 29, Visit 8/Day 43 and EOS/Day 57 Observations (MMRM Analysis, ITT Population)



EOS=end of study; LS mean=least-squares mean; ITT=intent to treat; MMRM=mixed-effects model for repeated measures; PANSS=Positive and Negative Syndrome Scale

Notes: Baseline was defined as the last nonmissing value before the first dose of RBP-7000 or placebo on Day 1. RBP-7000 was administered on Day 1 (baseline) and Day 29. Vertical lines at Day 1 and Day 29 denote injection days. Means $\pm$ standard error (SE) are shown.

Table 1 Study 09-0010: Phase III Efficacy and Safety Study Primary and Secondary Efficacy Results

Endpoints	Treatment	LS Means (SE)	Difference vs Placebo (95% CI)	P-value
Primary: PANSS Total	90 mg (N=111)	-15.367 (1.223)	-6.15 (-9.98; -2.31)	0.0004
	120 mg (N=114)	-16.456 (1.207)	-7.24 (-11.05; -3.43)	< 0.0001
	Placebo (N=112)	-9.219 (1.216)	--	--
Secondary: CGI-S	90 mg (N=111)	-0.868 (0.0662)	-0.35 (-0.56; -0.14)	0.0002
	120 mg (N=114)	-0.914 (0.0654)	-0.40 (-0.60; -0.19)	< 0.0001
	Placebo (N=112)	-0.518 (0.0659)	--	--

CI=confidence interval; LS=least squares; SE=standard error

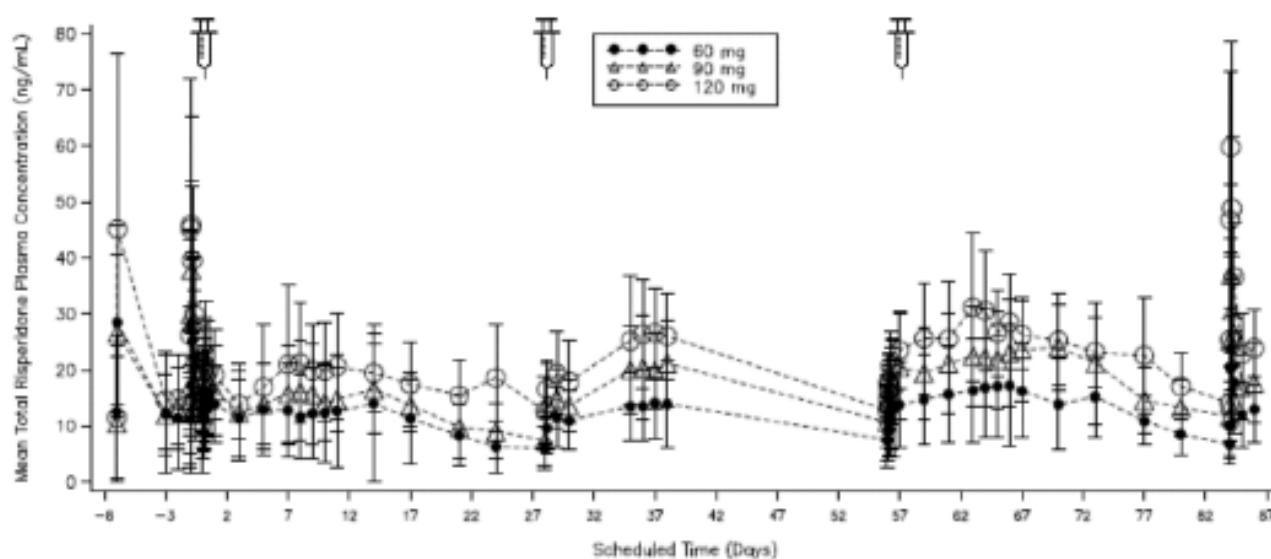
2.2 Was adequate PK bridging established between PERSERIS and the Listed Drug (LD), Risperdal?

Yes. Adequate bridging has been established between PERSERIS and Risperdal, the LD, indirectly.

The relative bioavailability study, Study RB-US-09-0009, was conducted to provide the PK bridge from PERSERIS to the generic oral risperidone tablet (i.e., ANDA 78871 by Workhardt), not the LD. This was an open label, multiple ascending dose study where 45 subjects were

divided into 3 cohorts. (a) The 1st cohort received 2 mg/day oral risperidone tablet for 7 days followed by 3 monthly injections of PERSERIS at 60 mg. (b) The 2nd cohort received 3 mg/day oral risperidone for 7 days followed by 3 monthly injections of PERSERIS at 90 mg. (c) The 3rd cohort received 4 mg/day oral risperidone for 7 days followed by 3 monthly injections of PERSERIS at 120 mg. Full PK profiles were assessed on day 1 and day 7 of oral dosing and similarly the full PK profile (day 1 to day 30) were assessed for all the 3 monthly dosing of PERSERIS. Mean Total Risperidone (i.e., Risperidone + 9-hydroxyrisperidone) Plasma Concentrations (+/- SD) for All Cohorts from Day -7 to Day 87 (which includes the initial 7 days of oral risperidone followed by 3 monthly SC injections of RBP-7000) are shown below.

Figure 2 Mean ($\pm$ SD) Total Active Moiety Plasma Concentration-time Profile for All Cohorts From Day -7 to Day 87 (Study 09-0009)



SD=standard deviation

Days -7 to -1: oral risperidone

Days 1, 29 and 57: SC injections of RBP-7000

Days 85 to 87: oral risperidone

Note: Total active moiety is referred to as total risperidone on the y-axis.

Circulating levels of total active moiety (risperidone + 9- hydroxyl risperidone) was compared between oral and PERSERIS injection. As seen in Table 2, overall similar average concentrations (C_{avg}) of total active moiety were reached after daily administration of oral risperidone tablets and SC injection of RBP-7000 every 28 days under steady-state conditions (i.e., 3 mg/day oral is similar to 90 mg PERSERIS and 4 mg/day oral is similar to 120 mg PERSERIS). Additionally, the C_{max} values were generally higher after oral risperidone than after RBP-7000 SC Injections. There was less fluctuation at steady state for PERSERIS injection (145% to 157%) compared with oral risperidone (285% to 380%). Though, the C_{max} itself were lower for PERSERIS compared to corresponding oral (i.e., 120 mg was lower than for 4 mg/day

and 90 mg was lower than for 3 mg/day), it is not likely to be clinically relevant since (a) the C_{avg} values were generally very similar for PERSERIS vs. oral and (b) the stand-alone efficacy study (RB-US-09-0010) clearly demonstrated that PERSERIS was efficacious at both 90 mg and 120 mg dose level.

Table 2 Comparison of Total active moiety between Oral Risperidone and RBP-7000 in Each Cohort (Study 09-0009)

Treatment	Parameter	2 mg Oral/ 60 mg SC	3 mg Oral/ 90 mg SC	4 mg Oral/ 120 mg SC
SC RBP-7000 (Injection 3)	C_{max} (Overall) (ng/mL) (N=10-15)	19.6 (49.4)	29.3 (35.2)	38.5 (24.9)
	C_{min} (Overall) (ng/mL) (N=10-15)	5.34 (49.0)	9.43 (35.5)	11.0 (23.5)
	C_{avg} (ng/mL) (N=10-14)	12.1 (45.2)	18.1 (34.9)	22.9 (16.6)
Oral Risperidone (Day -1)	C_{max} (ng/mL) (N=15)	28.6 (48.8)	34.2 (39.5)	49.2 (37.3)
	C_{min} (ng/mL) (N=15)	9.47 (87.7)	9.87 (54.4)	13.0 (40.1)
	C_{avg} (ng/mL) (N=15)	16.7 (67.2)	18.3 (42.3)	25.2 (34.6)

It was found out that the PK bridging study was conducted with an approved generic oral risperidone (ANDA 78871 by Workhardt), not the LD, through multiple information requests. It raised our concern regarding the study conduct in general. Therefore, an inspection of both the sites involved in the clinical trial of the PK bridging study was performed. OSIS performed the inspection and determined that it was acceptable to use the data from both sites for the PK bridging.

Though the PK bridging study for PERSERIS was not conducted with the listed drug, we find it acceptable since:

- 505(B)(2) committee agreed with the PK bridging conducted with an approved generic oral risperidone (ANDA 78871 by Workhardt) which is also an “AB” rated generic. The generic used was “AB” rated, which means that FDA has determined that this generic drug is bioequivalent to RISPERDAL (i.e., LD), hence is expected to have the same clinical effect and safety profile as RISPERDAL.
- The PK for the generic oral risperidone was determined to be similar to the PK for RISPERDAL from a published literature (Schizophrenia research, 70, 91-100, 2004).

A dedicated pivotal efficacy/safety study (Study RB-US-09-0010) shows that PERSERIS at both 90 mg and 120 mg dose level is efficacious, with statistically significant improvements in PANSS and CGI-S scores compared with placebo. Therefore, in addition to the PK-bridging there is an independent assessment of the efficacy of PERSERIS via the stand-alone efficacy study.

2.3 Was the to-be-marketed formulation used in the pivotal efficacy and relative bioavailability study?

Yes. The to-be-marketed formulation of PERSERIS was used in all the key clinical studies. The planned commercial formulation was used in the pivotal Phase 3 efficacy/safety study (Study 09-0010), relative bioavailability/PK-bridging study (Study RB-US-09-0009), and the other PK/clinical pharmacology studies (Study RB-US-09-0007 and Study RB-US-09-0008)

2.4 Was there any dose dumping observed with PERSERIS in the clinical trials? What studies were conducted to assess the effect of pressure, temperature or exercise on the release rate of drug from PERSERIS?

No. There was no evidence of dose dumping in the clinical trials conducted with PERSERIS.

- A detailed assessment of the individual subject data for all the subjects (N = around 100) administered with PERSERIS in three PK trials (007, 008 and 009) demonstrated that none of the subjects in PK trials showed any rapid or unexplainable rise in exposure of risperidone after the injection. The lack of any abrupt spikes in exposure of risperidone suggests that there was no dose dumping or leakage after the PERSERIS injection.
- The overall lack of any new or unexpected safety findings with PERSERIS injection compared to the oral risperidone also suggests there were no dose dumping.
- Additionally, the physiochemical properties of risperidone (i.e., practically insoluble in water and in aqueous solutions) also make it very unlikely that dose dumping into the systemic circulation is likely to occur in the clinic.
- There were no dedicated clinical studies conducted to assess the effect of pressure, temperature, or exercise on the release-rate of drug for PERSERIS. However, the potential of PERSERIS to dose-dump was evaluated based on *in vitro* studies, and nonclinical animal studies.
 - An *in vitro* study evaluated risperidone release over a 24-hour period under simulated conditions following (1) applying static pressure to depot, (2) applying intermittent pressure to the depot and (3) increased temperature of the bio-

relevant media to 42°C. The results from this study demonstrated that both increases in pressure or temperature did not induce drug release greater than 10% difference compared to the control depot.

- An in vivo rat study was conducted to assess the potential of RBP-7000 to dose-dump in the presence of physical pressure or exercise over 24 hours following a single SC injection of 90 mg risperidone in RBP-7000. A group of rats received controlled pressure manipulation of the injection site. Another group of rats were placed on a manually operated wheel 10 minutes post administration for 20 minutes of exercise. A further group of rats were a positive control and received no manipulation or exercise. The results from this study were comparable to those observed in the in vitro assay. Although there was some variability within the individual data, the mean and standard deviation of risperidone release from the implants and plasma total risperidone moiety concentrations were comparable in all groups signifying that no evidence of dose-dumping from the depot was observed with the addition of external stressors of exercise or applied pressure to the depot site.

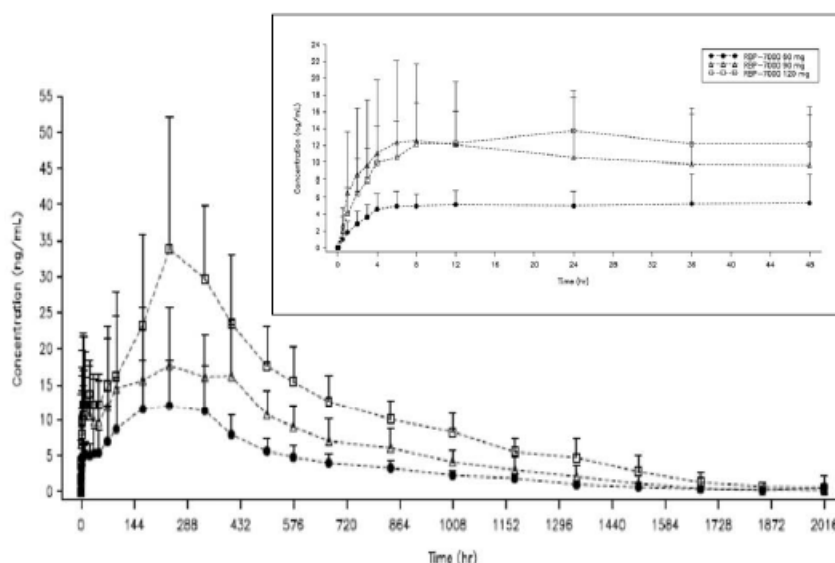
2.5 What were the clinical PK characteristics of single dose and multiple dose sub-cutaneous administration of PERSERIS?

The clinical PK characteristics of single dose and multiple dose sub-cutaneous administration of PERSERIS were determined in Study- 0007, 0008 and 0009.

Following a single SC injection of 60, 90 or 120 mg RBP-7000, risperidone plasma concentration increased rapidly with peak concentrations observed at 4 hours post-dose in all dose groups. After the first peak on Day 1, mean plasma risperidone concentrations decreased through approximately Day 3 and then increased again to reach a second peak between approximately Day 11 and Day 18. Following the second peak, risperidone plasma concentrations decreased gradually over time. The mean plasma terminal half-life for risperidone ranged from 208 to 266 hours (approximately 9 to 11 days), in line with the extended-release nature of the formulation.

For the total active moiety (risperidone + active metabolite), a similar pattern as risperidone was observed, although the first peak was approximately 50% to 60% lower than the second peak and was not always apparent on the plasma concentration-time profile. The first peak was observed at 8 to 24 hours post-dose, depending on the dose group; however, plasma concentrations close to the C_{max} were reached at 8 hours post-dose in all dose groups. The second peak was observed at Day 11. The mean plasma terminal half-life of the total active moiety ranged from 180 to 203 hours (approximately 8 days). The PK for total active moiety was generally dose-proportional across the 60 mg to 120 mg dose range. On repeat dosing, steady-state was attained by Day 57 (end of dosing interval for second injection) for total active moiety.

Figure 3 Mean (+ SD) Total Active Moiety Plasma Concentration-time Profile Following SC Injection of a Single Dose of 60, 90 or 120 mg of RBP-7000



SD=standard deviation

Table 3 Geometric Mean (CV%) PK Parameters of Total Active Moiety Following SC Injection of a Single Dose of 60, 90 or 120 mg of RBP-7000

Parameter	RBP-7000 60 mg (N=15)	RBP-7000 90 mg (N=15)	RBP-7000 120 mg (N=15)
Total Active Moiety			
C_{max} (Peak 1) (ng/mL)	5.70 (51.0)	11.3 (70.0)	15.0 (31.1)
C_{max} (Peak 2) (ng/mL)	14.9 (43.5)	22.7 (46.9) ^a	38.4 (39.5)
T_{max} (Peak 1) (hr)	24.1 (4.07, 48.1)	8.07 (6.07, 48.1)	24.1 (6.23, 48.2)
T_{max} (Peak 2) (hr)	240 (96.1, 336)	240 (48.1, 409) ^a	240 (72.2, 481)
C_{max} (Overall) (ng/mL)	14.9 (43.5)	23.8 (43.1) ^a	38.8 (38.7)
AUC_{inf} (ng*hr/mL)	6853 (31.1)	11584 (26.5) ^a	20688 (22.8)
$t_{1/2}$ (hr)	183 (38.4)	180 (36.7) ^a	203 (43.0)

CV=coefficient of variation; N=number of subjects; $t_{1/2}$ =plasma terminal half-life

T_{max} is presented as median values with range in parentheses.

2.6 Is PERSERIS suitable for use in patients who are known CYP2D6 poor metabolizers?

Yes. Based on the label for Risperdal “the pharmacokinetics of total active moiety (i.e., risperidone and 9-hydroxyrisperidone combined) after single and multiple doses, are similar in extensive and poor metabolizers”. Similarly, for PERSERIS, the PK for total active moiety was

similar in extensive and poor metabolizers of CYP2D6. Therefore, PERSERIS is suitable for use in patients who are known CYP2D6 poor metabolizers.

2.7 Is PERSERIS acceptable for use without any supplementation with oral risperidone?

Yes. The clinical PK profile of PERSERIS clearly demonstrates a rapid rise in total active moiety with concentrations reaching levels similar to the levels obtained on day 1 with oral dosing. The total drug concentrations reach around 12-15 ng/mL by day 1 with 90 mg and 120 mg PERSERIS. The exposure-response analysis for PANSS total scores indicate that these plasma levels result in substantial lowering of PANSS total scores. In the pivotal Phase III efficacy and safety study (09-0010), the mean PANSS score for RBP-7000 at both dose levels (90 and 120 mg) begin to separate from the placebo as early as 2 weeks (Day 15) after the first injection, which was the first post-baseline assessment. Additionally, in the MAD transition study (09-0009), the mean PANSS total scores and CGI-S scores remained consistent when transitioning from oral risperidone (2, 3 or 4 mg) to RBP-7000 (60, 90 or 120 mg). All these clearly suggest that PERSERIS requires neither a loading dose nor supplemental oral risperidone for efficacy.

2.8 What are the corresponding oral risperidone daily doses suitable for 90 mg PERSERIS and 120 mg PERSERIS?

Based on the PK- bridging study (RB-US-09-0009) and the Table below, oral risperidone doses of 3 mg/day and 4 mg/day are generally similar to PERSERIS dose of 90 mg and 120 mg, respectively. Circulating levels of total active moiety (risperidone + 9- hydroxyl risperidone) was compared between oral and PERSERIS injection. As seen in Table below, overall similar average concentrations (Cavg) of total active moiety were reached after daily administration of oral risperidone tablets and SC injection of RBP-7000 every 28 days under steady-state conditions (i.e., 3 mg/day oral is similar to 90 mg PERSERIS and 4 mg/day oral is similar to 120 mg PERSERIS).

Table 4 Comparison of Total active moiety between Oral Risperidone and RBP-7000 in Each Cohort (Study 09-0009)

Treatment	Parameter	2 mg Oral/ 60 mg SC	3 mg Oral/ 90 mg SC	4 mg Oral/ 120 mg SC
SC RBP-7000 (Injection 3)	C _{max} (Overall) (ng/mL) (N=10-15)	19.6 (49.4)	29.3 (35.2)	38.5 (24.9)
	C _{min} (Overall) (ng/mL) (N=10-15)	5.34 (49.0)	9.43 (35.5)	11.0 (23.5)
	C _{avg} (ng/mL) (N=10-14)	12.1 (45.2)	18.1 (34.9)	22.9 (16.6)
Oral Risperidone (Day -1)	C _{max} (ng/mL) (N=15)	28.6 (48.8)	34.2 (39.5)	49.2 (37.3)
	C _{min} (ng/mL) (N=15)	9.47 (87.7)	9.87 (54.4)	13.0 (40.1)
	C _{avg} (ng/mL) (N=15)	16.7 (67.2)	18.3 (42.3)	25.2 (34.6)

3 APPENDIX: POPULATION PK ANALYSES

The Applicant submitted four population PK reports: one each for Study RB-US-09-0008 and Study RB-US-09-0009, one for the combination of Studies RB-US-09-0008 and RB-US-09-0009 and one pooled analysis from Studies RB-US-09-0008, RB-US-09-0009 and RB-US-09-0010. This review focuses on the pooled analysis from the three studies. The Applicant also conducted a PK/PD analysis to establish a relationship between plasma concentrations of total active moiety (risperidone and 9-OH-risperidone) and clinical endpoints (PANSS total scores and CGI-S). Given the positive results of the pivotal efficacy study and the adequacy of the PK bridge, this analysis is not further reviewed.

The primary objective of the Applicant's population PK analysis was to characterize the PK of RB-7000 and assess the effects of covariates in patients with schizophrenia. Population PK models from earlier studies served as the basis for the model of the pooled data. A brief description of the studies used in the analysis is provided in Table 5. The final dataset included 10,671 observations from 315 subjects. A total of 249 values (11.42% of the dataset) were flagged as BLQ, but the majority of these values were observed pre-dose.

