CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Risperidone **PRIMARY REVIEWER**: Andre Jackson

NDA: 20272/20588 **TYPE:** NDA

FORMULATION: Oral Tablet **STRENGTH: 0.25mg, 0.5mg, 1 mg, 2mg, 3mg and 4mg**

APPLICANT: Johnson and Johnson Submission Dates:December 22, 2006

INDICATIONS: Schizophrenia , Bipolar Disorder

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EXECUTIVE SUMMARY

A study was done combining data from several centers in children and adolescents ages 5-18 yrs to determine if the pharmacokinetics were similar or different from that previously observed in adults. The study data from 3 study sites were analyzed by mixed effects modeling to identify any important covariates which impacted Risperidone pharmacokinetics in adolescents. These results were contrasted with those in adults. The study results indicated that weight normalized mean exposure, based upon trough levels prior to dosing, in children, adolescents and adults was comparable. Pharmacokinetics of the active moiety (risperidone + 9-hydroxy risperidone) and risperidone alone are comparable in children (less than 12 years), adolescents (12 to 17 years) and adults, after correction for body weight.. The recommended dose for schizophrenia is (b) (4) QD while that for bipolar should be initiated at 0.5 mg QD with adjustments of 0.5-1 mg/day as tolerated to a recommended dose of 2.5 mg/day. Based on the final results and the lack of a dose response no dose adjustments based on body weight are warranted in children and adolescents (between 10-17 years).

INTRODUCTION

Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. The absorption is not affected by food and thus risperidone can be given with or without meals.
Risperidone is metabolized by CYP2D6 to 9-hydroxy-risperidone, which has a similar pharmacological activity as risperidone. Risperidone plus 9-hydroxy-risperidone form the active antipsychotic fraction (active moiety). Another metabolic pathway of risperidone is N-dealkylation. Risperidone is subject to CYP2D6-mediated genetic polymorphism. Extensive metabolizers (EMs) convert risperidone rapidly into 9-hydroxy-risperidone, while poor metabolizers (PMs) convert it much more slowly. EMs, therefore, have

lower risperidone and higher 9-hydroxy-risperidone concentrations than PMs. The PK of the active moiety, after single and multiple doses are similar in EMs and PMs of CYP2D6.

After oral administration to psychotic patients, risperidone is eliminated with a half-life of about 3 hours. The elimination half-life of 9-hydroxy-risperidone and of the active moiety is 24 hours. Steady-state of risperidone is reached within 1 day in most patients. Steady state of 9-hydroxy-risperidone is reached within 4-5 days of dosing. Risperidone plasma concentrations are dose-proportional in the dose-range of 1 to 16 mg daily (0.5 to 8 mg b.i.d.).
Risperidone is rapidly distributed. The volume of distribution is 1 to 2 L/kg.
In plasma, risperidone is bound to albumin and alpha1-acid glycoprotein.
The plasma protein binding of risperidone is 88%, while that of 9-hydroxy-risperidone is 77%.

SUMMARY

Based on the current population PK analysis, pharmacokinetics of the active moiety and risperidone are comparable in children (less than 12 years), adolescents (12 to 17 years) and adults, after correction for body weight. Based on the final results of the covariate analysis for the active moiety, no dose adjustments based on body weight are warranted in children and adolescents (between 10-17 years).

COMMENTS TO MEDICAL REVIEWER

1. Pharmacokinetics of the active moiety (risperidone + 9-hydroxy risperidone) and risperidone alone are comparable in children (less than 12 years), adolescents (12 to 17 years) and adults, after correction for body weight.
2. Because of the lack of a dose response fixed dosing regimens are acceptable to OCP for schizophrenia or for bipolar I disorder.

OBJECTIVE OF THE ANALYSIS

The objectives of the population PK analysis of risperidone and the active moiety were:
• To get estimates of the typical PK parameters of risperidone and the active moiety in the target populations and of their inter- and intraindividual variability;
• To evaluate the effect of patients' demographic characteristics and other covariates on the PK of risperidone and the active moiety;
• To compare the PK of risperidone and the active moiety between children/adolescents and adults.