Table 5. Summary of the Studies Used in the Population PK Analysis

Study ID	Subjects	Doses	Description of data
RB-US-09-0008	Single ascending dose study in subjects with clinically stable schizophrenia	60 mg (N=15) 90 mg (N=15) 120 mg (N=15)	<u>Rich PK:</u> Pre-dose, 28 PK samples collected between Day 1 and Day 85
RB-US-09-0009	Multiple ascending dose in subjects with clinically stable schizophrenia	Oral 2 mg/SC RBP-7000 60 mg (N=15) Oral 3 mg/SC RBP-7000 90 mg (N=15) Oral 4 mg/SC RBP-7000 120 mg (N=15) Subjects received 3 doses of RBP-7000	<u>Rich PK:</u> Pre-dose, 19 samples after first and third injections and 8 samples after second injection and post oral dose period
RB-US-09-0010	Randomized, placebo-controlled efficacy and safety trial	90 mg RBP-7000 (2 injections separated by 28 days) (N=115) 120 mg RBP-7000 (2 injections separated by	<u>Sparse PK:</u> Day 1 (pre-dose first injection) Day 1-3, Day 8-15, Day 16-22, Day 29 (pre-dose), Day 29-31, Day 36-42, Day

		28 days) (N=115)	43-49 and Day 55-57
--	--	------------------	---------------------

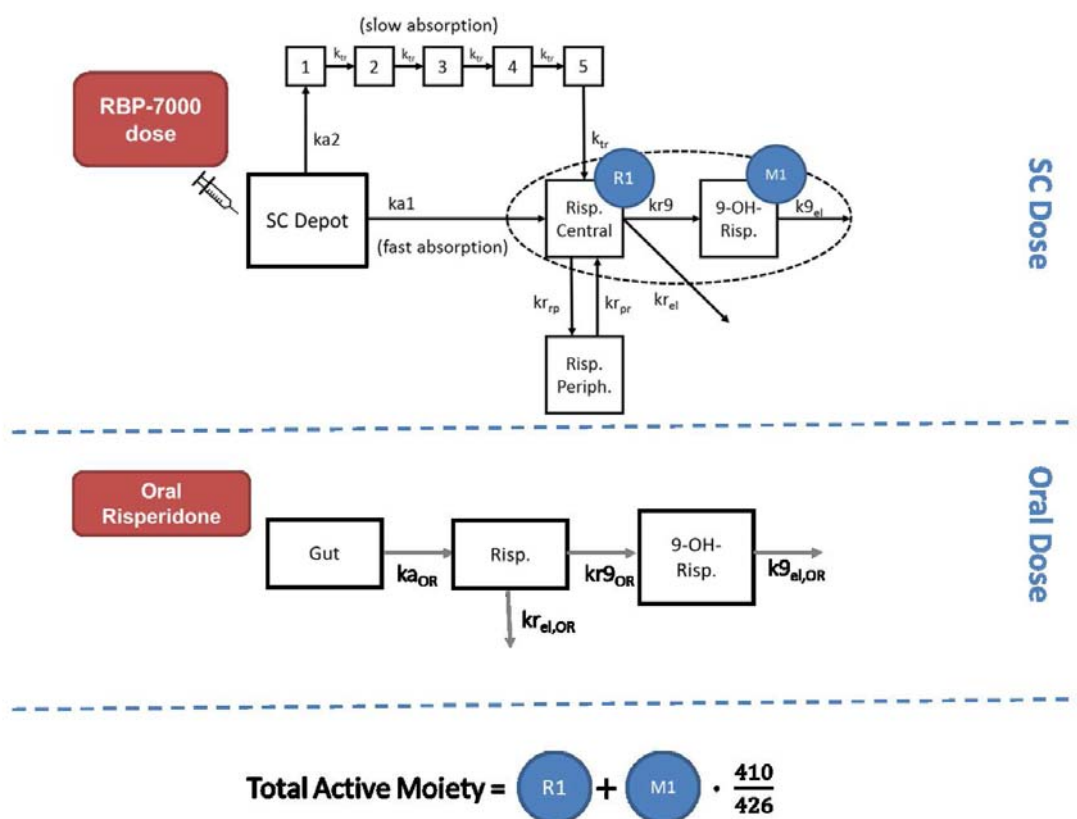
Source: Adapted from Table 1, page 14 of INDV-7000-M04.pdf

First, a population PK model for oral risperidone was developed to describe plasma exposure during Study RB-US-09-0009. Risperidone disposition was described using a one compartment model with first order absorption and first order elimination. A one compartment model was also used to describe the disposition of 9-hydroxyrisperidone. Risperidone was partly converted to 9-hydroxyrisperidone and partly eliminated by other routes. The apparent volume of distribution of risperidone and 9-hydroxyrisperidone were related by a constant scaling factor (SF) that was estimated ($V/F_{\text{risperidone}} = SF \times V/F_{\text{9-hydroxyrisperidone}}$). The parameters for this oral model were estimated and subsequently fixed during the development of the RBP-7000 model.

The RBP-7000 model included a dual absorption process to account for the observed double peak plasma concentration profiles. A two-compartment model with two first-order elimination processes was used to describe the disposition of risperidone. Disposition of 9-hydroxyrisperidone was described by a one compartment model with first order elimination. A diagram of the oral and RBP-7000 models is illustrated in Figure 4.

Inter-individual variability was assumed to follow a log-normal distribution with a diagonal variance-covariance matrix. Residual error was described with a combined proportional and additive model. The total active moiety was calculated as the sum of risperidone and 9-hydroxyrisperidone corrected by their respective molecular weights.

Figure 4. Oral and RBP-7000 Structural Models



Source: Figure 1 on page 23 of INDV-7000-M04.pdf

Based on exploratory plots and knowledge from previous analyses, only the effect of BMI on ka₁ and ka₂ and CYP2D6 phenotype on kr₉ were evaluated. 81% (N=255) of subjects in the analysis were extensive metabolizers (EMs), 10.2% (N=32) of subjects were intermediate metabolizers (IMs) and 2.2% (N=7) of subjects were poor metabolizers (PMs). Inconclusive and missing CYP2D6 phenotype were classified as extensive metabolizers. The effect of BMI was modeled as exponential and the effect of CYP2D6 was modeled as proportional. A forward addition (p < 0.05) and backwards deletion (p < 0.001) approach was used to test for the significance of covariate effects.

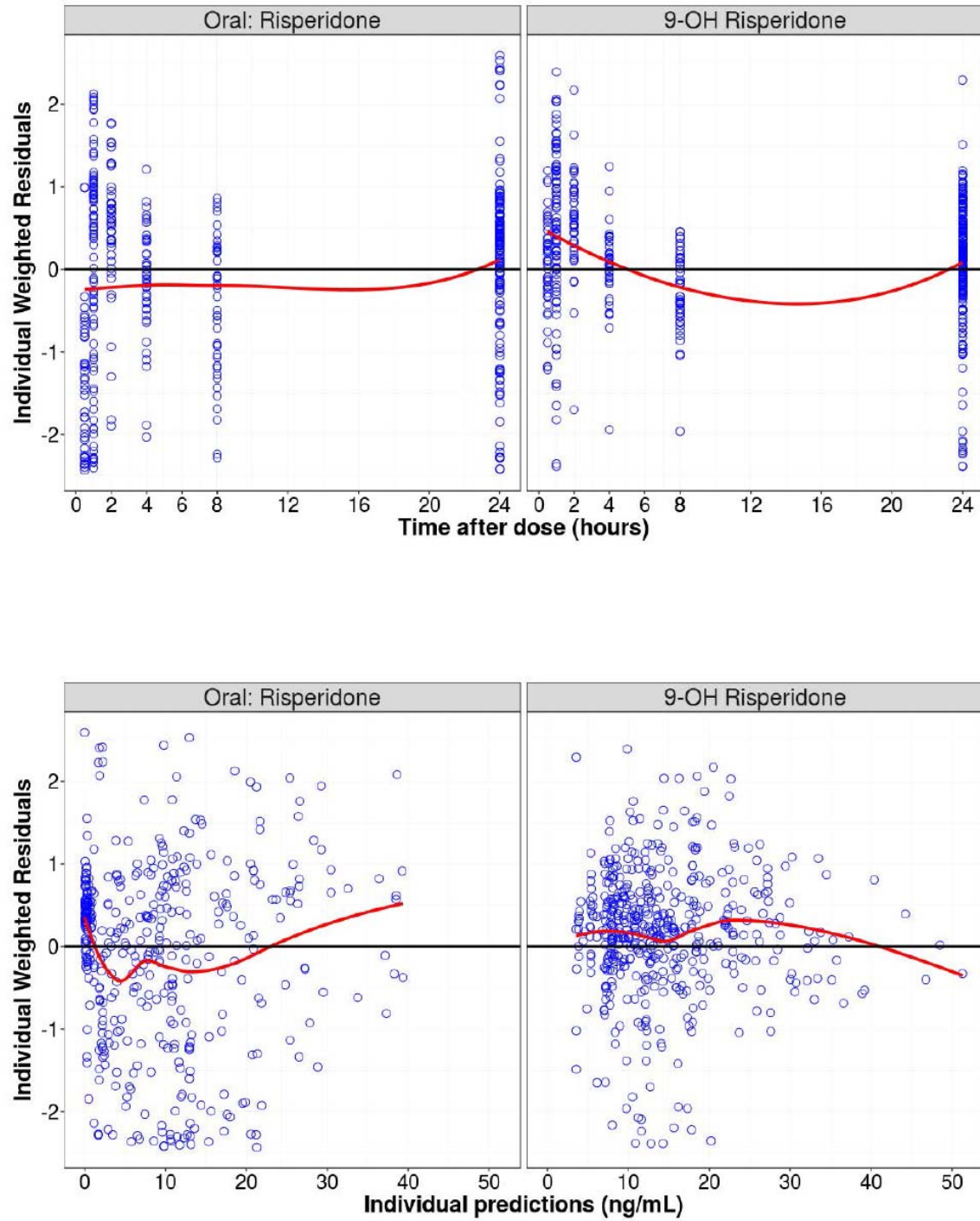
The parameter estimates from the final oral risperidone population PK model are summarized in Table 6 and goodness-of-fit plots are displayed in Figure 5.

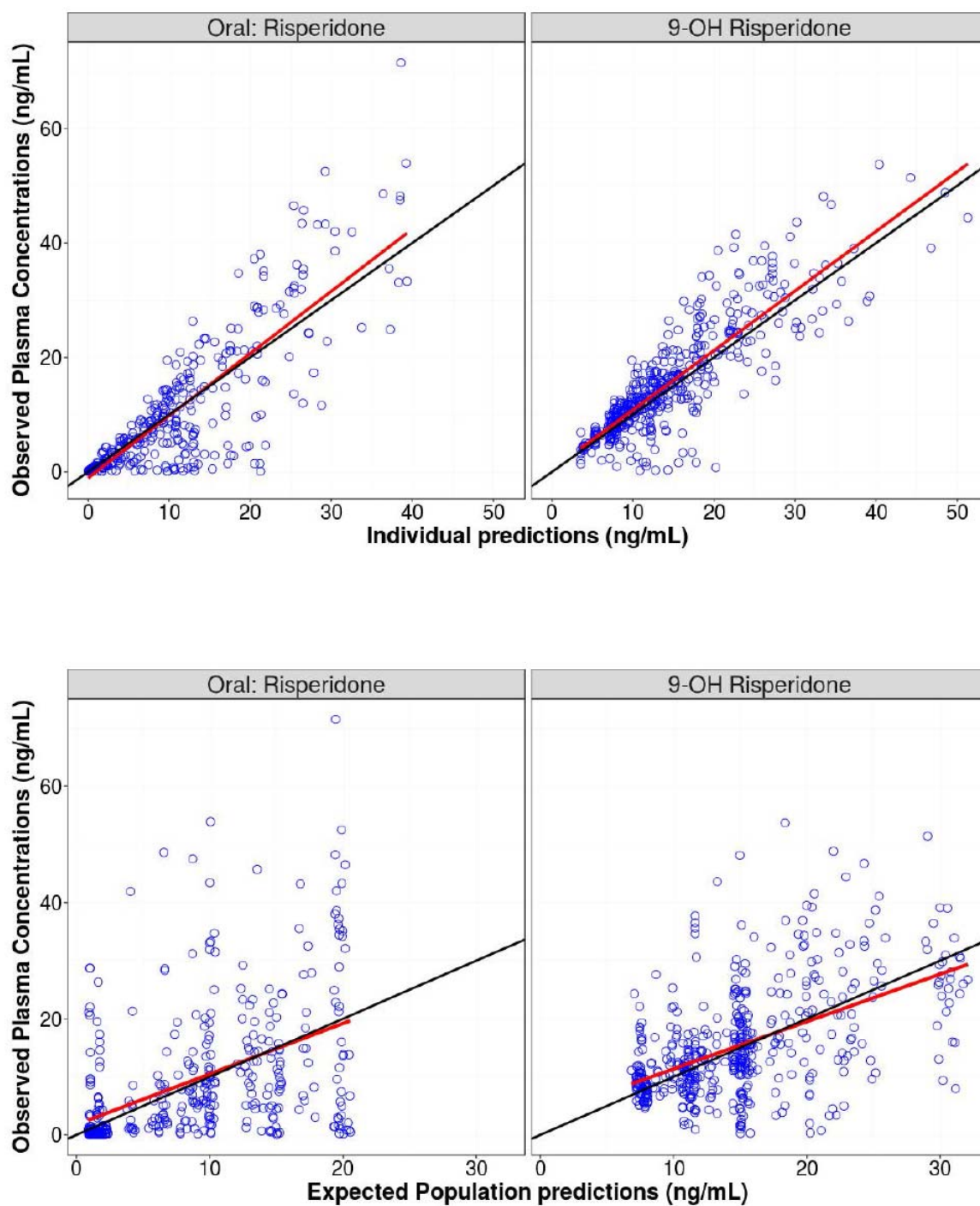
Table 6. Oral Risperidone PK Parameter Estimates

PK Parameter	Description	Oral Risperidone (RB-US-09-0009)	
		Estimate (RSE %)	%IIV (RSE %)
ka_{OR}	Oral risperidone absorption (hr^{-1})	4.07 (24.6)	0 (fixed)
V_{OR}	9-hydroxyrisperidone apparent central volume of distribution (L)	71.0 (9.4)	36.7 (17.1)
$kr_{el,OR}$	Rate constant for risperidone elimination by routes other than conversion into 9-hydroxyrisperidone (hr^{-1})	0.0298 (23.9)	69.3 (19.6)
$kr9_{OR}$	Rate constant for conversion of risperidone into 9-hydroxyrisperidone (hr^{-1})	0.108 (13.1)	86.9 (14.0)
$k9_{el,OR}$	Rate constant for 9-hydroxyrisperidone elimination (hr^{-1})	0.0758 (4.4)	15.8 (37.7)
SF	Scaling Factor for risperidone apparent central volume of distribution.	2.83 (10.0)	NA
		Residual Variability Estimate (%RSE)	
PROP	Proportional residual error (%)	40.9 (34.1 %)	
ADD	Additive residual error (ng/mL)	0.0409 (5.3 %)	

Source: Table 4, page 34, INDV-7000-M04.pdf.

Figure 5. Oral Risperidone Goodness-of-Fit Plots





Source: Figure 4, pages 34-35, INDV-7000-M04.pdf

The parameters from this model were fixed and the data were included in the final analysis for RBP-7000. The parameter estimates of the final model are summarized in Table 7 and the

goodness-of-fit plots are displayed in Figure 6. Only CYP2D6 on kr_9 and BMI on ka_1 remained significant and were included in the final model.

Table 7. Parameter Estimates for the Base and Final RBP-7000 Population PK Models

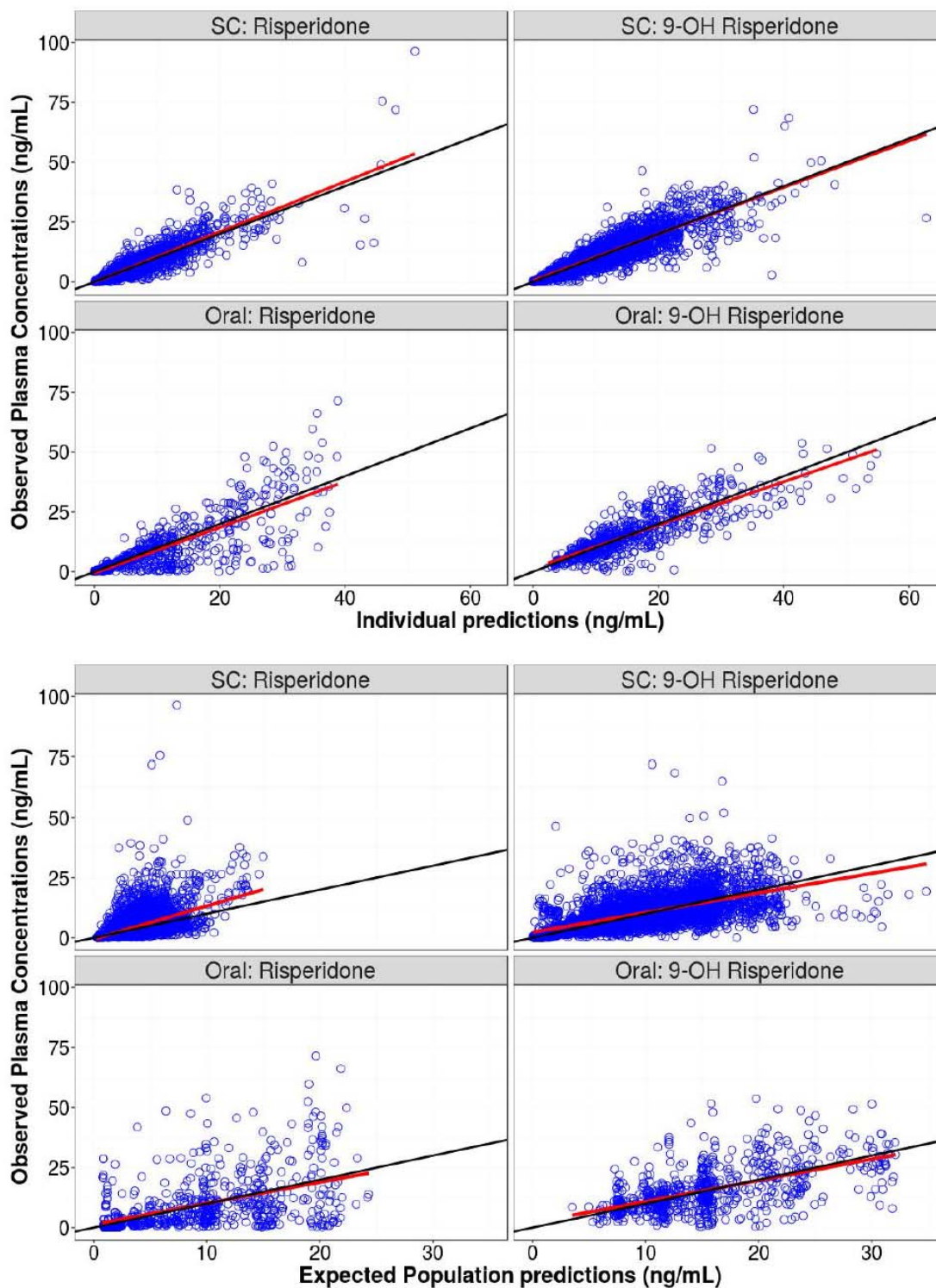
Parameter	Description	Base model		Final model		Bootstrap Results (N ^a =148)	
		Estimate (%RSE)	%IIV (RSE %)	Estimate (%RSE)	%IIV (RSE %)	Estimate (95 % CI)	%IIV (95% CI)
ka_1	Absorption rate constant for the rapid release from ATRIGEL SC depot (hr^{-1})	0.00605 (14.3)	49.8 (7.7)	0.00599 (21.5)	47.7 (8.0)	0.00584 (0.00457 - 0.00943)	47.9 (40.2 - 55.3)
ka_2	Absorption rate constant for the slow release from ATRIGEL SC depot (hr^{-1})	0.0188 (13.9)	58.2 (11.0)	0.0185 (21.5)	58.9 (11.5)	0.0183 (0.0136 - 0.0271)	59.0 (46.2 - 72.5)
kr_{el}	Risperidone elimination rate constant by other routes than conversion to 9-hydroxyrisperidone (hr^{-1})	0.0244 (29.8)	47.5 (30.3)	0.0225 (67.5)	52.7 (36.1)	0.0225 (0.0085 - 0.0374)	51.5 (3.7 - 86)
V	Apparent central volume of distribution of 9-hydroxyrisperidone (L)	140 (6.5)	34.6 (6.5)	139 (10.8)	34.5 (6.5)	140 (122 - 157)	34.7 (29 - 38.9)
k_{tr}	Transit rate constant (hr^{-1})	0.0237 (3.5)	38.7 (5.8)	0.0237 (3.43)	38.7 (6.0)	0.0237 (0.0219 - 0.0258)	38.5 (34.3 - 46.7)
kr_{rp}	Risperidone central to peripheral distribution rate constant (hr^{-1})	0.759 (8.2)	58.7 (11.9)	0.759 (8.41)	58.2 (10.8)	0.757 (0.630 - 0.916)	58.2 (45 - 71.7)
kr_{pr}	Risperidone peripheral to central distribution rate constant (hr^{-1})	0.00782 (14.8)	67.7 (9.3)	0.00781 (21.3)	67.6 (8.8)	0.00758 (0.00593 - 0.0118)	68.0 (57.8 - 78.7)
kr_9	Risperidone to 9-hydroxyrisperidone metabolic formation rate constant (hr^{-1})	0.160 (14.1)	68.7 (8.9)	0.187 (16.5)	53.6 (7.6)	0.191 (0.108 - 0.239)	52.0 (44.8 - 63.9)

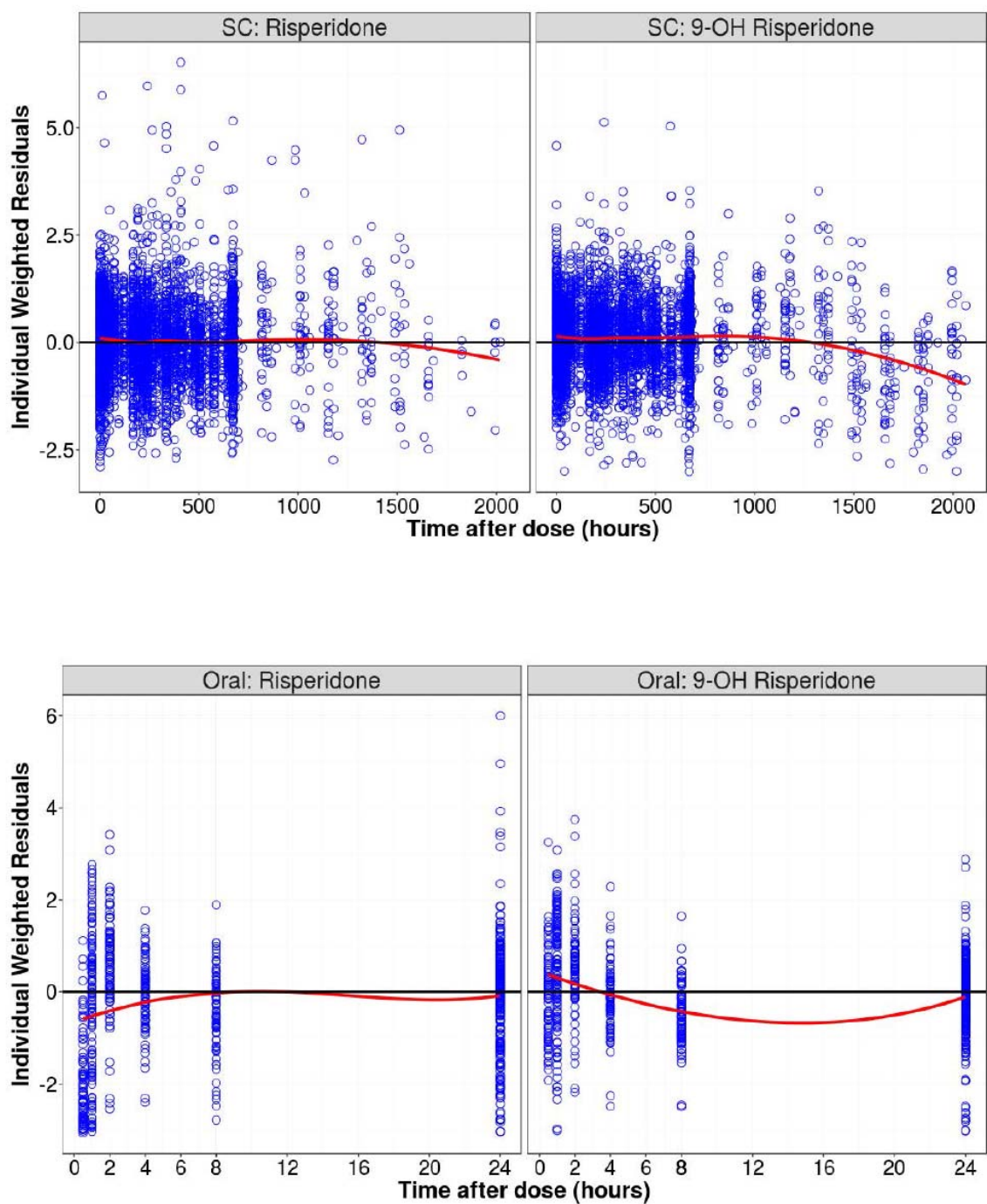
Parameter	Description	Base model		Final model		Bootstrap Results (N ^a =148)	
		Estimate (%RSE)	%IIV (RSE %)	Estimate (%RSE)	%IIV (RSE %)	Estimate (95 % CI)	%IIV (95% CI)
k_{9el}	9-hydroxyrisperidone elimination rate constant (hr^{-1})	0.0641 (5.0)	25.6 (12.9)	0.0652 (5.39)	24.4 (13.3)	0.0648 (0.0591 - 0.0713)	24.4 (17.1 - 30.4)
SF	Scaling factor for the apparent central volume of distribution of risperidone.	1.12 (14.0)	NA	1.11 (14.7)	NA	1.08 (0.858 - 1.88)	NA
BMI on ka_1	Effect on BMI on ka_1	NA	NA	0.0241 (33.7)	NA	0.0240 (0.0102 - 0.0361)	NA
CYP2D6 IM on kr_9	Fractional decrease of kr_9 in CYP2D6 intermediate metabolizers	NA	NA	0.468 (20.5)	NA	0.457 (0.214 - 0.655)	NA
CYP2D6 PM on kr_9	Fractional decrease of kr_9 in CYP2D6 poor metabolizers	NA	NA	0.929 (1.9)	NA	0.93 (0.884 - 0.954)	NA
Residual Variability							
Estimate (%RSE)							
PROP	Proportional residual error (%)	32.4 (2.4)		32.5 (2.41)		32.4 (31.1 - 34.4)	
ADD	Additive residual error (ng/mL)	0.0966 (21.8)		0.0956 (25.2)		0.0922 (0.0537 - 0.134)	

Note:

Source: Table 5, pages 42-33, INDV-7000-M04.pdf.i

Figure 6. RBP-7000 Goodness-of-Fit Plots

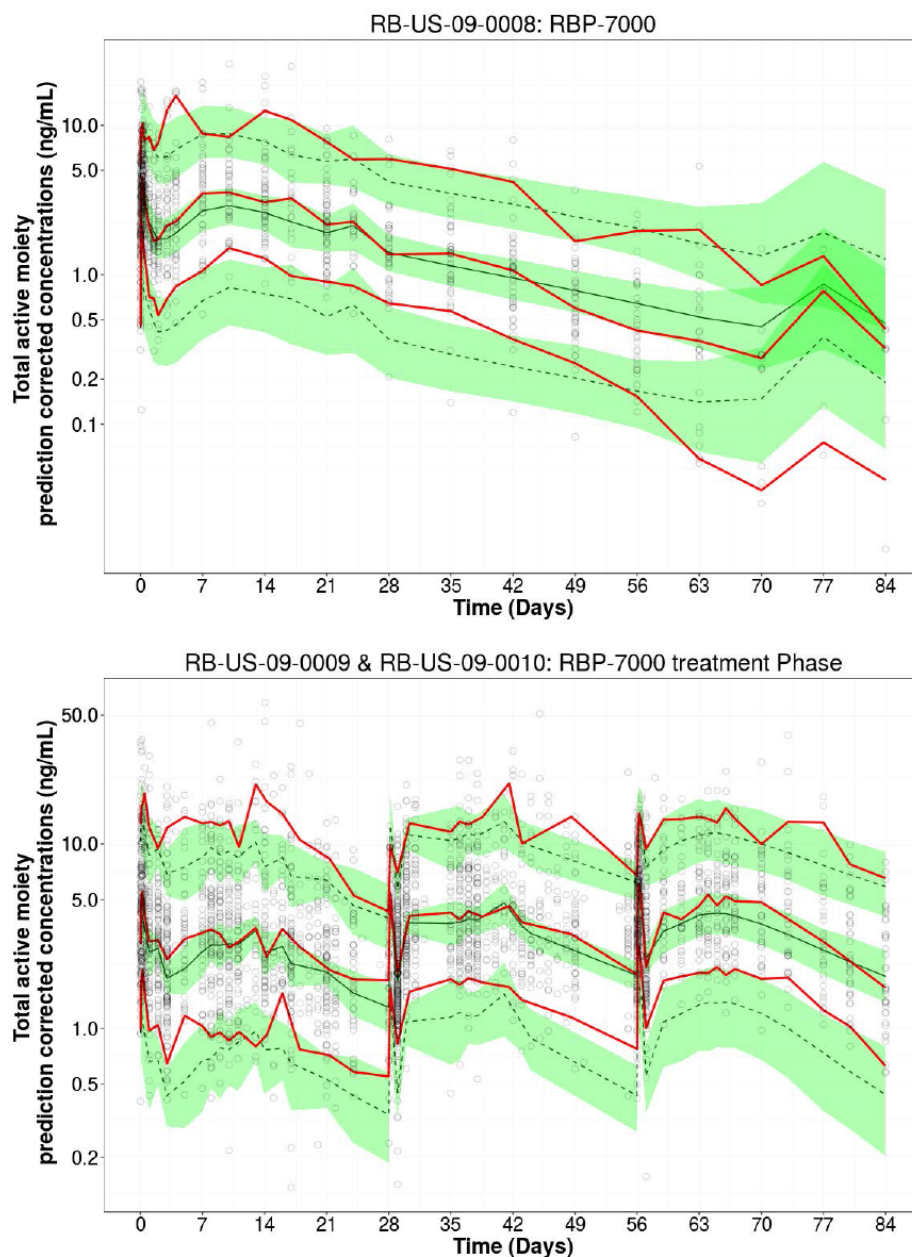




Source: Figure 6, pages 45-48, INDV-7000-M04.pdf.

Visual predictive checks for total active moiety are provided in Figure 7.

Figure 7. Prediction and Variability-Corrected Visual Predictive Check for Total Active Moiety after Single and Repeated Doses



Note:

Open circles represent the prediction and variability-corrected observed concentrations. Red solid lines represent the 5th, 50th and 95th percentiles of the prediction and variability-corrected observed concentrations. Black dashed lines represent the 5th, 50th and 95th percentiles of the prediction and variability-corrected simulated concentrations. Shaded green areas represent the 95% confidence intervals for the 5th, 50th and 95th percentiles of the simulated dataset replicates.

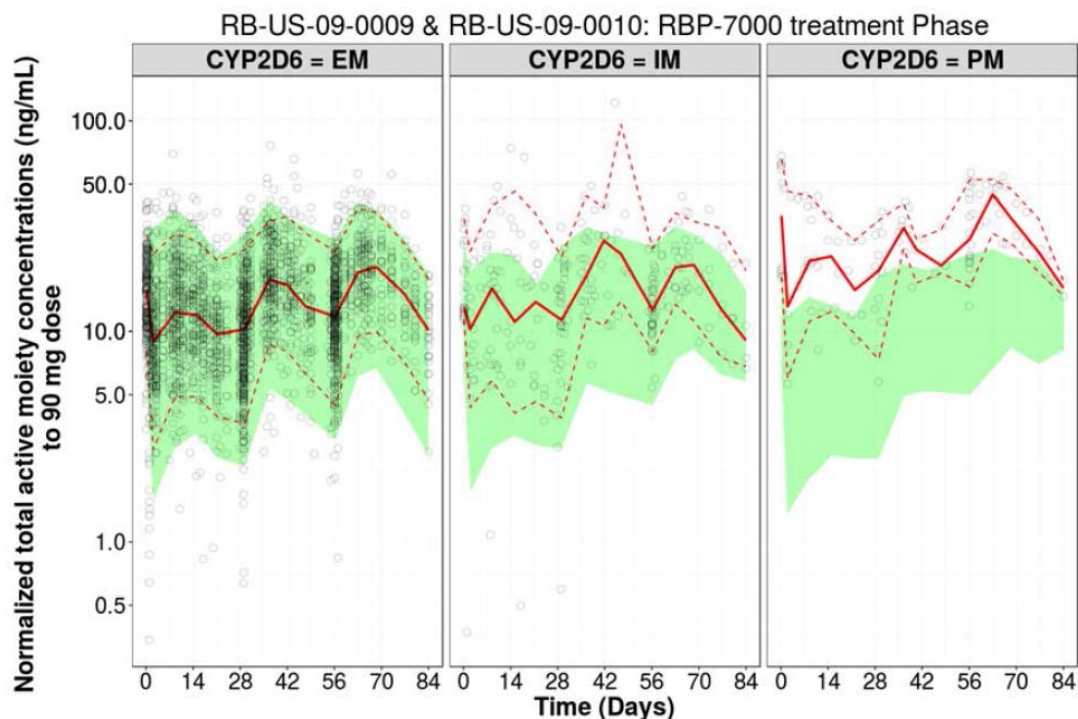
Source: Figure 8, Page 51, IND-7000-M04.pdf

Reviewer's Comments: The reviewer has the following concerns regarding the population PK analyses:

- The oral model does not appear to provide a reasonable description of the data. For example, for oral risperidone, early concentrations are not predicted well and the loess line for individual residuals vs. time is completely below the reference line. For 9-hydroxyrisperidone in the same plot there appears to be a trend in the loess line. Previous publications (e.g., Vermeulen et. al.) referenced by the applicant suggest that a two compartment disposition model is appropriate for both risperidone and 9-hydroxyrisperidone.*
- The RBP-7000 model also does not appear to be suitable for simulation purposes. The visual predictive check (Figure 7) for the total active moiety and for the individual components (not shown) does not show a particularly close match between the simulated and observed data, especially with regards to population variability. It is also noteworthy that the disposition model for risperidone is different for the two routes of administration. The applicant does not explain why the route of administration would influence risperidone disposition.*
- The Applicant did not estimate the fraction of the dose allocated to the two absorption process (fast and slow). In response to an information request, the Applicant stated that the fraction allocated to the two processes was driven by the absorption rate constant ka_1 and ka_2 , but from Figure 4 it appears that the entire dose goes through both pathways. It is also noteworthy that the same applicant, for a similar, approved product, estimated the fraction allocated to the two pathways. Parameter estimates of the model should be interpreted with caution.*

The visual predictive check for the effect of CYP2D6 phenotype on the concentration-time profile for the total active moiety is illustrated in Figure 8.

Figure 8. Visual Predictive Check for the Total Active Moiety Stratified by CYP2D6 Phenotype



Note:

Open circles represent the observed concentrations. Red solid lines represent the 5th, 50th and 95th percentiles of the observed concentrations. Shaded green area represents the 90% prediction intervals (between the 5th and 95th percentiles) of the simulated concentrations.

Source: Figure 10, page 54, INDV-7000-M04.pdf

Reviewer's Comments: The results in Figure 8 demonstrate that the model underestimates the total active moiety concentrations in IM and PM subjects. On the other hand, the data (as illustrated by the red lines) show general overlap between the three groups and suggest that a dose adjustment is not required in these groups. This finding is consistent other risperidone products.

4 APPENDIX: INDIVIDUAL STUDY REVIEWS

APPEARS THIS WAY ON ORIGINAL



CLINICAL PHARMACOLOGY STUDY REVIEW

Pharmacokinetic Study

Study # RB-US-09-0007

Study Period:

(b) (6)

NDA 210655

Title

An Open Label, Single Center, Single Dose, Phase I, First in Man Study of the Safety, Tolerability and Pharmacokinetic Profile of RBP-7000.

Objectives:

Primary:

- To assess the safety and tolerability of a subcutaneous (SC) injection of a single 60 mg dose of RBP-7000 in subjects with clinically stable schizophrenia.
- To characterize the pharmacokinetic (PK) profile of a SC injection of a single 60 mg dose of RBP-7000 in subjects with clinically stable schizophrenia.

Secondary:

- To compare the PK profile of RBP-7000 with RISPERDAL® CONSTA® historical data.

Study Design:

Methodology: This was an open label, single center, phase 1, first-in-man study, designed to evaluate the safety, tolerability, and PK profile of a single 60 mg dose of RBP-7000 in subjects with schizophrenia who are clinically stable and on medication other than risperidone. Twelve subjects were enrolled as inpatients with outpatient follow-up. Enrollment began initially with 3 subjects followed by the remaining 9 subjects. Additional subjects were only enrolled after the Sponsor had analyzed and reviewed the PK profiles for the first 3 subjects through Day 4. All 12 subjects completed at least 75% of PK blood draws and completed the study through Day 43. Therefore, replacement of subjects during the study was not required.

Subjects who continued to meet eligibility criteria received a single dose of 60 mg RBP-7000 in the morning of Day 1 after a 2-hour fast. Subjects were discharged from the CU at approximately 14 days post-dose after completion of all inpatient assessments (Day 15).

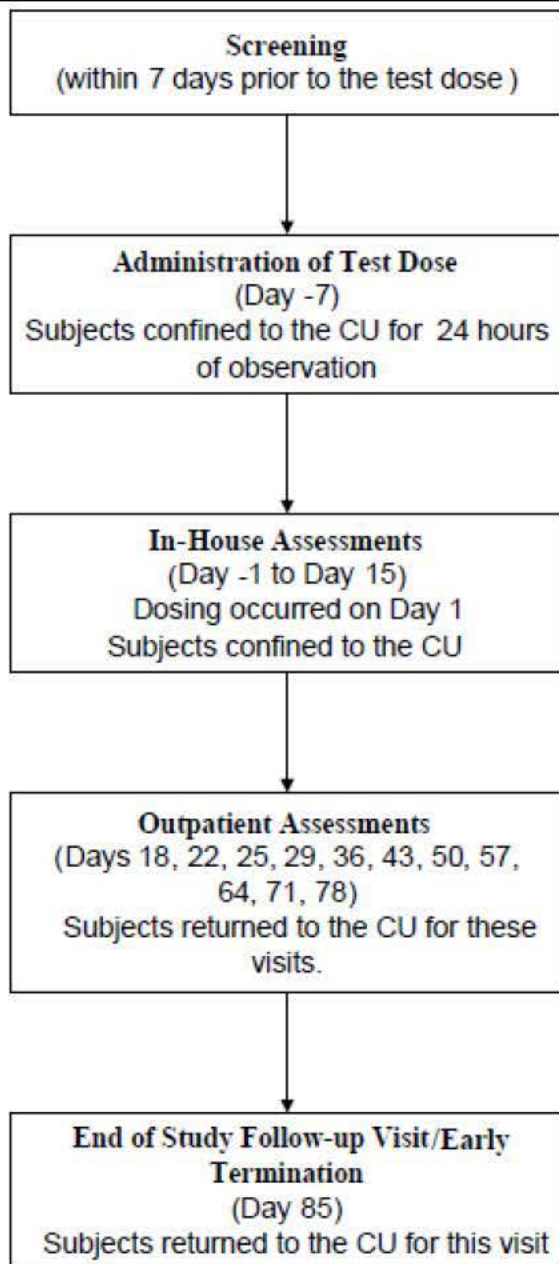
Subjects returned to the CU for study visits for approximately 10 additional weeks. An End of Study Follow-up visit/Early Termination (ET) was conducted on Day 85. All subjects continued their prescribed antipsychotic medication throughout the study period as well as all other neuroleptic non-risperidone medications.

Neurological and clinical symptom assessments (Positive and Negative Syndrome Scale [PANSS], Clinical Global Impressions-Schizophrenic Specific [CGI-SCH], Simpson-Angus Scale [SAS], Barnes Akathisia Scale [BAS], Abnormal Involuntary Movement Scale [AIMS] for Tardive Dyskinesia, and Columbia-Suicide Severity Rating Scale [C-SSRS]) were conducted at Screening, on the day of admission to the clinical unit (CU) (Day -1), and at specified post-dose visits throughout the study including the End of Study Follow-up visit/ET. Scale results were reviewed by the PI. CYP-2D6 genotyping was conducted at Screening. Tolerability was measured using SAS, which was conducted as described above.

Blood samples to assess the PK parameters were taken from pre-dose until approximately 84 days post-dose.

End of study procedures were conducted on Follow-up Day 85 (84 days post-dose) or ET to assess any adverse events (AEs) that were ongoing at the last visit, any new AEs that have developed, and for measurement of safety parameters.

Duration of Treatment: The treatment consisted of a 1 day dosing period followed by 14 days of in-patient assessments, 10 weeks of out-patient assessments and 1 day of end of study assessments. A 1-day test dosing period with oral risperidone occurred prior to treatment with RBP-7000.



Product Used:

- SC injection of RBP-7000 = 60 mg
- Single dose study

Test Product, Dose and Mode of Administration, Lot Number:

Each patient received a single dose of RBP-7000 60 mg (Lot 108, packaged and labeled Lot 102 Risperidone syringe, and Lot 105 ATRIGEL® Delivery System syringe), a mixture of the ATRIGEL® Delivery System and 60 mg risperidone, by SC administration. The ATRIGEL® Delivery System is composed of (b) (4) 80/20 poly DL-lactide-co-glycolide (PLGH) and (b) (4) N-methyl-2-pyrrolidone (NMP). RBP-7000 and the ATRIGEL® Delivery System were manufactured by (b) (4)

Route of Administration	Sub-cutaneous administration
PK Sampling Times and Parameters	Pharmacokinetics: The following PK parameters were calculated for both risperidone and total risperidone (risperidone + 9-hydroxyrisperidone): • Initial Burst Parameters: ◦ C_{max}: the maximum plasma concentration ◦ T_{max}: the time of occurrence of C_{max} ◦ AUC: the area under the plasma concentration versus time curve • Secondary Peak Parameters (if applicable): ◦ C_{max}: the maximum plasma concentration ◦ T_{max}: the time of occurrence of C_{max} ◦ C_{min}: the minimum plasma concentration, calculated between the initial burst and secondary peak ◦ T_{min}: the time of occurrence of C_{min}, calculated between the initial burst and secondary peak ◦ AUC: the area under the plasma concentration versus time curve • Overall Parameters: ◦ C_{max}: the maximum plasma concentration, over the 12-week post-dosing period ◦ T_{max}: the time of occurrence of C_{max}, calculated over the 12-week post-dosing period ◦ AUC_{last}: the area under the plasma concentration versus time curve from time zero to the last sampling time at which concentrations were at or above the limit of quantitation (LOQ) ◦ $AUC_{0-\infty}$: the area under the plasma concentration versus time curve from zero time to infinity (derived only if λ_z can be derived) ◦ λ_z (λ_z): the apparent elimination rate constant (if possible) ◦ $T_{1/2}$: the apparent elimination half life (if possible) ◦ C_{last}: the last plasma concentration. ◦ T_{last}: the time of the last plasma concentration The parameters listed above were calculated for both risperidone and for total risperidone (risperidone + 9-hydroxyrisperidone). Blood samples for PK assessments were collected at pre dose (0 hrs) and at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours post-dose on Day 1 as well as on Days 3, 4, 5, 8, 11, 15, 18, 22, 25, 29, 36, 43, 50, 57, 64, 71, 78, and 85 (at approximately the same time of day as dosing). In addition, the following windows were acceptable without deviation: ± 2 minutes for Day 1 up to 24 hours, ± 10 minutes for Days 3 through 15, and ± 2 days for Days 18 through 85.
Safety Parameters	

	Safety and tolerability were assessed by evaluating AEs, clinical laboratory assessments (biochemistry, hematology and urinalysis), electrocardiogram (ECG) measurements, neurological assessments, clinical symptom assessments, physical examination (PE) findings, local injection site tolerability, CYP-2D6 genotyping, and concomitant medications. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS Subjects were monitored for any AEs from the signing of informed consent until the end of the clinical study. Informed consent was obtained prior to the first study related procedure (Screening). Therefore, pre-dose events that were not causally related to the study drug but were related to study participation were captured by the PI as reportable AEs. The PI or a medically qualified designee reviewed each event and assessed its relationship to the study drug. Each sign or symptom was graded for severity, and the date and time of onset, cessation and resolution were recorded. Treatment of any adverse drug reaction (ADR) was evaluated and managed by a physician, either at the study site or at a nearby hospital emergency room, as appropriate.
PK Moieties	PK parameters for Risperidone, 9-hydroxyrisperidone, and total Risperidone (i.e., Risperidone + 9-hydroxyrisperidone) were quantified in plasma samples using a validated analytical method
PD Endpoint(s)	Neurological assessments (AIMS, SAS, and BAS) and clinical symptom assessments (PANSS, CGI-SCH, and C-SSRS) were performed by the PI or an appropriately trained, cross-trained, and qualified individual. The assessments were performed at Screening, on Day -1, Day 8, and Day 15, once a week as part of the outpatient assessments and at End of Study Follow-up visit/ET (Day 85).
Statistical Methods	

The statistical analyses were reported using summary tables, figures, and data listings. Continuous variables were summarized with counts (including number missing where applicable), means, standard deviations (SD), medians, minimums, and maximums. Categorical variables were summarized by frequency counts (including number missing) and by percentage of subjects in corresponding categories. PK parameters were summarized with counts (including number missing where applicable), means, SD, medians, minimums, and maximums. The number missing, where applicable, was included on the appropriate tables as a unique count. Select PK parameters, specifically concentration and AUC parameters, were additionally summarized by the geometric mean and coefficient of variation (% CV).