METHODS

Overview of Study Designs

The current analysis consisted of modeling the PK of risperidone and of the active moiety separately, in a pooled database including children, adolescents and adults with bipolar I disorder or schizophrenia following oral administration of risperidone. The following studies were used:

STUDY #	STUDY	DEMOGRAPHICS	FORMULATION
1	RIS –BIM-301	CHILDREN AND ADOLESCENTS (10-17 YRS)	0.25MG-4 MG TABLETS
2	RIS-USA-231	ADOLESCENTS (13-17 YRS)	0.1 MG/L AND 1.0 MG/ML SOLN
3	RIS-USA-160	CHILDREN AND ADOLESCENTS (5 to <12 YRS) (12 to < 18 YRS)	0.01 TO 0.08 mg/kg (b) (4) TABLETS
4	RIS-USA-239	ADULTS	TABLET
5	RIS-IND-2	ADULTS	TABLET
6	RIS-IND-25	ADULTS	(b) (4) TABLET
7	RIS-P01-103	ADULTS	TABLET
8	RIS-RSA-5	ADULTS	TABLET
9	R076477-SCH-102	ADULTS	TABLET

The 1-mg/mL oral solution is bioequivalent to the marketed 1-mg tablet. The marketed 1-mg tablet, when given as 2x1 mg or 4x1 mg tablets, is bioequivalent to marketed 2-mg and 4-mg risperidone tablets. Bioequivalence was also shown between the 0.5-mg research tablet (when given as 2x0.5 mg tablets) and the 1-mg marketed risperidone tablet.

ASSAY VALIDATION

ANALYTICAL

Two moieties were analyzed Risperidone and 9-hydroxy-risperidone.

Risperidone and active moiety (Risperidone + 9-hydroxy-risperidone) levels were reported.

Study RIS-BIM-301- (STUDY 1) CHILDREN AND ADOLESCENTS (10-17 YEARS)

Objective: assess the efficacy, safety, tolerability and PK of two dosage ranges of risperidone monotherapy (0.5 to 2.5 mg/day and 3 to 6 mg/day) versus placebo, and explore the PK/PD relationship to efficacy and safety.

Population: 169 enrolled (58 placebo and 101 risperidone) children and adolescents (10-17 years) with a DSM-IV diagnosis of Bipolar I disorder experiencing a manic or mixed episode (Young Mania Rating Scale ≥20).

Design: randomized, placebo-controlled, double-blind, 3-arm, multicenter Phase 3 study. The study was composed of a screening phase (with a

possible washout period) and a 3-week double blind treatment phase. Subjects were randomized to receive 1 of 3 oral treatments: placebo tablets, risperidone tablets 0.5 to 2.5 mg (Dosage Group A), or risperidone tablets 3 to 6 mg (Dosage Group B). Study medication was dosed once daily and titrated to reach the minimum of their assigned target dosage of 0.5 mg/day (Dosage Group A) and 3 mg/day (Dosage Group B) by Day 7. Further increases in the maximally tolerated dosage were to be made by Day 10. After Day 10, adjustments to the dosage were not to be made and subjects were to be maintained within the target dosage (0.5-2.5 mg/day for Dosage Group A and 3-6 mg/day for Dosage Group B) range from Days 10 to 21.

Plasma concentrations of the active moiety were calculated as the sum of risperidone and 9-hydroxy-risperidone. The relationship between the predose steady-state plasma concentrations of the active moiety and risperidone were used to determine the attainment of steady-state.

Plasma samples were taken on Day 14, one sample before drug intake and one at least 1 hour after. On Day 7 and on Day 21, one sample was collected before study drug intake.

(Day 21) and its efficacy parameter YMRS and safety parameters (QTcLD and SAS) was explored graphically via scatter plots.

Subjects who gave permission for DNA sample collection were genotyped for CYP2D6. At Day 7, the daily dose of risperidone was 0.5 mg and 2.0 mg in the Dosage Group A and B, respectively. At Day 14 and 21, the median daily dose of risperidone was 2.5 mg/day (range: 0.5-2.5 mg/day) for Dosage Group A and 5.0-6.0 mg/day (range 3.0-6.0 mg/day) in Dosage Group B.