Individual subject data obtained from the case report forms (CRFs), PK data, and any derived data were presented by subject in data listings. Data listings included all data collected from the initial Screening visit to the End of Study Follow-up visit/ET from all subjects enrolled. Screen failures were included in a separate listing, entitled Screen Failures.

Pharmacokinetic Variables:

Individual plasma concentrations were collected according to the schedule outlined in the protocol to compute PK parameters. The individual concentrations were summarized using descriptive statistics including arithmetic mean, median, SD, minimum, maximum, geometric mean and %CV at each time point. Plasma concentration values reported as below the lower limit of quantitation (LLOQ) were set to zero to compute the descriptive statistics except for the geometric mean and %CV. If at least one plasma concentration was below the LLOQ at a time point, the geometric mean was not presented. Mean and individual plasma concentrations versus time graphs were produced.

The PK parameters were derived using a non-compartmental approach and appropriate validated PK software (i.e. WinNonlin, Version 6.1) and were determined for both risperidone and for total risperidone (risperidone + 9-hydroxyrisperidone) using actual elapsed time values. Results were summarized using descriptive statistics including arithmetic mean, median, SD, minimum, maximum, geometric mean and %CV.

Safety:

Safety variables were analyzed on the safety population using descriptive statistics (count [including number missing where applicable], mean, SD, median, minimum and maximum) for continuous variables and frequency counts with percentages for discrete endpoints. Baseline was defined as the last non-missing value prior to dose on Day 1. No imputation of missing values was performed.

Analytical Method

Method Type	LC/MS/MS	Matrix	Plasma
Analytes	- Risperidone - 9-hydroxyrisperidone - Total Risperidone (i.e., Risperidone + 9-hydroxyrisperidone)		

Validation	▪ Method validated prior to use	☒ Yes ☐ No
	▪ Method validation acceptable	☒ Yes ☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☒ Yes ☐ No
	▪ Quality control samples range acceptable	☒ Yes ☐ No
	▪ Chromatograms provided	☒ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	▪ Overall performance acceptable	☒ Yes ☐ No

Study Population:

- 18-42 year old patients with a confirmed diagnosis of paranoid, residual, or undifferentiated schizophrenia were considered for inclusion.
- N= 12 subjects

Male and female subjects between the ages of 18 and 42 years, inclusive, with a confirmed diagnosis of paranoid, residual, or undifferentiated schizophrenia in a documented letter from the subject's psychiatrist or primary care provider, were eligible to participate in the study. Subjects who had been clinically stable for at least 60 days without hospitalization; had a body mass index (BMI) between 18 and 33 kg/m² inclusive and weighed at least 49.9 kg; and had given written informed consent were eligible for inclusion in the study.

Table 1: Demography of subjects

	Total (N = 12)
Age (years)	
n	12
Mean (SD)	34.3 (8.21)
Median	38.5
Min, Max	20, 41
Sex	
Male	8 (66.7%)
Female	4 (33.3%)
Ethnicity	
Hispanic or Latino	0 (0.0%)
Not Hispanic or Latino	12 (100.0%)
Race	
American Indian or Alaskan Native	0 (0.0%)
Asian	0 (0.0%)
Black or African American	12 (100.0%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)
White	0 (0.0%)
Multiple Races Checked	0 (0.0%)
Weight (kg)	
n	12
Mean (SD)	81.85 (13.692)
Median	84.05
Min, Max	53.6, 102.0
Height (cm)	
n	12
Mean (SD)	174.50 (7.618)
Median	175.15
Min, Max	160.0, 188.0

Inclusion Criteria:

Each subject had to meet the following criteria to be eligible for the study:

1. Age: ≥ 18 to ≤ 42 years.
2. Sex: male and female subjects were eligible for entry.
3. Confirmed diagnosis of paranoid, residual, or undifferentiated schizophrenia in a documented letter from the subject's psychiatrist or primary care provider.
4. Status: clinically stable subjects (subjects whom the PI established by medical record or by history from the subject and at least one reliable informant who resided with the subject, that the subject had been clinically stable for at least 60 days without hospitalization) were eligible to participate in the study.
5. Subjects with a body mass index (BMI) between 18 and 33 kg/m² inclusive and weighed at least 49.9 kg were eligible for entry.
6. Subjects who had given written informed consent.

Exclusion Criteria:

1. Subjects who took any risperidone product in the last 60 days prior to study screening.
2. Subjects with a history of cancer (excluding resected basal cell or squamous cell carcinoma of the skin) unless they had been disease free for ≥ 5 years.
3. Subjects with another active medical condition or organ disease that may have either compromised subject safety or interfered with the safety and/or outcome evaluation of the study drug. This included, but was not limited to the following abnormalities: total bilirubin > 2.5 mg/dL (51 μ mol/L), alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $> 3 \times$ the upper limit of normal (ULN) or clinically significant serum creatinine $> 2 \times$ ULN, international normalized ratio (INR) ≥ 2.0 . Other excluded medical conditions including, but not limited to, history of heart attack, brain injury, low blood pressure and clinically significant irregular heartbeat.
4. Subjects with known diagnosis of type 1 or 2 diabetes or subjects with an abnormal Hemoglobin A1c (HbA1c) at screening.
5. Subjects with clinically significant co-morbidities that could have affected near-term survival.
6. Subjects treated with any investigational drug within 30 days of beginning study screening.
7. Subjects with significant traumatic injury, major surgery or open biopsy within the past 4 weeks.
8. Subjects who received opioid or opioid-containing analgesics.
9. Subjects who consumed > 1 alcoholic drink per day within the last 30 days (defined as one ounce of 80 proof spirits, 12 ounces of beer, or 4 ounces of wine).
10. Subjects with prior allergic reactions or sensitivities to any component of RBP-7000.
11. Subjects with other concurrent uncontrolled illness that may have interfered with his or her ability to participate in the trial.
12. Subjects with other known contraindications or sensitivity to risperidone or other components of RBP-7000.
13. Women with a positive pregnancy test at Screening. Women of childbearing potential, who were pregnant or lactating, seeking pregnancy, or failing to take adequate contraceptive precautions, (e.g., an oral or injectable contraceptive, an approved hormonal implant or topical patch, an intrauterine device, abstinence. Female subjects who became sexually active must have agreed to use a double barrier method or barrier plus spermicide). A woman of childbearing potential is defined as any female who is less than 2 years post-menopausal or has not undergone a hysterectomy or surgical sterilization, e.g. bilateral tubal ligation, bilateral ovariectomy (oophorectomy).
14. Subjects with a positive urine drug screen for opiates, cocaine, amphetamines, methadone, marijuana, barbiturates, benzodiazepines, methamphetamine, phencyclidine, and tricyclic antidepressants unless the positive screen was determined to be secondary to an allowable concomitant medication.
15. Subjects with epilepsy or other seizure disorders, Parkinson's disease, or dementia.
16. Subjects who took bupropion, chlorpheniramine, cimetidine, clomipramine, doxepin, or quinidine.
17. Subjects who took clozapine, phenothiazines, or haloperidol.
18. Subjects who took serotonin reuptake inhibitors (e.g., fluoxetine, paroxetine) in the 30 days prior to beginning study screening.
19. Subjects who took medications, in addition to those listed above, which were expected to significantly interfere with the metabolism or excretion of risperidone and/or 9-hydroxyrisperidone, that may have been associated with a significant drug interaction with risperidone, or may have posed a significant risk to subjects' participation in the study.
20. Subjects who had been previously enrolled into the study.
21. Subjects who were unable, in the opinion of the PI, to comply fully with the study requirements.

PK Results

The PK parameters were determined for both risperidone and for total risperidone. For risperidone alone, the mean C_{max} values were similar for the initial burst and secondary peak, 3.85 ng/mL and 4.49 ng/mL, respectively; median T_{max} was 0.2 days (~5 hours) for the initial burst and 10 days for the secondary peak.

The mean AUC estimates for the initial burst and secondary peak were 3.50 ng•d/mL and 90.5 ng•d/mL, respectively. For the overall profile, the mean AUC_{last} and $AUC_{0-\infty}$ were 94.3 ng•d/mL and 108 ng•d/mL, respectively. The mean apparent elimination half-life for risperidone was 11.4 days (median was 9.06 days). In general, there was a moderate amount of inter-individual variability in PK parameters; %CV estimates was 38.8% for the C_{max} .

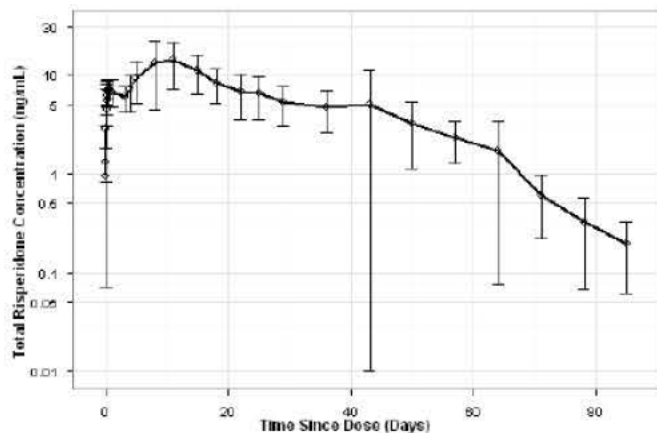
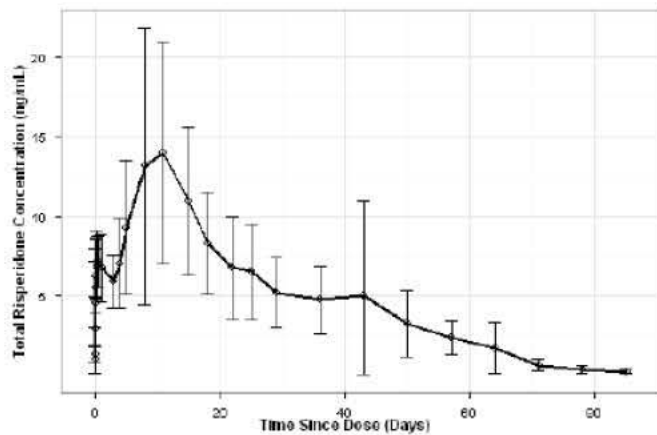
Table 1: Summary Statistics for Select Pharmacokinetic Parameters – Initial Burst and Secondary Peak Parameters

PK Parameter	Risperidone	Total Risperidone (Risperidone+9-Hydroxyrisperidone)
Initial Burst Parameters		
C_{max} (ng/mL)	3.85 (42.7%)	7.45 (27.6%)
T_{max} (days)	0.2 (0.1 – 0.3)	0.5 (0.2 – 1.0)
AUC (ng•days/mL)	3.50 (53.2%)	12.0 (47.3%)
Secondary Peak Parameters		
C_{max} (ng/mL)	4.49 (57.2%)	17.0 (41.8%)
T_{max} (days)	10.0 (7.0 – 21.0)	10.0 (7.0 – 42.0)
C_{min} (ng/mL)	1.29 (57.1%)	5.30 (32.7%)
T_{min} (days)	2.0 (1.0 – 3.0)	2.0 (1.0 – 3.0)
AUC (ng•days/mL)	90.5 (58.3%)	363 (34.5%)

Source: [Appendix 16.1.12, Pharmacokinetic Report](#)

Note: Summary statistics are presented using geometric mean (geometric %CV) or median (min-max) values.

Figure 1: Mean (SD) Total Risperidone (Risperidone + 9-Hydroxyrisperidone) Plasma Concentrations time Profile Following SC Injection of a Single Dose of 60 mg of RBP-7000.



Safety Results

Was there any death or serious adverse events?

☐ Yes ☒ No ☐ NA

A single SC injection of RBP 7000 was safe and well tolerated by the subjects in this first-in-man study as supported by the following results:

- There were no severe AEs, SAEs, deaths or discontinuations due to AEs.
- The most common related AEs, serum prolactin increased, injection site pain and aspartate aminotransferase (AST) increased, were all of mild severity.
- Although all subjects experienced related AEs, they were of mild or moderate severity.
- Laboratory results were generally stable during the study. The key finding was the observation of increased serum prolactin levels both as mean change from Baseline and in individual subject results. Clinically significant (CS) increases in serum prolactin levels correlated with AEs for increased serum prolactin. Elevated levels of AST were CS and correlated with AEs for AST increased in one of two subjects. Other notable trends that were not considered CS included increased mean levels of lymphocytes and glucose compared to Baseline at post-Baseline timepoints.
- There were no CS findings for vital signs, ECG or PE results.
- Neurological assessment scales did not reveal any increases in involuntary body movements, drug-induced parkinsonism or extra pyramidal symptoms (EPS), or akathisia.
- Clinical symptom assessment scales were stable or showed some improvement. No worsening of symptoms was observed.

Overall Sponsor Conclusions

Pharmacokinetic Conclusions:

Total risperidone peak plasma concentrations were reached rapidly for the initial burst (T_{max} 0.5 days) and were achieved at 10 days for the secondary peak. In the overall analysis, T_{max} was 10 days and the half life of total risperidone in plasma was extended ($T_{1/2}$ 8.04 days). Overall, the PK of risperidone after administration of RBP-7000 was similar to that observed after administration of RISPERDAL® CONSTA®. The variability in risperidone PK parameters was generally lower for the RBP-7000 formulation compared to RISPERDAL® CONSTA®; the variability in total risperidone PK parameters was approximately equivalent between formulations.

Safety Conclusions:

RBP-7000 was safe and well tolerated in the subjects in this first-in-man study. The absence of any safety signals and a safety profile similar to current risperidone products supports the continued development of RBP-7000 to address compliance issues with risperidone while minimizing risks to subjects.

Reviewer Comments and Conclusions

1. Study Design: *This was an Open Label, Single Center, Single Dose, Phase I, First in Man Study to assess the Safety, Tolerability and Pharmacokinetic Profile of RBP-7000. The overall study design was acceptable since:*
 - *It was a single dose study conducted at a low dose of 60 mg*
 - *18-42 year old adult patients with a confirmed diagnosis of paranoid, residual, or undifferentiated schizophrenia were included.*
 - *Adequate number of subjects (N= 12) were included in the study*
 - *The final to-be-marketed formulation of RBP-7000 was used in this study.*
2. Protocol deviation: *No major protocol deviations were reported.*
3. Data Analysis (i.e., any outliers etc.): *There were no outliers and the PK data from all subjects were included in the analysis.*
4. Bioanalytical Method: *A validated bio-analytical methodology was used which was acceptable.*
5. Inclusion and Exclusion Criteria: *The subject inclusion and exclusion criteria were acceptable since:*
 - *18-42 year old adult patients with a confirmed diagnosis of paranoid, residual, or undifferentiated schizophrenia were included.*
 - *The study excluded subjects who took any medications which were expected to interfere with the metabolism or excretion of risperidone and/or 9-hydroxyrisperidone or that may have been associated with a significant drug interaction with risperidone. This ensured that the PK of RBP-7000 is not impacted by extrinsic factors.*
 - *The study also excluded Subjects with organ disease or organ impairments (i.e., hepatic or renal impairments) that may have either compromised subject safety or interfered with the evaluation of PK, safety of RBP-7000.*

6. Pharmacokinetic findings: *We agree with the sponsor's PK analysis and conclusions from the study.*

CLINICAL PHARMACOLOGY STUDY REVIEW

Pharmacokinetic Study

Study # RB-US-09-0008

Study Period: 05-Apr-2011 to 03-Feb-2012

NDA 210655

Title

A Phase I, Open Label, Single Center, Single Ascending Dose Study of the Safety, Tolerability, and Pharmacokinetic Profile of RBP-7000 60mg, 90mg, and 120mg

Objectives:

- To assess the safety and tolerability of a subcutaneous (SC) injection of a single 60 mg, 90 mg, and 120 mg dose of risperidone in RBP-7000 in subjects with clinically stable schizophrenia
- To characterize the pharmacokinetics of a SC injection of a single 60 mg, 90 mg, and 120 mg dose of risperidone in RBP-7000 in subjects with clinically stable schizophrenia

Study Design:

Methodology:

This was an open-label, single-center, Phase 1, single ascending dose study, designed to evaluate the safety, tolerability, and pharmacokinetic (PK) profile of a single SC injection of 60 mg, 90 mg, and 120 mg dose of risperidone in RBP-7000 in subjects with clinically stable schizophrenia who were not taking risperidone. A total of 45 subjects received a single dose of 1 of the 3 dose levels. A sequential cohort design was employed. Treatment was initiated in 3 cohorts using a dose-rising approach in which safety and tolerability at a lower dose were confirmed before introducing a higher dosage level to a different cohort of subjects:

- Cohort 1: 60 mg risperidone in RBP-7000 (RBP-7000 60 mg)

- Cohort 2: 90 mg risperidone in RBP-7000 (RBP-7000 90 mg)
- Cohort 3: 120 mg risperidone in RBP-7000 (RBP-7000 120 mg)

Each of the 3 dose level cohorts comprised 15 subjects. All subjects received RBP-7000.

All 15 subjects in Cohort 1 (60 mg) were dosed. Dosing of 3 subjects in Cohort 2 (90 mg) commenced after a safety and tolerability review of the data from Day 1 to Day 15 of the 60 mg arm had been completed. This review process used predefined safety and tolerability variables with participants from both the study site and sponsor. A safety and tolerability review of the data from Day 1 to Day 15 of the first 3 subjects in Cohort 2 was performed before the remaining 12 subjects were injected with RBP-7000 90 mg. After safety and tolerability review of the data from Day 1 to Day 15 of the RBP-7000 90 mg arm, 3 subjects in Cohort 3 (120 mg) were injected with RBP-7000 120 mg. A safety and tolerability review of the data from Day 1 to Day 15 of the first 3 subjects in Cohort 3 was performed before the remaining 12 subjects were injected with RBP-7000 120 mg.

After the informed consent form (ICF) was signed and the initial screening assessments completed and reviewed by the principal investigator (PI), eligible subjects were admitted to the residential unit of the clinical site for test dose screening (1 to 7 days after initial screening). During this visit, subjects received a single oral dose of 0.25 mg risperidone under supervision to assess any medication tolerability issues. Subjects were discharged from the residential unit after approximately 24 hours of observation.

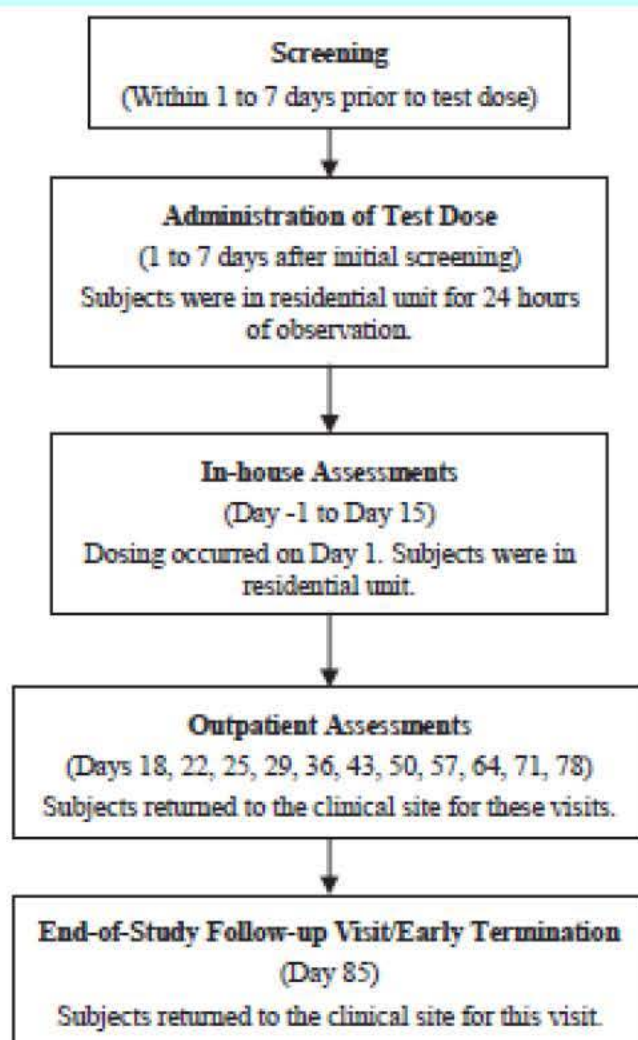
Subjects who continued to be eligible for the study returned to the residential unit approximately 7 days after the test dose of oral risperidone and were expected to stay in the residential unit for approximately 14 days. Following admission to the residential unit on Day -1, subjects who continued to meet eligibility criteria received a SC injection of a single dose of RBP-7000 60 mg, 90 mg, or 120 mg on the morning of Day 1 after a 2-hour fast (water was allowed). Subjects were discharged from the residential unit at approximately 14 days post-injection after all inpatient assessments were completed (Day 15). Subjects returned to the clinical site for study visits each week for approximately 10 additional weeks. All subjects continued their currently prescribed antipsychotic medication throughout the study period as well as all other neuroleptic non-risperidone medications.

Additional safety parameters assessed during the study were: clinical laboratory assessments (serum chemistry, hematology, and urinalysis), vital signs, ECG measurements, adverse events (AEs), concomitant medications, physical examination findings, and local injection site tolerability.

Neurological and clinical symptom assessments included the Positive and Negative Syndrome Scale (PANSS), Abnormal Involuntary Movement Scale (AIMS), Clinical Global Impression-Schizophrenia (CGI-SCH), Simpson-Angus Scale (SAS), Barnes Akathisia Scale (BAS), and Columbia Suicide Severity Rating Scale (C-SSRS).

CYP-2D6 genotyping was conducted on Day 1 only.

Duration of Treatment: Subjects received a single oral test dose of 0.25 risperidone during screening. One SC dose of RBP-7000 (60 mg, 90 mg, or 120 mg) was administered on Day 1, followed by 14 days of inpatient assessments, 10 weeks of outpatient assessments, and 1 day of end of study assessments.



Product Used:

- SC injection of RBP-7000 = 60 mg, 90 mg and 120 mg
- Single dose study with the final to-be-marketed formulation

Test Product, Dose and Mode of Administration, Lot Number: Subcutaneous administrations of RBP-7000 60 mg, 90 mg, and 120 mg were a mixture of the Atrigel® Delivery System and 60 mg, 90 mg, or 120 mg risperidone, respectively: RBP-7000 60 mg, Lot 119; RBP-7000 90 mg, Lot 120; and RBP-7000 120 mg, Lot 121.	
Route of Administration	Sub-cutaneous administration
PK Sampling Times and Parameters	Pharmacokinetics: The following PK parameters were calculated for both risperidone and total risperidone (risperidone + 9-hydroxyrisperidone): • Initial Burst Parameters: ◦ C_{max}: the maximum plasma concentration ◦ T_{max}: the time of occurrence of C_{max} ◦ AUC: the area under the plasma concentration versus time curve • Secondary Peak Parameters (if applicable): ◦ C_{max}: the maximum plasma concentration ◦ T_{max}: the time of occurrence of C_{max} ◦ C_{min}: the minimum plasma concentration, calculated between the initial burst and secondary peak ◦ T_{min}: the time of occurrence of C_{min}, calculated between the initial burst and secondary peak ◦ AUC: the area under the plasma concentration versus time curve • Overall Parameters: ◦ C_{max}: the maximum plasma concentration, over the 12-week post-dosing period ◦ T_{max}: the time of occurrence of C_{max}, calculated over the 12-week post-dosing period ◦ AUC_{last}: the area under the plasma concentration versus time curve from time zero to the last sampling time at which concentrations were at or above the limit of quantitation (LOQ) ◦ $AUC_{0-\infty}$: the area under the plasma concentration versus time curve from zero time to infinity (derived only if λ_z can be derived) ◦ λ_z (λ_z): the apparent elimination rate constant (if possible) ◦ $T_{1/2}$: the apparent elimination half life (if possible) ◦ C_{last}: the last plasma concentration ◦ T_{last}: the time of the last plasma concentration The parameters listed above were calculated for both risperidone and for total risperidone (risperidone + 9-hydroxyrisperidone). Blood samples for PK assessments were collected at pre-injection (0 hours, within 15 minutes prior to dosing) and at 0.5, 1, 2, 3, 4, 6, 8, and 12 hours post-injection on Day 1, Day 2 (24 and 36 hours post-injection), and Days 3, 4, 5, 8, 11, 15, 18, 22, 25, 29, 36, 43, 50, 57, 64, 71, 78, and 85 (at approximately the same time of day as dosing). In addition, the following windows were acceptable without deviation: ± 2 minutes for Day 1 up to Day 2, ± 10 minutes for Days 3 through 15, and ± 2 days for Days 18 through 85.
Safety Parameters	Safety: Safety assessments included clinical laboratory assessments (serum chemistry, hematology, and urinalysis), vital signs, electrocardiogram (ECG) measurements, AEs, concomitant medications, physical examination findings, and local injection site tolerability.

PK Moieties	PK parameters for Risperidone, 9-hydroxyrisperidone, and total Risperidone (i.e., Risperidone + 9-hydroxyrisperidone) were quantified in plasma samples using a validated analytical method
PD Endpoint(s)	Neurological and Clinical Symptom Assessments: The neurological and clinical symptom assessments for this study were selected to elucidate the CNS-related tolerability profile of RBP-7000. Although they were related to safety, they were not considered primary safety endpoints. Any findings from these tests that were considered clinically relevant were entered as AEs, and evaluated with other primary safety data as such. The following assessments were used: PANSS, AIMS, CGI-SCH, SAS, BAS, and C-SSRS.
Statistical Methods	Any AEs that occurred after signing of the ICF until 56 days after the last study subject assessment day were included in the safety analysis. Treatment emergent adverse events (TEAEs; post administration of RBP-7000), AEs, and those AEs that worsened during the study after injection of RBP-7000, were reported separately from AEs that were not treatment emergent. All TEAEs were listed and tabulated by treatment, severity, relationship to therapy, and primary system organ class. In addition, tabulations were provided of AEs that occurred between the test dose and the actual study dose of RBP-7000. Descriptive statistics were provided for hematology, serum chemistry, and urinalysis results. Vital sign and ECG data were summarized using descriptive statistics. Local injection site tolerability was assessed and was summarized by category and severity using frequency counts. All neurological and clinical symptom assessment variables were summarized using descriptive statistics at each post-baseline time point. Changes from baseline were also summarized. Values were summarized by dose group, and graphical representations of mean variables versus dose were prepared for each variable. Pharmacokinetic Variables: The PK analysis included concentration-time data of risperidone, 9-hydroxyrisperidone, and total risperidone, the initial burst or early peak plasma concentrations, secondary peak plasma concentrations (if applicable), and the entire PK sampling period. <u>Initial Burst Parameters (0 to 48 hours; Day 1 to Day 3):</u> C_{max} (maximum risperidone and total risperidone plasma concentrations); T_{max} (time of the maximum risperidone and total risperidone plasma concentrations); and AUC_{0-48} (area under the risperidone and total risperidone plasma concentration-time curves from time-zero to 48 hours), and $AUC_{0-T_{max}}$ (area under the risperidone, 9-hydroxyrisperidone, and total risperidone plasma concentration-time curves from time-zero to t_{max}). <u>Secondary Peak Parameters (if applicable) (Day 3 – Day 29):</u> C_{max}; T_{max}; C_{min} (minimum risperidone and total risperidone plasma concentrations); T_{min} (time of occurrence of risperidone and total risperidone C_{min}); and $AUC_{Day\ 3-Day\ 29}$ (area under the risperidone and total risperidone plasma concentration-time curves from Day 3 to Day 29).

APPEARS THIS WAY ON ORIGINAL



Analytical Method

Method Type	LC/MS/MS	Matrix	Plasma
Analytes	- Risperidone - 9-hydroxyrisperidone - Total Risperidone (i.e., Risperidone + 9-hydroxyrisperidone)		

Validation	▪ Method validated prior to use	☒ Yes ☐ No
	▪ Method validation acceptable	☒ Yes ☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☒ Yes ☐ No
	▪ Quality control samples range acceptable	☒ Yes ☐ No
	▪ Chromatograms provided	☒ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	▪ Overall performance acceptable	☒ Yes ☐ No

Study Population:

- 18-65 year old Male and Female patients with a confirmed diagnosis of paranoid, residual, or undifferentiated schizophrenia were considered for inclusion.
- N= 45 subjects

Male and female subjects aged ≥ 18 to ≤ 65 years who had a confirmed diagnosis of paranoid, residual, or undifferentiated schizophrenia in a documented letter from the subject's psychiatrist or primary care provider were considered for inclusion. Subjects also had to be clinically stable (subjects whom the PI established by medical record or by history from the subject and at least 1 reliable informant, that the subject had been clinically stable for at least 60 days without hospitalization), have a body mass index between 18 and 33 kg/m², weigh at least 49.9 kg, and give written informed consent to be considered eligible for inclusion in the study.

Table 1: Demography of subjects

	RBP-7000 60 mg (N=15)	RBP-7000 90 mg (N=15)	RBP-7000 120 mg (N=15)	Overall (N=45)
Age (years)				
Mean $\pm$ SD	41.1 $\pm$ 12.80	44.2 $\pm$ 9.53	43.87 $\pm$ 8.94	43.04 $\pm$ 10.41
Range (minimum, maximum)	18, 61	24, 57	29, 55	18, 61
Gender (n, %)				
Male	13 (86.7)	12 (80.0)	7 (46.7)	32 (71.1)
Female	2 (13.3)	3 (20.0)	8 (53.3)	13 (28.9)
Race (n, %)				
Black or African American	14 (93.3)	15 (100.0)	14 (93.3)	43 (95.6)
White	1 (6.7)	0 (0.0)	1 (6.7)	2 (4.4)

Inclusion Criteria:

Each subject had to meet the following criteria to be eligible for the study:

1. Subjects aged ≥ 18 to ≤ 65 years.
2. Male and female subjects were eligible.
3. Subjects with confirmed diagnosis of paranoid, residual, or undifferentiated schizophrenia in a documented letter from the subject's psychiatrist or primary care provider.
4. Clinically stable subjects (subjects whom the PI established by medical record or by history from the subject and at least 1 reliable informant, that the subject had been clinically stable for at least 60 days without hospitalization).
5. Subjects with body mass index (BMI) between 18 and 33 kg/m² and weight of at least 49.9 kg.
6. Subjects who gave written informed consent.

Exclusion Criteria:

Subjects who met any of the following criteria were excluded from the study:

1. Subjects taking any risperidone product within the last 60 days prior to study screening.
2. Subjects with a history of cancer (excluding resected basal cell or squamous cell carcinoma of the skin) unless they had been disease free for ≥ 5 years.
3. Subjects with another active medical condition or organ disease that could have either compromised subject safety or interfered with the safety and/or outcome evaluation of the study drug. This included, but was not limited to the following abnormalities: total bilirubin > 2.5 mg/dL ($51 \mu\text{mol/L}$), alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $> 3 \times$ the upper limit of normal (ULN) or clinically significant serum creatinine $> 2 \times$ ULN, international normalized ratio (INR) ≥ 2.0 . Other excluded medical conditions included, but were not limited to: history of heart attack, brain injury, low blood pressure, and clinically significant irregular heartbeat as interpreted by the PI.
4. Subjects who were known to have acquired immune deficiency syndrome or to be human immunodeficiency virus (HIV) positive.
5. Subjects with evidence or history of significant hepatic disorder, including acute or chronic hepatitis B and acute hepatitis C. Subjects with hepatitis C antibody and liver functions ≤ 1.5 times the ULN could be included in the study.
6. Subjects with known diagnosis of type 1 or 2 diabetes or subjects with a clinically significant abnormal hemoglobin A1c (HbA1c) at screening as interpreted by the PI.

7. Subjects with clinically significant comorbidities that could affect near-term survival.
8. Subjects treated with any investigational drug within the last 30 days prior to study screening.
9. Subjects with significant traumatic injury, major surgery, or open biopsy within the last 4 weeks prior to study screening.
10. Subjects receiving opioid or opioid-containing analgesics within the last 30 days prior to study screening.
11. Subjects consuming > 1 alcoholic drink per day within the last 30 days prior to study screening (defined as 1 oz. of 80 proof spirits, 12 cz. of beer, or 4 oz. of wine).
12. Subjects with prior allergic reactions, sensitivities, or other known contraindications to any component of RBP-7000 (i.e., risperidone, poly [DL-lactide-co-glycolide], or N-methylpyrrolidone).
13. Subjects with other concurrent uncontrolled illness that may have interfered with the ability to participate in the study.
14. Women with a positive pregnancy test at screening. Women of childbearing potential, who were pregnant or lactating, seeking pregnancy, or failing to take adequate contraceptive precautions (e.g., an oral or injectable contraceptive, an approved hormonal implant or topical patch, or an intrauterine device). Should a female subject become sexually active, she must have agreed to use a double-barrier method or barrier plus spermicide. A woman of childbearing potential was defined as any female who was less than 2 years post-menopausal or had not undergone a hysterectomy or surgical sterilization, e.g., bilateral tubal ligation or bilateral ovariectomy (oophorectomy). Females who were post-menopausal were confirmed by the follicle stimulating hormone (FSH) test at initial screening.
15. Subjects with a positive urine drug screen for opioids, cocaine, amphetamines, methadone, marijuana, barbiturates, benzodiazepines, methamphetamine, phencyclidine, or tricyclic antidepressants unless the positive screen was determined to be secondary to an allowable concomitant medication.
16. Subjects with epilepsy or other seizure disorders, Parkinson's disease, or dementia.
17. Subjects taking bupropion, chlorpheniramine, cimetidine, clomipramine, doxepin, or quinidine within the last 30 days prior to study screening.
18. Subjects taking clozapine, phenothiazines, aripiprazole, or haloperidol within the last 30 days prior to study screening.
19. Subjects taking serotonin reuptake inhibitors (e.g., fluoxetine, paroxetine) within the last 30 days prior to study screening.
20. Subjects taking medications, in addition to those listed above, which may have been expected to significantly interfere with the metabolism or excretion of risperidone and/or 9-hydroxyrisperidone that may have been associated with a significant drug interaction with risperidone, or may have posed a significant risk to subjects' participation in the study.
21. Subjects who had been previously injected with RBP-7000 in this study.

PK Results

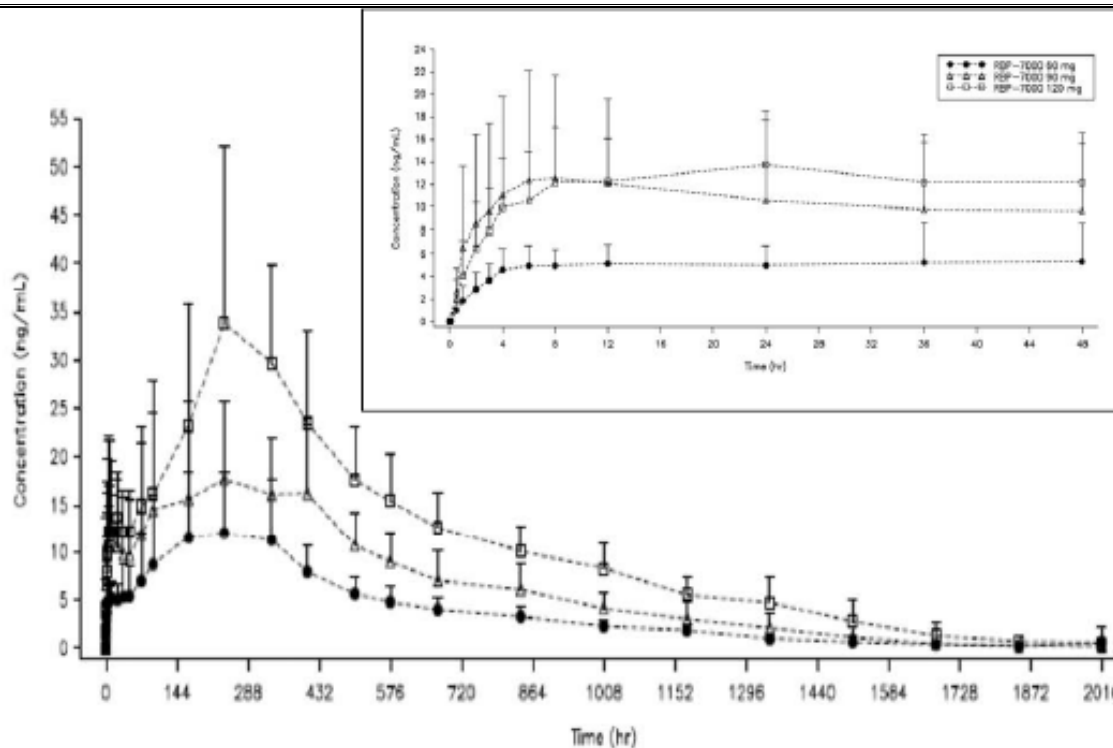
The PK analyses were performed on all subjects (n=45) who received an injection of RBP-7000 and had an adequate number of PK blood draws.

Following a single SC injection of 60, 90 or 120 mg RBP-7000, risperidone plasma concentration increased rapidly with peak concentrations observed at 4 hours post-dose in all dose groups. After the first peak on Day 1, mean plasma risperidone concentrations decreased through approximately Day 3 and then increased again to reach a second peak between approximately Day 11 and Day 18 (Figure 3). Following the second peak, risperidone plasma concentrations decreased gradually through the 84-day sampling period. Risperidone concentrations fell below the LLOQ between Days 50 and 85 in some subjects; however, some other subjects had quantifiable risperidone concentrations up to Day 85 in all dose groups. The mean plasma terminal half-life for risperidone ranged from 208 to 266 hours (approximately 9 to 11 days), in line with the extended-release nature of the formulation.

Following a single SC injection of 60, 90 or 120 mg RBP-7000, mean 9-hydroxyrisperidone plasma concentrations increased through Day 11. The first peak observed for risperidone was not apparent for the 9-hydroxy metabolite. The mean plasma terminal half-life ranged from 196 to 223 hours (approximately 8 to 9 days) for 9-hydroxyrisperidone.

For the total active moiety, a similar pattern as risperidone was observed, although the first peak was approximately 50% to 60% lower than the second peak and was not always apparent on the plasma concentration-time profile. The first peak was observed at 8 to 24 hours post-dose, depending on the dose group; however, plasma concentrations close to the C_{max} were reached at 8 hours post-dose in all dose groups. The second peak was observed at Day 11. The mean plasma terminal half-life of the total active moiety ranged from 180 to 203 hours (approximately 8 days).

Figure 1: Mean (+ SD) Total Active Moiety Plasma Concentration-time Profile Following SC Injection of a Single Dose of 60, 90 or 120 mg of RBP-7000 (Study 09-0008)



SD=standard deviation

Source: CSR 09-0008 Figure 2

Table 1: Geometric Mean (CV%) PK Parameters of Risperidone, 9-Hydroxyrisperidone and Total Active Moiety Following SC Injection of a Single Dose of 60, 90 or 120 mg of RBP-7000 (Study 09-0008)

Parameter	RBP-7000 60 mg (N=15)	RBP-7000 90 mg (N=15)	RBP-7000 120 mg (N=15)
Risperidone			
C _{max} (Peak 1) (ng/mL)	2.98 (45.1)	5.62 (79.5)	7.76 (42.3)
C _{max} (Peak 2) (ng/mL)	3.91 (72.9)	6.05 (81.4) ^a	10.7 (79.3)
T _{max} (Peak 1) (hr)	4.07 (1.07, 12.1)	4.07 (1.07, 6.07)	4.25 (2.07, 48.1)
T _{max} (Peak 2) (hr)	240 (96.1, 336)	288 (72.1, 409) ^a	336 (168, 648)
C _{max} (Overall) (ng/mL)	4.22 (67.3)	8.45 (64.6) ^a	12.5 (67.4)
AUC _{inf} (ng*hr/mL)	1752 (50.0) ^b	2892 (60.7) ^c	6800 (77.8) ^d
t _{1/2} (hr)	266 (69.9) ^b	224 (53.4) ^a	208 (45.6) ^d
9-Hydroxyrisperidone			
C _{max} (Peak 1) (ng/mL)	3.96 (56.2)	7.87 (69.5)	8.10 (45.2)
C _{max} (Peak 2) (ng/mL)	11.2 (46.4)	18.2 (41.8) ^a	28.0 (48.5)
T _{max} (Peak 1) (hr)	36.1 (8.07, 48.1)	24.1 (8.08, 48.1)	48.0 (12.2, 48.3)
T _{max} (Peak 2) (hr)	240 (96.1, 336)	240 (48.1, 386) ^a	240 (72.2, 481)
C _{max} (Overall) (ng/mL)	11.2 (46.4)	18.4 (40.8) ^a	28.0 (48.5)
AUC _{inf} (ng*hr/mL)	5416 (35.1) ^a	9003 (23.6) ^b	13809 (32.3)
t _{1/2} (hr)	222 (60.6) ^a	196 (38.3) ^b	223 (41.2)
Total Active Moiety			
C _{max} (Peak 1) (ng/mL)	5.70 (51.0)	11.3 (70.0)	15.0 (31.1)
C _{max} (Peak 2) (ng/mL)	14.9 (43.5)	22.7 (46.9) ^a	38.4 (39.5)
T _{max} (Peak 1) (hr)	24.1 (4.07, 48.1)	8.07 (6.07, 48.1)	24.1 (6.23, 48.2)
T _{max} (Peak 2) (hr)	240 (96.1, 336)	240 (48.1, 409) ^a	240 (72.2, 481)
C _{max} (Overall) (ng/mL)	14.9 (43.5)	23.8 (43.1) ^a	38.8 (38.7)
AUC _{inf} (ng*hr/mL)	6853 (31.1)	11584 (26.5) ^b	20688 (22.8)
t _{1/2} (hr)	183 (38.4)	180 (36.7) ^b	203 (43.0)

CV=coefficient of variation; N=number of subjects; t_{1/2}=plasma terminal half-life

T_{max} is presented as median values with range in parentheses.

Dose Proportionality

Risperidone AUC_{inf} increased more than dose proportional and the results showed a statistically significant difference from unity (1.0000) in the dose proportionality analysis ($\beta_1=1.865$; $p=0.021$). C_{max} (OVR) increased more than dose proportional; however, the difference from unity was not statistically significant ($\beta_1=1.575$; $p=0.067$).

9-hydroxyrisperidone AUC_{inf}, C_{max} (OVR), and AUC_{last} tended to increase more than dose proportional as depicted by the associated slope values greater than unity (β_1 , pvalue): 1.346, $p=0.052$; 1.318, $p=0.218$; and 1.402, $p=0.032$, respectively. The difference was statistically significant only for AUC_{last}.

In the analysis of total exposure of risperidone, AUC_{inf} increased more than dose proportional ($\beta_1=1.576$, $p<0.001$). AUC_{last} and C_{max} showed the same trend: $\beta_1=1.593$, $p<0.001$ and 1.371, $p=0.107$, respectively. The difference from unity was statistically significant for AUC_{last}, but not for C_{max}.

Overall, the exposures of risperidone, 9-hydroxyrisperidone, and total risperidone increased more than dose proportional for SC doses ranging between 60mg and 120mg.

Safety Results

Was there any death or serious adverse events? ☐ Yes ☒ No ☐ NA

Overall, RBP-7000 was well tolerated. No subject had a SAE or an AE that led to discontinuation or withdrawal from the study. The most frequently reported TEAEs were injection site pain and headache, both reported by more subjects in the RBP-7000 90 mg treatment group. The severity of both injection site pain and headache was mild in all cases. In general, injection site pain lasted only a few minutes.

Six subjects reported constipation; all in the RBP-7000 120 mg group. There were 6 reports of blood prolactin increased of which 4 were in the RBP-7000 120 mg group. The increase in serum prolactin level is consistent with the known pharmacology of risperidone. Overall, a slight upward trend was seen in supine systolic blood pressure, and the mean supine heart rate increased from baseline through Day 22 for all treatment groups. Through Day 22, the mean respiratory rate increased from baseline for all treatment groups and then lowered and remained stable for the rest of the study. Other safety observations, such as hematology, serum chemistry, urinalysis, and ECGs did not present any safety concerns.

Neurological and Clinical Assessments Results:

For the PANSS, the positive and negative subscales showed improvement over time (mean change from baseline to follow-up/early termination [Day 85]). However, no clinical impact was observed after a single dose of RBP-7000. The highest level of improvement from baseline in both subscales was observed in the RBP-7000 120 mg treatment group. Slight improvement was seen in the general psychopathology component.