STUDY RIS USA 301-STUDY 1
First Sampling Date: January 6, 2004

Study dates:

	starting date	completion date
Sample receipt (Experimental starting date):		(b) (4)
Sample analysis:		

(b) (4)

STUDY RIS-USA-231 (STUDY 2) ADOLESCENTS

Objective: assess the efficacy, safety, tolerability and PK of risperidone during 8 weeks randomized, double-blind, parallel-group, multicenter study in adolescents (aged 13-17 years) with schizophrenia and suffering from an acute episode of treatment and to explore the PK/PD relationship to efficacy and safety.

Population: 279 enrolled adolescents with schizophrenia.

Design: randomized, double-blind, parallel-group, multicenter Phase 3 study.

Subjects were randomized to receive 1 of 2 risperidone treatments: low dose (<50 kg: 0.007-0.012 mg/kg/day; >50 kg: 0.35-0.6 mg/day) and high dose (<50 kg: 0.07-0.12 mg/kg/day; >50 kg: 3.5-6 mg/day) (dose range: post protocol amendment 3). Study medication was provided as an oral solution containing risperidone at concentrations of either 0.1 mg/mL or 1 mg/mL. Study

medication was dosed once daily (o.d.) or twice daily (b.i.d.) and titrated to the target dosage by Day 12.

The relationship between the predose steady-state plasma concentrations of the active moiety (Day 56) and selected efficacy parameters (PANSS and CGI) and safety parameters (QTcLD and SAS) was explored graphically via scatter plots. Subjects who gave permission for DNA sample collection were genotyped for CYP2D6.

Limited blood samples were collected at Days 28 (pre- and post dose) and 56 (predose) for the determination of plasma concentrations of risperidone and 9-hydroxy-risperidone in patients treated with risperidone. Plasma concentrations of the active moiety were calculated as the sum of risperidone and 9-hydroxy-risperidone. Post dose samples were collected between 1-2 hours after drug intake; only predose samples collected between 6-48 hours (b.i.d. regimen) or 8-36 hours (o.d. regimen) were included in the analysis.

There were two additional adult studies that were used to compare with the adolescent and child data. These were subjects with bipolar disorder (Studies RIS-USA-23928 and RIS-IND-229) with sparse sampling.

Analytical
Study BIM-231-STUDY 2
First Sampling Date: May 14, 2001

Study dates:

	starting date	completion date
Sample receipt (Experimental starting date):		(b) (4)
Sample analysis:	(b) (4)	

STUDY RIS-USA-160 (STUDY 3)- CHILDREN AND ADOLESCENTS

Objective: determine the PK and safety of risperidone (0.01 to 0.08 mg/kg/day, b.i.d. dosing), 9-hydroxy-risperidone and of the active moiety at steady state.

Population: 24 children and adolescents (aged 5 years to less than 18 years).

Design: open-label, multicenter, Phase 1 study with 2 periods: screening/run-in (7 to 30 Days) i.e., a maintenance dose of risperidone and a single day for PK monitoring and check-out.

The subjects were divided into 2 groups: 12 children (aged 6-11 years and weighing between 20-61 kg) and 12 adolescents (aged 12-16 years and weighing between 33-92 kg). A complete urinary output was also collected: from 0 to 6 hours, and from 6 to 12 hours after dosing. Subjects were phenotyped for CYP2D6 using the risperidone metabolic ratio (i.e., $AUC_{TSS,risperidone}/AUC_{TSS,9\text{-}hydroxy\text{-}risperidone}$), and genotyped for CYP2D6. Subjects with a risperidone metabolic ratio higher than 1 were categorized as PMs for CYP2D6, and subjects with a ratio of less than 1 as EMs for CYP2D6. The daily dose of risperidone ranged between 0.25 - 1.5 mg b.i.d. for children, and between 0.75 - 1.75 mg b.i.d. for adolescents, or expressed per kg body weight equivalent to a range of 0.024 - 0.074 mg/kg/day (mean 0.049 mg/kg/day) for children, and 0.016 - 0.076 mg/kg/day (mean 0.041 mg/kg/day) for adolescents.