The overall mean total score for the severity of illness from the CGI-SCH decreased (improved) from baseline (2.62) to follow-up/early termination (Day 85; 2.36) by a mean change of -0.27 (95% CI -0.44, -0.09); however, there were no obvious differences between the 3 treatment doses.

Minor mean overall changes from baseline were observed with the AIMS, SAS, and BAS. With the exception of a few subjects, suicidal ideation remained stable throughout the study.

Overall Sponsor Conclusions

Following single SC injections of 60 mg to 120 mg risperidone in 45 subjects with confirmed diagnosis of paranoid, residual, or undifferentiated schizophrenia, the following PK, neurological and clinical assessment, and safety results were observed:

Pharmacokinetic Conclusions:

- For risperidone, mean $T_{1/2}$ tended to be shorter with increasing doses (ranging from 319.304 hr at 60 mg to 223.404 hr at 120 mg. For 9-hydroxyrisperidone, mean $T_{1/2}$ was 263.467 hr, 211.563 hr, and 243.763 hr for the 60 mg, 90 mg, and 120 mg doses, respectively. For total risperidone, mean $T_{1/2}$ was 196.396 hr, 191.261 hr, and 222.820 hr for the 60 mg, 90 mg, and 120 mg doses, respectively.
- Median risperidone T_{max} in the initial burst (INT) was 4.067 hr for the 60 mg and 90 mg doses and 4.250 hr for the 120 mg dose. The secondary peak increased with increasing doses at median T_{max} (SEC) values of 240.067 hr, 288.125 hr, and 336.233 hr for the 60 mg, 90 mg, and 120 mg doses, respectively. Corresponding increases were also seen for 9-hydroxyrisperidone and total risperidone.
- Median 9-hydroxyrisperidone T_{max} in the INT was 36.067 hr, 24.067 hr, and 48.017 hr for the 60 mg, 90 mg, and 120 mg doses, respectively. The secondary peak increased with increasing doses at median T_{max} (SEC) values of 240.067 hr, 240.067 hr, and 240.250 hr for the 60 mg, 90 mg, and 120 mg doses, respectively.
- Median total risperidone T_{max} in the INT was 24.067 hr, 8.067 hr, and 24.067 hr for the 60 mg, 90 mg, and 120 mg doses, respectively. The secondary peak increased with increasing doses at median T_{max} (SEC) values of 240.067 hr, 240.067 hr, and

240.250 hr for the 60 mg, 90 mg, and 120 mg doses, respectively.

- Mean risperidone C_{avg} increased with increasing doses: 2.026 ng/mL, 3.369 ng/mL, and 7.085 ng/mL for the 60 mg, 90 mg, and 120 mg doses, respectively. Corresponding increases were also seen for 9-hydroxyrisperidone and total risperidone.
- Mean risperidone AUC_{inf} increased with increasing doses: 1951 hr*ng/mL, 3355 hr*ng/mL, and 8595 hr*ng/mL for the 60 mg, 90 mg, and 120 mg doses, respectively. Corresponding increases were also seen for 9-hydroxyrisperidone and total risperidone.
- Overall, the exposures of risperidone, 9-hydroxyrisperidone, and total risperidone increased more than dose proportional.

Neurological and Clinical Assessments Conclusions:

- The positive and negative subscales of the PANSS showed improvement over time; however, no clinical impact was observed after a single dose of RBP-7000. Slight improvement was seen in the general psychopathology component.
- The overall mean total score for the severity of illness from the CGI-SCH decreased (improved) from baseline; however, there were no obvious differences between the 3 treatment groups.
- Minor mean overall changes from baseline were observed with the AIMS, SAS, and BAS.
- Suicidal ideation remained stable throughout the study.

Safety Conclusions:

- Overall, RBP-7000 was safe and was well tolerated after injecting 60mg, 90mg, and 120mg dose of risperidone in RBP-7000.
- No subject had a SAE or an AE that led to discontinuation or withdrawal from the study.
- There were some reports of blood prolactin increased, primarily in the RBP-7000 120 mg group. This possibly indicates that this particular dosage level was the most pharmacologically meaningful.
- Other safety observations, such as hematology, serum chemistry, urinalysis, and ECGs did not present any safety concerns.

Reviewer Comments and Conclusions

1. *Study Design:* This was a Phase 1, Open Label, Single Center, Single Ascending Dose Study to assess the Safety, Tolerability and Pharmacokinetic Profile of RBP-7000. The overall study design was acceptable since:
 - It was a single ascending dose study conducted after an initial single dose study at 60 mg was determined to be safe and tolerated in this patient population. The escalation of dose was gradual (i.e., 60 mg to 90 mg to 120 mg) and was acceptable.
 - Adult male and female patients (18-65 years) with a confirmed diagnosis of paranoid, residual, or undifferentiated schizophrenia were included.
 - Adequate number of subjects (N= 15 per dose level) were included in the study

o *The final to-be-marketed formulation of RBP-7000 was used in this study.*

2. *Protocol deviation:* *No major protocol deviations were reported.*
3. *Data Analysis (i.e., any outliers etc.):* *There were no outliers and the PK data from all subjects were included in the analysis.*
4. *Bioanalytical Method:* *A validated bio-analytical methodology was used which was acceptable.*
5. *Inclusion and Exclusion Criteria:* *The subject inclusion and exclusion criteria were acceptable since:*
 - *Adult male and female patients (18-65 years) with a confirmed diagnosis of paranoid, residual, or undifferentiated schizophrenia were included.*
 - *The study excluded subjects who took any medications which were expected to interfere with the metabolism or excretion of risperidone and/or 9-hydroxyrisperidone or that may have been associated with a significant drug interaction with risperidone. This ensured that the PK of RBP-7000 is not impacted by extrinsic factors.*
 - *The study also excluded Subjects with organ disease or organ impairments (i.e., hepatic or renal impairments) that may have either compromised subject safety or interfered with the evaluation of PK, safety of RBP-7000.*
6. *Pharmacokinetic findings:* *We agree with the sponsor's PK analysis and conclusions from the study.*

CLINICAL PHARMACOLOGY STUDY REVIEW

Pharmacokinetic Study

Study # RB-US-09-0009

Study Period:

(b) (6)

NDA 210655

Title

A Phase 2A, Open-Label, Multiple Ascending Dose Study of the Safety, Tolerability, Pharmacokinetics, and Primary Pharmacodynamic Markers of Efficacy of 60 mg, 90 mg, and 120 mg of Risperidone in RBP-7000 Subcutaneous Injections in Subjects with Clinically Stable Schizophrenia.

Objectives:

Objectives:

Primary Objectives: To assess the safety and tolerability of multiple subcutaneous (SC) injections of 60 mg, 90 mg, and 120 mg doses of risperidone in RBP-7000 in subjects with clinically stable schizophrenia who were on a stable oral risperidone dose of 2 mg, 3 mg, or 4 mg.

To evaluate the pharmacokinetic (PK) profiles of risperidone, 9-hydroxyrisperidone, and total active moiety after multiple SC injections of 60 mg, 90 mg, and 120 mg of risperidone in RBP-7000 in subjects on a stable oral risperidone dose of 2 mg, 3 mg, or 4 mg.

Secondary objectives: To evaluate the switch from oral risperidone to risperidone in RBP-7000 SC injections for efficacy markers using the positive and negative symptom scale (PANSS) and the Clinical Global Impression Scale (CGI) as the primary markers of efficacy.

To evaluate the switch from oral risperidone to RBP-7000 SC injections using the Abnormal Involuntary Movement Scale (AIMS) for Tardive Dyskinesia, the Simpson-Angus Scale (SAS), the Barnes Akathisia Scale (BAS), and the Columbia-Suicide Severity Rating Scale (C-SSRS) as safety markers.

Study Design:

Methodology:

This was an open-label, Phase 2A, multiple-ascending dose study performed at 2 sites. The study was designed to evaluate the safety, tolerability, and PK profile of multiple SC injections of 60 mg, 90 mg, and 120 mg doses of risperidone in the RBP-7000 formulation in subjects with clinically stable schizophrenia who were on a previous stable dose of 2 mg, 3 mg, or 4 mg of oral risperidone, or on a previous stable oral risperidone dose other than 2

mg, 3 mg, or 4 mg, or were not on an antipsychotic. Forty-five (45) subjects received 3 treatments of one of the 3 dose levels of risperidone in RBP-7000. Treatment was initiated in 3 cohorts using a dose-ascending approach. Each of the 3 dose levels was comprised of 15 subjects. The 2 mg, 3 mg, and 4 mg oral dose groups received RBP-7000 SC injections of 60 mg, 90 mg, and 120 mg risperidone, respectively.

All 15 subjects in Cohort 1 received 60 mg of risperidone in RBP-7000, all 15 subjects in Cohort 2 received 90 mg of risperidone in RBP-7000, and all 15 subjects in Cohort 3 received 120 mg of risperidone in RBP-7000. Each Cohort was split into 2 sub-groups: An A group comprised of 5 subjects and a B group comprised of the remaining 10 subjects. Cohort 1A subjects received 60 mg of risperidone in RBP-7000. A safety and tolerability review of the data from subjects in Cohort 1A from Day 1 to Day 15 was conducted; if there were no limiting safety concerns found, the remaining 10 subjects in Cohort 1 (Cohort 1B) were dosed with 60 mg of risperidone in RBP-7000, and the first 5 subjects in Cohort 2 (Cohort 2A) were dosed with 90 mg of risperidone in RBP-7000. A safety and tolerability review of the data from subjects in Cohort 2A from Day 1 to Day 15 was conducted; if there were no limiting safety concerns found, the 10 subjects in Cohort 2B were dosed with 90 mg of risperidone in RBP-7000, and the 5 subjects in Cohort 3A were dosed with 120 mg of risperidone in RBP-7000. A safety and tolerability review of the data from Day 1 to Day 15 of the subjects in Cohort 3A was performed before the remaining 10 subjects in Cohort 3B were injected with 120 mg of risperidone in RBP-7000. On-demand PK data analysis and review was to be performed as deemed necessary.

After the informed consent had been signed, initial screening assessments were completed and reviewed by the principal investigator (PI). Oral risperidone of 2 mg, 3 mg, or 4 mg was to be taken once daily by subjects already on those doses during the screening period (Day -28 through Day -15). For those subjects not on an antipsychotic and those subjects that were on oral risperidone doses other than 2 mg, 3 mg, or 4 mg, oral risperidone conversion and stabilization starting at 2 mg/day, occurred from Day -14 to Day -8 to achieve oral risperidone dose levels of 2 mg, 3 mg, or 4 mg. On Day -7, eligible subjects completed baseline safety assessments and predose PK sampling at the clinical unit (CU) and began the first of 7 days of oral dosing of risperidone as provided for the study. Subjects returned to the CU as outpatients to receive their respective oral doses of 2 mg, 3 mg, or 4 mg of risperidone once daily from Day -6 to Day -4. Subjects were admitted to the CU on the morning of Day -3 to be administered their respective oral dose and to have a PK sample taken prior to dosing. A 1-hour (hr) fast (water was allowed) was required before and after oral dosing on Day -3, Day -2, Day -1, and on all subsequent dosing days through the end of the study. A PK profile was obtained on Day -1.

On the morning of Day 1, subjects on oral risperidone doses of 2 mg, 3 mg, and 4 mg received SC injections of single doses of 60 mg, 90 mg, and 120 mg of risperidone in RBP-7000, respectively. A complete PK profile was obtained after the initial SC injection of RBP-7000. Subjects were discharged from the CU approximately 14 days post injection after all inpatient assessments had been completed (Day 15). Subjects returned to the CU as outpatients at prescribed intervals over the course of 13 days for safety evaluations and PK sample collection.

At the end of the 13-day outpatient follow-up period, subjects were admitted to the CU 1 day prior to the scheduled dosing day and received their second SC injection of RBP-7000 in the same manner as their first dose. Select PK samples were obtained during the ensuing

inpatient stay, and subjects were discharged from the CU approximately 48 hrs post second injection, after all inpatient assessments had been completed. Subjects were readmitted to the CU 4 days later for safety evaluations and PK sample collection and remained for a 4-night inpatient stay. Subjects returned to the CU as outpatients at prescribed intervals over the course of 17 days for safety evaluations and PK sample collection.

At the end of the second injection follow-up period, subjects were admitted to the CU 1 day prior to the scheduled dosing day and received their third and final SC injection of RBP-7000 in the same manner as their first and second doses. A complete PK profile was obtained. Subjects were discharged from the CU approximately 14 days post injection after all inpatient assessments had been completed. Subjects returned to the CU as outpatients at prescribed intervals over the course of 13 days for safety evaluations and PK sample collection.

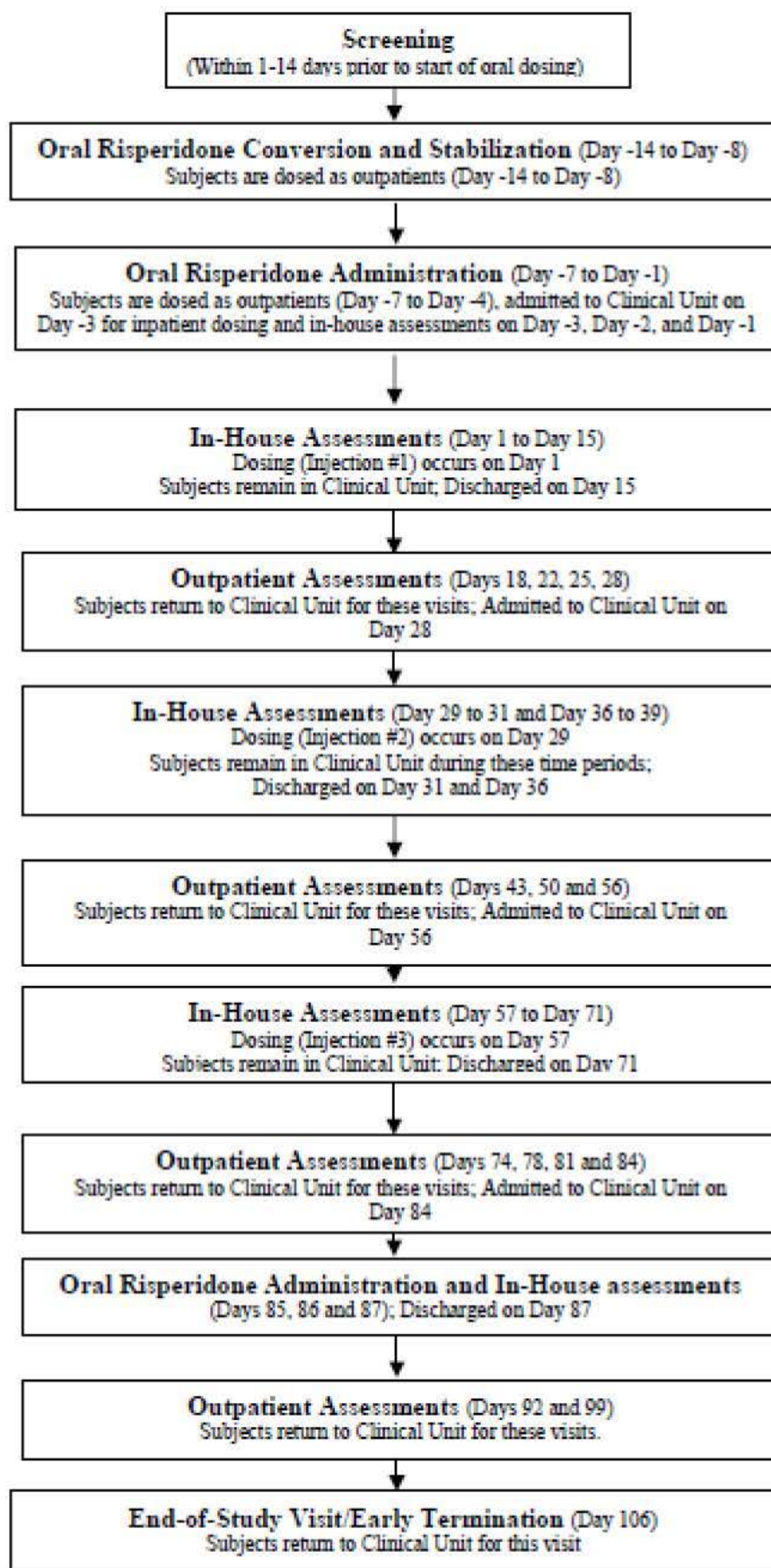
At the end of the third injection 13-day outpatient follow-up period, subjects were admitted to the CU and were administered oral risperidone at their original dose before the first SC injection (2 mg, 3 mg, or 4 mg once daily) beginning on Day 85. Subjects remained in the CU for an additional 48 hrs. After discharge on Day 87, subjects returned to the CU as outpatients for 3 weekly assessments. The third and final weekly visit at approximately Day 106 was the end-of-study (EOS) visit.

During inpatient periods, subjects were allowed excursions (day or night) from the CU as deemed appropriate by the PI and as did not interfere with study procedures or with PK, safety, or efficacy evaluations. Subjects were allowed a ± 1 -day window for outpatient visits, and a ± 2 -day window for RBP-7000 injections 2 and 3. All subsequent (post-dose) visits and study activities were linked to the actual dosing day. Intervals and timing were governed by the schedule of study events relative to the actual dosing day.

Neurological and clinical symptom assessments (PANSS, AIMS, CGI, SAS, BAS, and C-SSRS) were conducted at screening, and at select visits throughout the study, including the EOS visit, for safety and efficacy review. Scale results were reviewed by the PI. CYP-2D6 genotyping was conducted at screening only. Other safety parameters assessed during the study were clinical laboratory assessments (serum chemistry, hematology, and urinalysis), vital signs, electrocardiogram (ECG) measurements, AEs, concomitant medications, body weight, physical examination findings, and local injection site tolerability.

Blood samples to assess PK parameters were taken from pre-injection until approximately Day 86.

EOS procedures were conducted on Day 106 to collect a final measurement of safety parameters and to assess any AEs that were ongoing at the last visit or any new AEs that had developed.



Product Used:

- SC injection of RBP-7000
Subcutaneous administrations of RBP-7000 60 mg, 90 mg, and 120 mg were a mixture of the Atrigela® Delivery System and 60 mg, 90 mg, or 120 mg risperidone, respectively: RBP-7000 60 mg, Lot 119; RBP-7000 90 mg, Lot 120; and RBP-7000 120 mg, Lot 136.
- Oral Risperidone used was U.S. approved oral generic versions of RISPERDAL – ANDA 78871 by Workhardt (see appendix for details)

Route of Administration**Oral and Sub-cutaneous administration**

The study schedule was designed so that each of the 3 injections of RBP-7000 was separated by a maximum of 30 days. There was a maximum of 21 days between the screening visit and the initial oral pretreatment visit. Periods of oral risperidone dosing (7 days for oral conversion and stabilization [if applicable], 7 days oral pretreatment, and 3 days at the end of the study) were designed to insure smooth transitions from oral risperidone dosing at 2 mg, 3 mg, or 4 mg to RBP-7000 SC injections (60 mg, 90 mg, or 120 mg) and then back again to original oral risperidone doses of 2 mg, 3 mg, and 4 mg. All oral in-clinic and SC dosing occurred in the morning, under fasted conditions; water was allowed. SC dosing was performed at a site on the abdomen that had adequate amounts of subcutaneous tissue and did not have excessive pigment, nodules, lesions, or hair. Subsequent injections were performed on the opposite side of the abdomen from the last injection.

PK Sampling Times and Parameters

Subcutaneous administration initial burst PK parameters for risperidone, 9-hydroxyrisperidone, and total risperidone (approximately 0 to 24 hours; Day 1 to Day 2 relative to each injection)

C_{max}	Maximum plasma concentration, determined directly from individual concentration-time data.
T_{max}	Time of the maximum plasma concentration; reported to 2 decimal places.
AUC_{0-24}	Area under the plasma concentration-time curve from time zero to 24 hours; calculated using the linear trapezoidal rule.