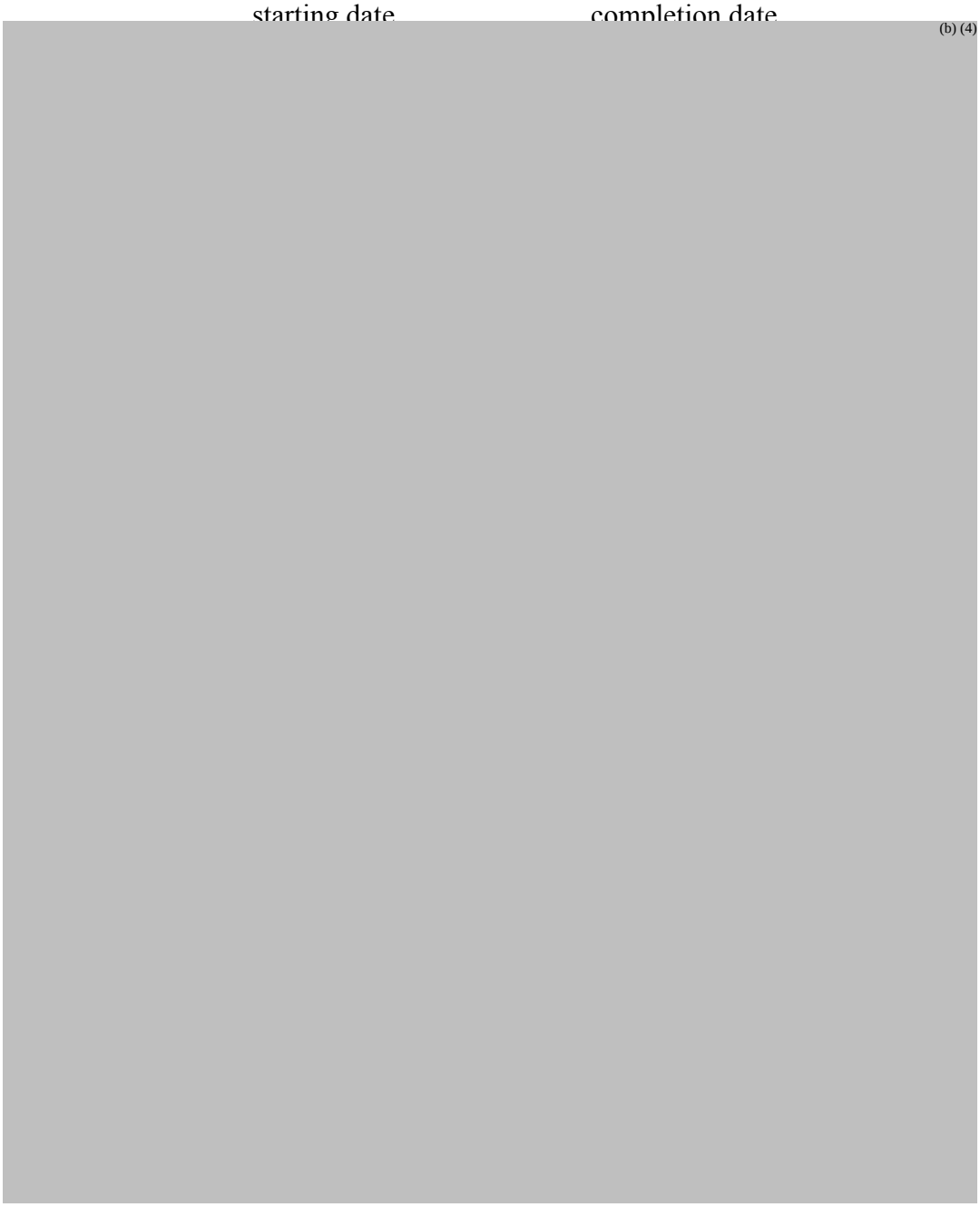
Blood samples were collected immediately before (0 hour), and 2, 4, 8, and 12 hours after the morning dose on the PK monitoring day.