	Subcutaneous administration overall PK Profile for risperidone, 9-hydroxyrisperidone, and total risperidone for injections 1 and 3 <table border="1"> <tr> <td>C_{max}</td><td>Maximum plasma concentrations over the 12-week post-dosing period, determined directly from individual concentration-time data.</td></tr> <tr> <td>AUC_{tau}</td><td>Area under the plasma concentration-time curve of injection 1 or 3 from time zero to time tau (where tau=28 days); calculated using the linear trapezoidal rule. Interpolation or extrapolation will be used if necessary.</td></tr> <tr> <td>C_{avg}</td><td>The average of plasma concentrations calculated as AUC_{tau} / tau (tau = 28 days)</td></tr> <tr> <td>T_{max}</td><td>Time of the maximum plasma concentration over the PK profile; reported to 2 decimal places.</td></tr> <tr> <td>C_{last}</td><td>The last quantifiable plasma concentration determined directly from individual concentration-time data.</td></tr> <tr> <td>C_{min}</td><td>Minimum plasma concentration, calculated over the PK profile.</td></tr> <tr> <td>T_{last}</td><td>Time of the last measureable plasma concentration during dosing interval; reported to 2 decimal places.</td></tr> <tr> <td>% Fluctuation</td><td>The degree of fluctuation of measureable risperidone, 9-hydroxyrisperidone, and total risperidone plasma concentrations calculated as $(C_{max} - C_{min}) / C_{avg}$, expressed as a percentage.</td></tr> <tr> <td>Swing</td><td>The swing of risperidone, 9-hydroxyrisperidone, and total risperidone plasma concentrations calculated as $(C_{max} - C_{min}) / C_{min}$.</td></tr> <tr> <td>$C_{trough}$</td><td>Predose plasma concentrations collected during the SC administration period on days 1, 29, 57, and 85.</td></tr> </table> Similar PK parameters were also assessed for oral risperidone (day -7 to -1 and Day 85 to 87) <u>PK sampling times:</u> - Oral = Day -7 at pre-dose and 1 hr, Day -3 and Day -2 at pre-dose, Day -1 at pre-dose and at 0.5, 1, 2, 4, and 8 hours. - SC = At pre-dose, within 15 minutes prior to dosing, and at 1, 2, 3, 4, 6, and 12 hr and then trough levels on day 2,4,6,8,9,10,11,12, 15,18,22,25,28 after the 1st injection as well as after the 3rd injection.	C_{max}	Maximum plasma concentrations over the 12-week post-dosing period, determined directly from individual concentration-time data.	AUC_{tau}	Area under the plasma concentration-time curve of injection 1 or 3 from time zero to time tau (where tau=28 days); calculated using the linear trapezoidal rule. Interpolation or extrapolation will be used if necessary.	C_{avg}	The average of plasma concentrations calculated as AUC_{tau} / tau (tau = 28 days)	T_{max}	Time of the maximum plasma concentration over the PK profile; reported to 2 decimal places.	C_{last}	The last quantifiable plasma concentration determined directly from individual concentration-time data.	C_{min}	Minimum plasma concentration, calculated over the PK profile.	T_{last}	Time of the last measureable plasma concentration during dosing interval; reported to 2 decimal places.	% Fluctuation	The degree of fluctuation of measureable risperidone, 9-hydroxyrisperidone, and total risperidone plasma concentrations calculated as $(C_{max} - C_{min}) / C_{avg}$, expressed as a percentage.	Swing	The swing of risperidone, 9-hydroxyrisperidone, and total risperidone plasma concentrations calculated as $(C_{max} - C_{min}) / C_{min}$.	C_{trough}	Predose plasma concentrations collected during the SC administration period on days 1, 29, 57, and 85.
C_{max}	Maximum plasma concentrations over the 12-week post-dosing period, determined directly from individual concentration-time data.																				
AUC_{tau}	Area under the plasma concentration-time curve of injection 1 or 3 from time zero to time tau (where tau=28 days); calculated using the linear trapezoidal rule. Interpolation or extrapolation will be used if necessary.																				
C_{avg}	The average of plasma concentrations calculated as AUC_{tau} / tau (tau = 28 days)																				
T_{max}	Time of the maximum plasma concentration over the PK profile; reported to 2 decimal places.																				
C_{last}	The last quantifiable plasma concentration determined directly from individual concentration-time data.																				
C_{min}	Minimum plasma concentration, calculated over the PK profile.																				
T_{last}	Time of the last measureable plasma concentration during dosing interval; reported to 2 decimal places.																				
% Fluctuation	The degree of fluctuation of measureable risperidone, 9-hydroxyrisperidone, and total risperidone plasma concentrations calculated as $(C_{max} - C_{min}) / C_{avg}$, expressed as a percentage.																				
Swing	The swing of risperidone, 9-hydroxyrisperidone, and total risperidone plasma concentrations calculated as $(C_{max} - C_{min}) / C_{min}$.																				
C_{trough}	Predose plasma concentrations collected during the SC administration period on days 1, 29, 57, and 85.																				
Safety Parameters	Neurological and Clinical Symptom Assessments: Neurological assessments and clinical symptom assessments included the PANSS, CGI, AIMS, BAS, SAS, and C-SSRS. Safety: Safety was assessed using AEs, clinical laboratory evaluations (serum chemistry, hematology, and urinalysis), vital signs, ECG evaluations, local injection site tolerability, and analyses for changes in body weight and prolactin levels.																				
PK Moieties	PK parameters for Risperidone, 9-hydroxyrisperidone, and total Risperidone (i.e., Risperidone + 9-hydroxyrisperidone) were quantified in plasma																				

	samples using a validated analytical method
PD Endpoint(s)	To evaluate the switch from oral risperidone to risperidone in RBP-7000 SC injections for efficacy markers using the positive and negative symptom scale (PANSS) and the Clinical Global Impression Scale (CGI) as the primary markers of efficacy. To evaluate the switch from oral risperidone to RBP-7000 SC injections using the Abnormal Involuntary Movement Scale (AIMS) for Tardive Dyskinesia, the Simpson-Angus Scale (SAS), the Barnes Akathisia Scale (BAS), and the Columbia-Suicide Severity Rating Scale (C-SSRS) as safety markers. Neurological and Clinical Symptom Assessments: Neurological assessments and clinical symptom assessments included the PANSS, CGI, AIMS, BAS, SAS, and C-SSRS.
Statistical Methods	The software used for all summary statistics and statistical analyses was SAS® Version 9.1 or higher (see Section 8, SAS Institute, Inc.). Most continuous data were summarized with the following descriptive statistics: number of observations, mean, standard deviation (SD), median, minimum, and maximum. Categorical data were summarized with frequencies and percentages. Missing data were not imputed. Safety: The results of statistical analyses were reported using summary tables, figures, and data listings. The safety analyses (including demographic data included data from all subjects who received a dose of risperidone in RBP-7000. Continuous variables were summarized using descriptive statistics, and categorical variables were reported as frequency counts. Neurological assessments and clinical symptom assessments: The results of the assessments and change from baseline were reported as summary tables, figures, and data listings. The Positive Scale Score, Negative Scale Score, General Psychopathology Scale Score, and Total Score were summarized using descriptive statistics at initial screening, baseline, and at each post-baseline time point. All scores were analyzed separately. Pharmacokinetics: The PK parameters for risperidone, 9-hydroxyrisperidone, and total risperidone will be derived from the individual concentration versus time data using a non-compartmental approach with WinNonlin®, version 5.2 or higher. PK parameters at each dose were summarized using descriptive statistics, including arithmetic mean, median, SD, minimum, maximum, geometric mean, and %CV. Where applicable, the number missing (the number of individuals for which a calculated PK parameter could not be determined) was included in the appropriate tables as a unique count. The SC administration of the overall (Injection 1 and 3) PK parameters C_{max}, area under the plasma concentration-time curve of injection 1 or 3 from time zero to time tau (where tau=28 days (AUC_{tau}), and average of plasma concentrations calculated as AUC_{tau}/tau (tau = 28 days) (C_{avg}) for risperidone, 9-hydroxyrisperidone, and total risperidone were compared across each dose level to assess dose proportionality (ie, proportionality of a change in systemic exposure with a change in dose). Statistical analyses were done using a power model with mixed effects¹⁵ of the following general form: $\ln(PK) = \ln(\beta_0) + \beta_1 \cdot \ln(Dose) + e,$

where

PK was the pharmacokinetic parameter tested (eg, C_{max} or AUC)

$\ln(\beta_0)$ was the y-intercept,

β_1 was the slope (a value of $\beta_1 \approx 1$ indicates dose proportionality), and

ε was an error term

The estimate of β_1 and its 90% confidence interval (CI) was reported along with the associated p-value for proportionality. A significant difference from unity (1.0000) and lack of proportionality was defined a priori as $p < 0.05$.

Steady state was assessed for the oral and SC risperidone dose using Helmert's method,¹⁵ where a series of contrasts compared the mean concentration of the first time point to the pooled mean over all remaining time points. The second contrast compared the mean at the second time point to the pooled mean over all remaining time points. Testing continued until the contrast was not statistically significant at the 0.5 level. The first time point included in this last contrast was concluded to be the dosing interval on which steady state was attained.

Analytical Method

Method Type	LC/MS/MS	Matrix	Plasma
Analytes	- Risperidone - 9-hydroxyrisperidone - Total Risperidone (i.e., Risperidone + 9-hydroxyrisperidone)		

Validation	▪ Method validated prior to use	☒ Yes ☐ No
	▪ Method validation acceptable	☒ Yes ☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☒ Yes ☐ No
	▪ Quality control samples range acceptable	☒ Yes ☐ No
	▪ Chromatograms provided	☒ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	▪ Overall performance acceptable	☒ Yes ☐ No

Study Population:

- 18-65 year old patients with a confirmed diagnosis of paranoid, residual, or undifferentiated schizophrenia were considered for inclusion.
- N= 45 subjects (15 subjects got 2 mg oral risperidone and 60 mg SC RBP-7000; 15 subjects got 3 mg oral risperidone and 90 mg SC RBP-7000; and 15 subjects got 4 mg oral risperidone and 120 mg SC RBP-7000)

Diagnosis and Main Criteria for Inclusion:

Male and female subjects aged ≥ 18 to ≤ 65 years who had a confirmed diagnosis of paranoid, residual, or undifferentiated schizophrenia were considered for inclusion. Subjects also had to be clinically stable with no hospitalizations for acute exacerbations within 3 months of screening and a screening total PANSS score ≤ 60 for at least 60 days without hospitalization). Subjects had to have a body mass index between 18 and 33 kg/m², weigh at least 49.9 kg, and provide written informed consent to be considered eligible for inclusion in the study.

Table 1: Demography of subjects

	Category or Statistic	Cohort 1 RBP-7000 60 mg (N=15)	Cohort 2 RBP-7000 90 mg (N=15)	Cohort 3 RBP-7000 120 mg (N=15)	Overall (N=45)
Gender - n (%)	Male	8 (53.3)	11 (73.3)	14 (93.3)	33 (73.3)
	Female	7 (46.7)	4 (26.7)	1 (6.7)	12 (26.7)
Race - n (%)	White	7 (46.7)	4 (26.7)	4 (26.7)	15 (33.3)
	Black or African American	7 (46.7)	11 (73.3)	10 (66.7)	28 (62.2)
	American Indian or Alaska Native	0	0	0	0
	Asian	0	0	0	0
	Native Hawaiian or Other Pacific Islander	0	0	0	0
	Other	1 (6.7)	0	1 (6.7)	2 (4.4)
Ethnicity - n (%)	Hispanic or Latino	1 (6.7)	2 (13.3)	0	3 (6.7)
	Not Hispanic or Latino	14 (93.3)	13 (86.7)	15 (100.0)	42 (93.3)
CYP-2D6 Genotype - n (%)	Intermediate	3 (20.0)	0	1 (6.7)	4 (8.9)
	Poor	1 (6.7)	1 (6.7)	0	2 (4.4)
	Extensive	11 (73.3)	14 (93.3)	14 (93.3)	39 (86.7)
Age (yr)	n	15	15	15	45
	Mean	43.7	42.5	41.7	42.6
	SD	9.98	9.93	7.96	9.16
	Median	47.0	43.0	43.0	45.0
	Min, Max	27, 54	20, 54	28, 53	20, 54
Weight (kg)	n	15	15	15	45
	Mean	83.76	84.07	92.63	86.82
	SD	16.279	13.707	14.075	14.980
	Median	85.60	84.60	93.20	88.50
	Min, Max	49.6, 106.0	59.7, 107.2	64.0, 119.6	49.6, 119.6
Height (cm)	n	15	15	15	45
	Mean	172.19	175.50	174.41	174.03
	SD	8.731	11.137	8.346	9.372
	Median	172.70	172.70	172.10	172.70
	Min, Max	153.0, 183.0	160.0, 195.0	165.1, 191.7	153.0, 195.0
BMI (kg/m ²)	n	15	15	15	45
	Mean	28.13	27.35	30.43	28.64
	SD	4.487	4.176	3.911	4.309
	Median	29.80	27.10	31.20	29.50
	Min, Max	19.4, 34.2	20.0, 34.0	20.8, 34.5	19.4, 34.5

Inclusion Criteria:

Diagnosis and Main Criteria for Inclusion:

Male and female subjects aged ≥ 18 to ≤ 65 years who had a confirmed diagnosis of paranoid, residual, or undifferentiated schizophrenia were considered for inclusion. Subjects also had to be clinically stable with no hospitalizations for acute exacerbations within 3 months of screening and a screening total PANSS score ≤ 60 for at least 60 days without hospitalization). Subjects had to have a body mass index between 18 and 33 kg/m², weigh at least 49.9 kg, and provide written informed consent to be considered eligible for inclusion in the study.

1. Sex: male and female.
2. Age: ≥ 18 to ≤ 65 years.
3. Diagnosis of paranoid, residual, or undifferentiated schizophrenia as defined by Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision (DSM-IV-TR) criteria.
4. Status: clinically stable subjects defined as subjects with no hospitalizations for acute exacerbations within 3 months of screening and screening total PANSS score ≤ 60 .
5. Subjects with a body mass index (BMI) between 18.0 and 35.0 kg/m² and who weigh at least 49.9 kg.
6. Subjects who had given written informed consent.

Exclusion Criteria:

Subjects who met any of the following criteria were excluded from the study:

1. Subjects taking any risperidone sustained-release formulation within the 60 days prior to study screening.
2. Subjects taking the following concurrent medication/over-the-counter (OTC) products:
 - Inducers or inhibitors of CYP-2D6 within 14 days or 7 half-lives (whichever occurred last) prior to study screening
 - Bupropion, chlorpheniramine, cimetidine, clomipramine, doxepin, or quinidine within 30 days prior to study screening
 - Clozapine, phenothiazines, aripiprazole, haloperidol, or any other antipsychotic other than oral risperidone within 14 days prior to study screening
 - Selective serotonin reuptake inhibitors (SSRIs) (eg, fluoxetine, paroxetine) or serotonin-norepinephrine reuptake inhibitors (SNRIs) (eg, venlafaxine, desvenlafaxine, duloxetine) within 30 days prior to study screening
 - Opioids or opioid-containing analgesics within 14 days prior to study screening
 - Medications, in the addition to those listed above, which may have been expected to significantly interfere with the metabolism or excretion of risperidone and/or 9-hydroxyrisperidone, that may have been associated with a significant drug interaction with risperidone, or that may have posed a significant risk to subjects' participation in the study.
3. Subjects with a history of cancer (with the exception of resected basal cell or squamous cell carcinoma of the skin) unless they had been disease free for ≥ 5 years.
4. Subjects with another active medical condition or organ disease that may have either compromised subject safety or interfered with the safety and/or outcome evaluation of the study drug.
5. Subjects with evidence or history of a significant hepatic disorder that may have either compromised subject safety or interfered with the safety and/or outcome evaluation of the study drug. Individuals with acute hepatitis (including, but not limited to, hepatitis B or hepatitis C) or individuals with 1) total bilirubin >1.5 x the upper limit of normal (ULN) or 2) alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 x ULN were excluded.

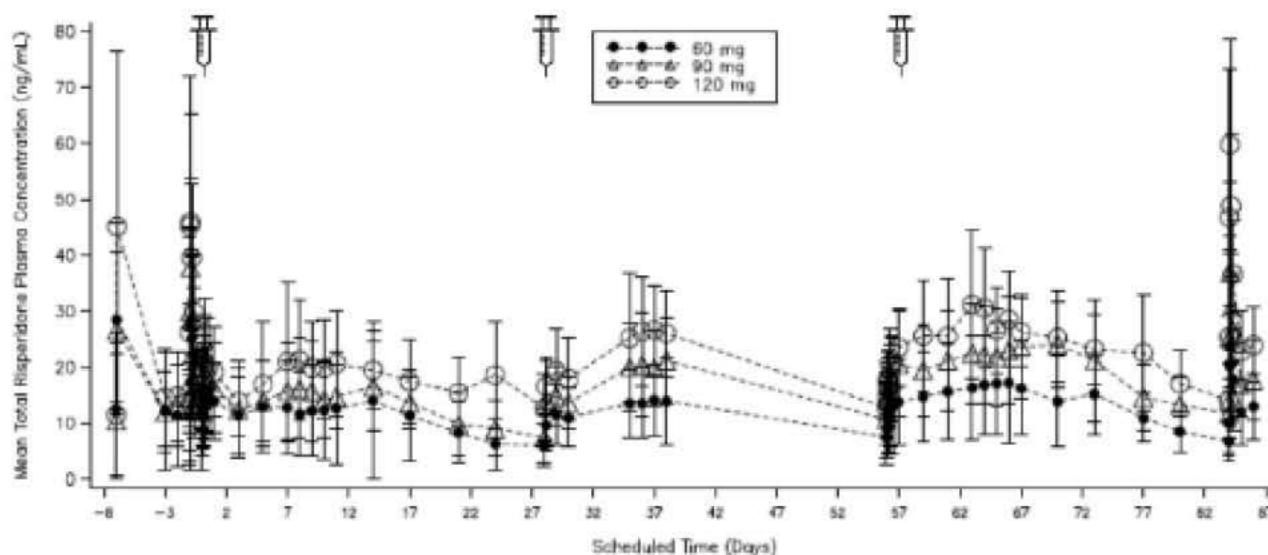
Subjects with hepatitis C antibody (HCA) and AST, ALT, or alkaline phosphatase (ALP) >2 x ULN and total bilirubin >1.5 x ULN were excluded.

6. Subjects with a history of renal disease or a creatinine clearance of less than 80 mL/min (as determined by the Cockcroft Gault formula) at screening.
7. Subjects with an international normalized ratio (INR) ≥ 2.0 at screening.
8. Subjects with a history of orthostatic hypotension, syncope, significant low white blood cell (WBC) count (ie, absolute neutrophil count $\leq 1.5 \times 10^9/L$), or drug induced leucopenia or other medical conditions including, but not limited to, history of heart attack (ie, myocardial infarction) or brain injury (ie, traumatic with loss of consciousness and/or cardiovascular accident) within a year of screening and clinically significant low blood pressure or arrhythmias as interpreted by the PI.
9. Subjects with Bazett's corrected QT interval (QTcB) >450 msec (male) or >470 msec (female) at screening. Subjects with a QTcB above these levels due to a benign right bundle branch block can be included in the study at the discretion of the PI.
10. Subjects who are known to have acquired immunodeficiency syndrome (AIDS) or to be human immunodeficiency virus (HIV) positive.
11. Subjects with suicidal ideation with intent and plan (C-SSRS affirmative answers to questions 4 and 5 of the ideation section) or suicide attempts within the last six months, as noted on the C-SSRS or subjects with uncontrolled depression, in the opinion of the PI.
12. Subjects with known diagnosis of type 1 or 2 diabetes or subjects with hemoglobin A1c (HbA1c) $\geq 7.0\%$ at screening.
13. Subjects who had participated in a clinical trial within 30 days prior to study screening.
14. Subjects with significant traumatic injury, major surgery, or open biopsy within 30 days prior to study screening.
15. Subjects who meet the DSM-IV-TR criteria for alcohol abuse or dependence within the last six months prior to screening.
16. Subjects with prior allergic reactions, sensitivities, or other known contraindications to any component of RBP-7000 (ie, risperidone, PLG, PLGH, or NMP).
17. Women with a positive pregnancy test at screening or women of childbearing potential, who are pregnant or lactating, seeking pregnancy, or failing to take adequate contraception methods (eg, an oral or injectable hormonal contraceptive, an approved hormonal implant or topical patch, an intrauterine device, a double barrier method, or a barrier plus spermicide). If a woman of childbearing potential became sexually active, she had to agree to use one of the contraception methods listed above. A woman of childbearing potential was defined as any female who was less than 2 years postmenopausal or had not undergone a hysterectomy or surgical sterilization, eg, bilateral tubal ligation, bilateral ovariectomy (oophorectomy). Females that were postmenopausal were to be confirmed by the follicle stimulating hormone (FSH) test at initial screening.
18. Subjects with a positive urine drug screen anytime through Day -1 for opioids, cocaine, amphetamines, methadone, cannabinoids, barbiturates, benzodiazepines,

Results

Mean Total Risperidone (i.e., Risperidone + 9-hydroxyrisperidone) Plasma Concentrations ($\pm$ SD) for All Cohorts from Day -7 to Day 87 (which includes the initial 7 days of oral risperidone followed by 3 monthly SC injections of RBP-7000) are shown below.

Figure 1: Mean ($\pm$ SD) Total Active Moiety Plasma Concentration-time Profile for All Cohorts From Day -7 to Day 87 (Study 09-0009)



SD=standard deviation

Days -7 to -1: oral risperidone

Days 1, 29 and 57: SC injections of RBP-7000

Days 85 to 87: oral risperidone

Note: Total active moiety is referred to as total risperidone on the y-axis.

Table 1: Geometric Mean (%CV) PK Parameters of Total Active Moiety Following Repeated SC Injections of 60, 90 or 120 mg of RBP-7000 (Study 09-0009)

Phase	Parameter	Statistic	RBP-7000 60 mg	RBP-7000 90 mg	RBP-7000 120 mg
Injection 1	C _{max} (Peak 1) (ng/mL)	N	15	15	15
		Geo Mean	16.1	17.7	21.7
		%CV	53.5	44.8	39.5
	C _{max} (Peak 2) (ng/mL)	N	15	15	15
		Geo Mean	17.3	20.5	30.4
		%CV	64.9	38.3	31.3
	T _{max} (Peak 1) (hr)	N	15	15	15
		Median	6.00	6.00	6.00
		Range	3.00, 23.8	2.00, 12.0	2.00, 24.0
	T _{max} (Peak 2) (hr)	N	15	15	15
		Median	168	264	192
		Range	23.8, 504	24.0, 579	24.0, 574
	C _{max} (Overall) (ng/mL)	N	15	15	15
		Geo Mean	19.3	22.0	31.9
		%CV	62.2	35.0	29.7
	C _{min} (Overall) (ng/mL)	N	15	15	15
		Geo Mean	4.61	6.31	8.52
		%CV	68.2	61.6	33.9
	C _{avg} (Overall) (ng/mL)	N	15	15	11
		Geo Mean	9.32	12.1	18.2
		%CV	59.7	43.5	24.6
	AUC ₀₋₂₄ (ng*hr/mL)	N	15	15	11
		Geo Mean	6264	8107	12232
		%CV	59.7	43.5	24.6

Phase	Parameter	Statistic	RBP-7000 60 mg	RBP-7000 90 mg	RBP-7000 120 mg
Injection 3	C _{max} (Peak 1) (ng/mL)	N	14	15	10
		Geo Mean	13.4	18.8	22.9
		%CV	52.9	45.9	28.6
	C _{max} (Peak 2) (ng/mL)	N	14	15	10
		Geo Mean	19.5	29.3	38.5
		%CV	49.0	35.2	24.9
	T _{max} (Peak 1) (hr)	N	14	15	10
		Median	17.9	24.0	24.0
		Range	6.00, 24.0	3.00, 24.1	6.00, 24.0
	T _{max} (Peak 2) (hr)	N	14	15	10
		Median	228	264	216
		Range	23.8, 408	24.0, 408	168, 504
	C _{max} (Overall) (ng/mL)	N	14	15	10
		Geo Mean	19.6	29.3	38.5
		%CV	49.4	35.2	24.9
	C _{min} (Overall) (ng/mL)	N	14	15	10
		Geo Mean	5.34	9.43	11.0
		%CV	49.0	35.5	23.5
	C _{avg} (Overall) (ng/mL)	N	14	14	10
		Geo Mean	12.1	18.1	22.9
		%CV	45.2	34.9	16.6
	AUC ₀₋₂₄ (ng*hr/mL)	N	14	14	10
		Geo Mean	8102	12144	15370
		%CV	45.2	34.9	16.6

Systemic Exposure Comparison of RBP-7000 With Oral Risperidone Tablets

Plasma exposure at steady-state was compared between oral risperidone (Day -1) and RBP-7000 (Injection 3) in each cohort of 15 subjects switching from 2 mg to 60 mg, from 3 mg to 90 mg and from 4 mg to 120 mg in Study 09-0009. Overall, similar average concentrations (C_{avg}) of risperidone and total active moiety were reached after daily administration of oral risperidone tablets and SC injection of RBP-7000 every 28 days under steady-state conditions. Additionally, the C_{max} values were generally higher after oral risperidone than after RBP-7000 SC Injections 1 and 3. There was less fluctuation at steady state for risperidone following SC RBP-7000 (145% to 157%) compared with oral risperidone (285% to 380%).