ANALYTICAL

STUDY RIS-USA-160-STUDY 3

starting date completion date

(b) (4)



STUDY RIS-USA-239-(STUDY 4)-ADULTS

Objective: assess the efficacy, safety, tolerability and PK of dosage range (1

to 6 mg/day) of risperidone compared to placebo during 3 weeks of treatment, and explore the PK/PD relationship.

Population: 259 treated (125 placebo, 134 risperidone) adult patients with Bipolar I Disorder who are suffering a manic episode.

Design: randomized, placebo-controlled, double-blind, parallel-group, multicenter Phase 3 study. Flexible doses of risperidone (1 to 6 mg/day) or placebo were administered. Patients were titrated and evening doses were adjusted through the end of treatment period. Only subjects randomized to the risperidone treatment group were taken into account in the current analysis.

ANALYTICAL

STUDY RIS-USA-239-STUDY 4

Trial dates: Start: 29 November 2000 | end: 23 May 2002

	starting date	completion date
Sample receipt:	(b) (4)	
Sample analysis:		

(b) (4)

STUDY RIS-IND-2 (STUDY 5) ADULTS

Objective: To assess the efficacy and safety of risperidone dosage range (1 to 6 mg/day)compared with placebo during 3 weeks of treatment in subjects with Bipolar I disorder suffering a manic or mixed episode. The primary efficacy measure was the change in mean YMRS total score from baseline to endpoint.

Population: 290 treated (144 placebo, 146 risperidone) adult patients with Bipolar I Disorder who are suffering a manic or mixed episode.

Design: randomized, placebo-controlled, double-blind, parallel-group, multicenter Phase 3 study. A flexible doses of risperidone (1 to 6 mg/day) or placebo were administered, after dose escalation. Randomized patients were stratified by the presence or absence of psychotic features at baseline and by center. Following randomization and the initiation of double-blind study drug therapy, a minimum of 7 full days of inpatient hospitalization was required. Subjects assigned to the risperidone treatment group received a single 3-mg dose on Day 1.

Table 3-3: Dosing Schedule for the Double-Blind Phase (RIS–IND-2)

Day	Placebo (mg/day)	Risperidone (mg/day)
1	0	3
2	0	2-4
3	0	1-5
4-21	0	1-6

Sampling

Sparse PK samples were taken on week 1 and week 3. All blood for PK samples were drawn immediately before the intake of trial medication (predose), except that on Day 7 a second sample was to be drawn post-dose at least 1 hour after the first withdrawal.

ANALYTICAL

RIS-IND-2: STUDY=5

Trial dates: Start: 12 Mar 2001 | end: 24 Dec 2001

Study dates

Starting date Completion date

Sample receipt (b) (4)

Sample analysi

(b) (4)

STUDY RIS-IND25-(STUDY 6)- ADULTS

Objective: To determine the oral bioequivalence of a single dose of 2 mg risperidone given as a (b) (4) tablet (F556) with that of the 2-mg conventional RISPERDAL tablet (F37) in healthy volunteers.

The primary objective was to show bioequivalence with respect to

risperidone and active moiety. Additionally, the bioavailability of 9-hydroxyrisperidone was compared.

TRIAL DESIGN AND PLAN

This was an open-label, randomized, phase I trial with a 2-treatment, 2-period crossover design balanced for residual effect in healthy subjects.
In total, 40 subjects (22M/18F)were to receive a single dose of 2 mg risperidone as a [redacted] (b) (4) tablet (Treatment A) and as a RISPERDAL tablet (Treatment B). A washout period of at least 10 days was foreseen between both treatments (max. 3 weeks). Each intake was to be followed by a 96-hour evaluation period for pharmacokinetics and safety assessments.