Table 2: Comparison of Risperidone Plasma Exposure (for both risperidone alone and total risperidone) Between Oral Risperidone and RBP-7000 in Each Cohort (Study 09-0009)

Treatment	Parameter	2 mg Oral/ 60 mg SC	3 mg Oral/ 90 mg SC	4 mg Oral/ 120 mg SC
Risperidone				
Oral Risperidone (Day -1)	C_{max} (ng/mL) (N=14-15)	13.0 (79.5)	17.1 (48.5)	21.0 (60.0)
	C_{min} (ng/mL) (N=14-15)	0.667 (223)	0.453 (219)	0.689 (120)
	C_{avg} (ng/mL) (N=10-11)	4.75 (132)	4.81 (104)	6.81 (61.1)
SC RBP-7000 (Injection 1)	C_{max} (Overall) (ng/mL) (N=15)	6.48 (100)	7.14 (67.8)	9.78 (41.7)
	C_{min} (Overall) (ng/mL) (N=15)	1.04 (97.9)	1.26 (122)	1.77 (67.1)
	C_{avg} (ng/mL) (N=11-15)	2.44 (103)	2.80 (95.2)	4.79 (49.5)
SC RBP-7000 (Injection 3)	C_{max} (Overall) (ng/mL) (N=10-15)	6.33 (84.9)	9.42 (90.4)	10.9 (47.4)
	C_{min} (Overall) (ng/mL) (N=10-15)	1.39 (72.4)	2.32 (98.3)	2.60 (43.2)
	C_{avg} (ng/mL) (N=10-14)	3.37 (87.6)	4.85 (94.8)	5.79 (43.3)
Oral Risperidone (Day 85)	C_{max} (ng/mL) (N=10-14)	11.9 (65.0)	17.4 (68.4)	30.0 (52.1)
	C_{min} (ng/mL) (N=10-14)	1.71 (109)	2.28 (102)	3.03 (79.6)
	C_{avg} (ng/mL) (N=10-14)	4.42 (89.9)	5.67 (97.8)	8.45 (64.6)
Total Active Moiety				
Oral Risperidone (Day -1)	C_{max} (ng/mL) (N=15)	28.6 (48.8)	34.2 (39.5)	49.2 (37.3)
	C_{min} (ng/mL) (N=15)	9.47 (87.7)	9.87 (54.4)	13.0 (40.1)
	C_{avg} (ng/mL) (N=15)	16.7 (67.2)	18.3 (42.3)	25.2 (34.6)
SC RBP-7000 (Injection 1)	C_{max} (Overall) (ng/mL) (N=15)	19.3 (62.2)	22.0 (35.0)	31.9 (29.7)
	C_{min} (Overall) (ng/mL) (N=15)	4.61 (68.2)	6.31 (61.6)	8.52 (33.9)
	C_{avg} (ng/mL) (N=11-15)	9.32 (59.7)	12.1 (43.5)	18.2 (24.6)

Treatment	Parameter	2 mg Oral/ 60 mg SC	3 mg Oral/ 90 mg SC	4 mg Oral/ 120 mg SC
SC RBP-7000 (Injection 3)	C _{max} (Overall) (ng/mL) (N=10-15)	19.6 (49.4)	29.3 (35.2)	38.5 (24.9)
	C _{min} (Overall) (ng/mL) (N=10-15)	5.34 (49.0)	9.43 (35.5)	11.0 (23.5)
	C _{avg} (ng/mL) (N=10-14)	12.1 (45.2)	18.1 (34.9)	22.9 (16.6)
Oral Risperidone (Day 85)	C _{max} (ng/mL) (N=10-14)	22.9 (43.5)	36.9 (41.5)	61.1 (30.4)
	C _{min} (ng/mL) (N=10-14)	7.43 (60.1)	10.8 (44.9)	18.2 (37.0)
	C _{avg} (ng/mL) (N=10-14)	14.6 (47.1)	22.6 (34.0)	33.5 (27.0)

C_{avg}=average plasma concentration over the dosing interval; C_{min}=minimum plasma concentration over the dosing interval; N=number of subjects
Geometric mean (%CV) are shown.

Dose Proportionality Assessment of RBP-7000

Dose proportionality across the 60 mg- to 120 mg range was assessed by injection number using the power model applied to log-transformed PK parameters. Systemic exposure (AUCtau, Cmax) to risperidone, 9-hydroxyrisperidone and total active moiety increased in an approximately dose-proportional manner. The slope was close to unity and the difference from unity was not statistically significant. After Injection 3 (steady-state), a 2-fold increase in dose resulted in a 1.7-fold increase in both Cmax and AUCtau for risperidone, in a 2.1-fold increase in Cmax and a 2.0-fold increase in AUCtau for 9-hydroxyrisperidone, and in a 2.0-fold increase in Cmax and a 1.9-fold increase in AUCtau for total active moiety.

Table 3: Statistical Analysis of Dose Proportionality (Study 09-0009)

Phase	PK Parameter	Slope Estimate (beta1) ^a	90% CI of Slope	P-value ^b
Risperidone				
Injection 1	AUC _{tau} (ng*hr/mL)	0.888	0.192, 1.585	0.788
	C _{max} (ng/mL)	0.570	-0.071, 1.211	0.266
Injection 3	AUC _{tau} (ng*hr/mL)	0.800	0.143, 1.457	0.610
	C _{max} (ng/mL)	0.816	0.155, 1.477	0.641
9-Hydroxyrisperidone				
Injection 1	AUC _{tau} (ng*hr/mL)	0.936	0.516, 1.355	0.798
	C _{max} (ng/mL)	0.788	0.438, 1.139	0.315
Injection 3	AUC _{tau} (ng*hr/mL)	1.016	0.686, 1.346	0.934
	C _{max} (ng/mL)	1.062	0.698, 1.426	0.777
Total Active Moiety				
Injection 1	AUC _{tau} (ng*hr/mL)	0.921	0.502, 1.339	0.751
	C _{max} (ng/mL)	0.701	0.328, 1.073	0.184
Injection 3	AUC _{tau} (ng*hr/mL)	0.934	0.590, 1.279	0.750
	C _{max} (ng/mL)	0.978	0.599, 1.358	0.924

CI=confidence interval

a Power Model: $\ln(PK) = \ln(\beta_0) + \beta_1 \ln(\text{Dose}) + C$, where PK is the pharmacokinetic parameter tested, $\ln(\beta_0)$ is the y intercept, β_1 is the slope and C is an error term.

b Significant difference from unity (1.0000), defined as $P < 0.05$.

Steady-State Analysis

Assessment of steady-state of risperidone, 9-hydroxyrisperidone and total active moiety for RBP-7000 SC doses of 60, 90 and 120 mg was carried out using Helmert's method applied to plasma concentration at trough (C_{trough}) values on Days 29, 57 and 85. A series of contrasts compared the mean C_{trough} value of the first time point with the pooled mean over all remaining time points for each dose level. The second contrast compared the mean C_{trough} value at the second time point with the pooled mean over all remaining time points for each dose level. Testing continued until the contrast was not statistically significant. The first time point included in this last contrast was concluded to be the dosing interval on which steady-state was attained. Steady-state was attained by Day 57 (end of dosing interval for second injection) for all analytes. Plasma concentrations after Injection 1 were close to steady-state levels for risperidone, 9-hydroxyrisperidone and total active moiety.

Table 4: Assessment of Steady-State of RBP-7000 (Study 09-0009)

Cohort	Day	N	Geometric LS Mean	Geometric LS Mean Ratio	90% CI of Ratio	P-value ^a
Total Active Moiety						
Cohort 1 RBP-7000 60 mg	Day 29	15	5.02	0.848	(0.593, 1.214)	0.444
	Day 57	14	5.95	1.012	(0.663, 1.544)	0.963
	Day 85	14	5.88			
Cohort 2 RBP-7000 90 mg	Day 29	15	6.50	0.636	(0.489, 0.826)	0.006
	Day 57	15	9.76	0.910	(0.670, 1.236)	0.606
	Day 85	14	10.73			
Cohort 3 RBP-7000 120 mg	Day 29	11	11.63	0.909	(0.711, 1.162)	0.514
	Day 57	10	12.02	0.883	(0.659, 1.183)	0.475
	Day 85	10	13.61			

CI=confidence interval; C_{trough}=plasma concentration at trough; LS=least squares; N=number of subjects

a An analysis of variance (ANOVA) was performed with the natural log-transformed C_{trough} as the dependent variable with day as fixed effect. Ratio was for comparing the geometric mean concentration of the corresponding study day with the geometric mean concentration pooled over all remaining days; P-value was for testing if the corresponding ratio of geometric LS means was 1.

Safety Results

Was there any death or serious adverse events? ☐ Yes ☒ No ☐ NA

- No deaths, no withdrawals due to AEs, and no AEs of severe intensity were reported. One SAE for psychotic disorder (increased psychosis) was reported in the 120 mg treatment group; this was considered to be not related to study drug.
- The most frequently reported TEAEs were for weight increased (26.7%, 60 mg group; 33.3%, 90 mg group; and 20.0%, 120 mg group) and headache (20.0%, 60 mg group; 20.0%, 90 mg group; and 6.7%, 120 mg group).
- No AEs were reported for increased blood prolactin levels.
- There were no instances where the severity of an injection site reaction was classified as severe and only three instances (one each for erythema, inflammation/swelling, and pain) where the severity was determined to be of moderate intensity.
- No significant differences were observed between the 3 dose groups on the change in body weight analysis or on the change in prolactin level analysis.

Overall Sponsor Conclusions

Pharmacokinetic Conclusions:

- Following oral risperidone administration on Day -1 (prior to RBP-7000 administration) and on Day 85 (after RBP-7000 administration), risperidone, 9-hydroxyrisperidone, and total risperidone exposure parameters AUC₀₋₂₄, C_{max}, and C_{avg} tended to increase with the increase in the oral risperidone dose from 2 mg to 4 mg
- Following oral risperidone at the three dose levels of 2 mg, 3 mg, and 4 mg, total risperidone median T_{max} was 2 hrs on Days -1 and 85, risperidone median T_{max} ranged from 1-2 hrs on Day -1 and was 2 hrs on Day 85, and 9-hydroxyrisperidone median T_{max} was observed later between 2 to 4 hrs on Day -1 and between 3 to 8 hrs on Day 85.
- Following oral risperidone dosing, geometric mean accumulation (Rac) ratios of AUC₀₋₂₄ and C_{max} ranged from 0.9 to 1.3 and 0.8 to 1.2, respectively, in total risperidone, 1.1 to 1.5 and 0.9 to 1.2, respectively, in risperidone, and 0.8 to 1.2 and 0.8 to 1.2, respectively, in 9-hydroxyrisperidone, indicating no apparent accumulation of total risperidone, risperidone, and 9-hydroxyrisperidone on Day 85 compared to Day -1.
- Post RBP-7000 injection 1, median T_{max} of the initial burst was 4 to 6 hrs in total risperidone, risperidone, and 9-hydroxy risperidone at all 3 dose levels and was prolonged after injection 3 to 18 to 24 hrs in total risperidone and 24 hrs in 9-hydroxy risperidone, while remained unchanged at 4 to 6 hrs in risperidone. Median T_{max} of secondary peak was observed between 8-12 days post dose in total risperidone, 6-10 days post dose in risperidone, and 8 to 10 days in 9-hydroxyrisperidone at all three dose levels following RBP-7000 injections 1 and 3.
- Exposure (AUC_{tau}, C_{max}, and C_{avg}) to total risperidone, risperidone, and 9-hydroxyrisperidone increased approximately proportionally with increasing multiple SC injections (1 and 3) of RBP-7000 in the dose range of 60 mg to 120 mg with 90% CI inclusive of 1, slope being close to unity, and the difference from unity not being statistically significant for all three parameters.
- Accumulation ratios (Rac; geometric mean) of overall AUC_{tau} and C_{max} following SC RBP-7000 injection 3 relative to injection 1, ranged from 1.2 to 1.6 and 0.97 to 1.3, respectively, in total risperidone; 1.2 to 1.7 and 0.9 to 1.3, respectively, in risperidone; and 1.2 to 1.6 and 0.99 to 1.3, respectively, in 9-hydroxyrisperidone across the dose range, with the highest ratio seen for 90 mg dose group, which indicated little/no apparent accumulation of total risperidone, risperidone, and 9-hydroxy risperidone.
- Average concentrations post oral risperidone on Days -1 and 85 were higher by about 1.5 to 2.0 fold compared to overall C_{avg} after RBP-7000 injection 1 but approximately similar to overall C_{avg} after RBP-7000 injection 3.
- Steady state was achieved by Day -3 for total risperidone and 9-hydroxy risperidone and Day -7 for risperidone after oral risperidone administration between Days -7 to -1. Steady state was achieved by Day 86 for total risperidone, risperidone, and 9-hydroxyrisperidone following oral risperidone administration from Day 85 to 87.

Neurological and Clinical Symptom Assessments Results and Conclusions:

- The PANSS positive scale total scores, PANSS general psychopathology scale total scores, and PANSS total scores demonstrated no obvious change from baseline over the RBP-7000 treatment period for the 60 mg and 90 mg groups, indicating that the baseline scores achieved by oral risperidone were maintained during the RBP-7000 treatment period. There was a slight improvement over the scores achieved by oral risperidone at baseline in the 120 mg group. The maximum improvement, a -2.5 change from baseline in the 120 mg group, was observed for the mean PANSS total scores.
- For the PANSS negative scale total score, there were notable differences among the dose groups at baseline. The 60 mg treatment group had the lowest mean PANSS negative scale total score at baseline, which was maintained over the RBP-7000 treatment period. This was consistent with findings reported in the literature that low doses of risperidone attenuate negative symptoms of schizophrenia with a low incidence of extra pyramidal symptoms.² Thus, patients with a high baseline negative PANSS score may benefit more from 60 mg, while patients with a high baseline positive PANSS score might benefit more from 120 mg.
- For the AIMS mean total scores, CGI mean scores, SAS mean total scores, and BAS mean total scores there was little or no change from baseline observed over the RBP-7000 treatment period and no obvious differences between the 3 RBP-7000 treatment groups.
- Three subjects reported suicidal ideation during the RBP-7000 treatment period, 1 in each of the three treatment groups. All three subjects had a previous history for suicidal ideation, and there were no actual suicide attempts during the study.
- Overall, treatment with RBP-7000 maintained or slightly improved the neurological and clinical symptom assessments after the baseline oral risperidone stabilization period.

Safety Results and Conclusions:

- No deaths, no withdrawals due to AEs, and no AEs of severe intensity were reported. One SAE for psychotic disorder (increased psychosis) was reported in the 120 mg treatment group; this was considered to be not related to study drug.
- The most frequently reported TEAEs were for weight increased (26.7%, 60 mg group; 33.3%, 90 mg group; and 20.0%, 120 mg group) and headache (20.0%, 60 mg group; 20.0%, 90 mg group; and 6.7%, 120 mg group).
- No AEs were reported for increased blood prolactin levels.
- There were no instances where the severity of an injection site reaction was classified as severe and only three instances (one each for erythema, inflammation/swelling, and pain) where the severity was determined to be of moderate intensity.
- No significant differences were observed between the 3 dose groups on the change in body weight analysis or on the change in prolactin level analysis.

Reviewer Comments

- *Study Design:* This was a Phase 2A, Open Label, Multiple Ascending Dose Study to assess the Safety, Tolerability and Pharmacokinetic Profile of RBP-7000. It was designed to evaluate the pharmacokinetic (PK) profiles of risperidone, 9-hydroxyrisperidone, and total active moiety after multiple SC injections of 60 mg, 90 mg, and 120 mg of risperidone in RBP-7000 in subjects on a stable oral risperidone dose of 2 mg, 3 mg, or 4 mg. The overall study design was acceptable since:
 - It was a multiple ascending dose study conducted at 3 dose levels of RBP-7000 (i.e., 60 mg to 90 mg to 120 mg) and provided the PK-bridging (i.e., relative bioavailability) to the oral risperidone doses of 2 mg, 3 mg, or 4 mg, respectively.
 - Adult male and female patients (18-65 years) with a confirmed diagnosis of paranoid, residual, or

undifferentiated schizophrenia were included.

- Adequate number of subjects (Total 45 with N= 15 per dose level) were included in the study
- The final to-be-marketed formulation of RBP-7000 was used in this study.

- Protocol deviation: No major protocol deviations were reported.
- Data Analysis (i.e., any outliers etc.): There were no outliers and the PK data from all subjects were included in the analysis.
- Bioanalytical Method: A validated bio-analytical methodology was used which was acceptable.
- Inclusion and Exclusion Criteria: The subject inclusion and exclusion criteria were acceptable since:
 - Adult male and female patients (18-65 years) with a confirmed diagnosis of paranoid, residual, or undifferentiated schizophrenia were included.
 - The study excluded subjects who took any medications which were expected to interfere with the metabolism or excretion of risperidone and/or 9-hydroxyrisperidone or that may have been associated with a significant drug interaction with risperidone. This ensured that the PK of RBP-7000 is not impacted by extrinsic factors.
 - The study also excluded Subjects with organ disease or organ impairments (i.e., hepatic or renal impairments) that may have either compromised subject safety or interfered with the evaluation of PK, safety of RBP-7000.

Pharmacokinetic findings: We agree with the sponsor's PK analysis and conclusions from the study. RBP-7000 (long acting SC injection) demonstrated linear PK from 60 mg to 120 mg dose level and reached steady state levels by the end of 2nd monthly dose.

Circulating levels of total active moiety (risperidone + 9- hydroxyl risperidone) was compared between oral and PERSERIS injection. As seen in Table below, overall similar average concentrations (C_{avg}) of total active moiety were reached after daily administration of oral risperidone tablets and SC injection of RBP-7000 every 28 days under steady-state conditions (i.e., 3 mg/day oral is similar to 90 mg PERSERIS and 4 mg/day oral is similar to 120 mg PERSERIS). Additionally, the C_{max} values were generally higher after oral risperidone than after RBP-7000 SC Injections. Overall, the range of exposure in oral dosing (i.e., C_{max} to C_{min}) completely bracketed the exposure range observed with PERSERIS injection. Thus, at 3 mg/day oral, the range (C_{max} to C_{min}) of exposure bracketed the exposure with 90 mg PERSERIS. Similarly, at 4 mg/day oral, the range (C_{max} to C_{min}) of exposure bracketed the exposure with 120 mg PERSERIS.

Table: Comparison of Total active moiety between Oral Risperidone and RBP-7000 in Each Cohort (Study 09-0009)

Treatment	Parameter	2 mg Oral/ 60 mg SC	3 mg Oral/ 90 mg SC	4 mg Oral/ 120 mg SC
SC RBP-7000 (Injection 3)	C _{max} (Overall) (ng/mL) (N=10-15)	19.6 (49.4)	29.3 (35.2)	38.5 (24.9)
	C _{min} (Overall) (ng/mL) (N=10-15)	5.34 (49.0)	9.43 (35.5)	11.0 (23.5)
	C _{avg} (ng/mL) (N=10-14)	12.1 (45.2)	18.1 (34.9)	22.9 (16.6)

Oral Risperidone (Day -1)	C_{max} (ng/mL) (N=15)	28.6 (48.8)	34.2 (39.5)	49.2 (37.3)
	C_{min} (ng/mL) (N=15)	9.47 (87.7)	9.87 (54.4)	13.0 (40.1)
	C_{avg} (ng/mL) (N=15)	16.7 (87.2)	18.3 (42.3)	25.2 (34.6)

Thus, a clear PK-bridge was established for *PERSERIS* to the approved generic oral risperidone (ANDA 78871 by Workhardt) but not the Listed Drug, *Risperdal*. However, based on the recommendation of 505(B)(2) committee it was determined to be acceptable.

Though PK bridging the study for *PERSERIS* was not conducted with the listed drug, we find it acceptable since:

- PK bridging study was conducted with an approved generic oral risperidone (ANDA 78871 by Workhardt) which is also an “AB” rated generic. Therefore, FDA has determined that this generic drug is not only bioequivalent to *RISPERDAL*, but also can be expected to have the same clinical effect and safety profile as *RISPERDAL*.
- A dedicated pivotal efficacy/safety study (Study RB-US-09-0010) shows that *PERSERIS* at both 90 mg and 120 mg dose level is efficacious, with statistically significant improvements in PANSS and CGI-S scores compared with placebo. Therefore, in addition to the PK-bridging there is an independent assessment of the efficacy of *PERSERIS* via the stand-alone efficacy study.

APPENDIX:

Details of U.S. approved ANDA 78871 by Workhardt (oral generic versions of RISPERDAL) used in the study

Two sites were used to conduct study RB-US-09-0009 (Sites 101 and 102). Accurate documentation is available for Manufacturer and NDC number for risperidone tablets used for for both sites. Both sites used generic risperidone manufactured by Wockhardt Ltd, and details including strength, NDC and lot number (for Site 102) are provided in [Table 1](#) and [2](#):

Table 1: Oral Risperidone Tablets Used at Site 101 (Wockhardt USA INC)

Strength	NDC Number	Lot Number
2 mg	64679-557-02	
3 mg	64679-571-04	
4 mg	64679-572-04	

Table 2: Oral Risperidone Tablets Used at Site 102 (Wockhardt Ltd)

Strength	NDC Number	Lot Number
2 mg	64679-557-02	DL12850
3 mg	64679-571-02	DL12853
4 mg	64679-572-04	DM11474

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PRAVEEN BALIMANE
07/11/2018

KEVIN M KRUDYS
07/16/2018

HAO ZHU
07/16/2018