DOSING AND PK SAMPLING

Table 3-1: Flowchart

Trial day [a]	Time	Drug intake [b]	PK blood sample	Other
Pretrial day (Screening)				Physical examination, laboratory safety, ECG, BP, HR, pregnancy test
Day –1 (Baseline)				ECG, HR, BP, drug screen, urine pregnancy test
Day 1	predose		X	HR, BP, Laboratory safety [c]
	0 h	X		
	0.25 h		X	
	0.5 h		X	
	1 h		X	
	1.5 h		X	
	2 h		X	
	3 h		X	
	4 h		X	HR, BP, Standard meal [d]
	5 h		X	
	6 h		X	
	8 h		X	HR, BP
	12 h		X	
	16 h		X	
Day 2	24 h		X	HR, BP
	32 h		X	
Day 3	48 h		X	
Day 4	72 h		X	
Day 5 (end of the session)	96 h		X	Physical examination, laboratory safety, ECG, BP, HR [e]

a) In each session, Treatment A or B was administered according to the randomization scheme.

b) Treatment A: single oral administration of a 2-mg risperidone [redacted] (b) (4) tablet.
Treatment B: single oral administration of a 2-mg risperidone RISPERDAL tablet.

c) Laboratory safety sample only predose Session 1.

d) All meals served at the trial centre were scheduled and standardized on Day 1. However, only the first meal following drug intake is mentioned in the flowchart.

e) All these assessments were performed at the end of the trial only.

ANALYTICAL

RIS-IND-25: (STUDY 6)
Trial dates: Start: 07 November 2000 | end: 19 January 2001

(b) (4)

Sample receipt:
Analytical Study Plan:
Sample analysis:

(b) (4)

STUDY RIS-P01-103-(STUDY 7)- ADULTS

Objective: The primary objective of this study was to demonstrate the bioequivalence, with respect to risperidone and its active moiety, of a single oral dose of risperidone given as a 4-mg orally-disintegrating tablet and as a 4-mg conventional RISPERDAL tablet.

Study Design

This was a single-center, Phase 1, open, randomized, 2-way crossover bioequivalence study in 40 subjects with schizophrenia or schizoaffective disorder. The study consisted of 2 treatment periods, 5 days per period, separated by a washout period of at least 10 days between administration of study drug on Day 1 of Period 1 and administration of study drug on Day 1 of Period 2 The study duration was approximately 6 weeks (including the screening period). Subjects remained in the study facility for approximately 18 days.

DOSING AND PK SAMPLING

Table 1. Time and event schedule for study RIS-PO1-RO3

(Study RIS-P01-103)

Study Day	Time	Drug Intake[a]	PK Blood Sampling	Other Procedures[b]
Prestudy (screening)	≤3 weeks before Day 1 of Period 1			Informed consent signed; inclusion/exclusion criteria; record body weight, height, demographic information; physical examination; psychiatric/medical history; smoking history; blood samples collected for hematology and serum chemistry; urine sample for urinalysis; breath alcohol test; serum pregnancy test for women; urine drug test; ECG; BP, HR recorded
Day -3				Admission to study center
Day -1 or Day 1 of Period 1, predose				Breath alcohol test; urine drug test; urine pregnancy test for women
The procedures below occur in both Period 1 and Period 2[b]:				
Day 1	predose		X	Start of semi-recumbent position
	0 h	X[c]		
	0.25 h		X	
	0.5 h		X	
	0.75 h		X	
	1 h		X	
	1.5 h		X	
	2 h		X	End of semi-recumbent position.
	3 h		X	
	4 h		X	Standard meal served[d]
	5 h		X	
	6 h		X	
	8 h		X	
	12 h		X	
Day 2	16 h		X	
	24 h		X	
	36 h		X	
Day 3	48 h		X	
Day 4	72 h		X	
Day 5 of Period 1	96 h		X	
End of Study				
End of Study (Day 5 of Period 2 or Early Termination)	96 h		X	Physical Examination; blood samples collected for hematology and serum chemistry; urine sample collected for urinalysis; ECG; BP and HR recorded; discharge

[a] A 10-day washout period separated the dose of study medication on Day 1 of Period 1 from the dose administered on Day 1 of Period 2.

[b] Adverse events were recorded and monitored beginning with the first study-related procedure through the posttreatment procedures at the end of the study. Concomitant therapies were recorded throughout the study.

[c] One treatment was given in each period, either Treatment A (1 oral conventional RISPERDAL 4-mg tablet) or Treatment B (1 risperidone 4-mg orally-disintegrating tablet). Subjects fasted for 10 hours before drug administration and continued fasting until 4 hours after dose administration. They refrained from water intake for 2 hours before until 2 hours after dose administration.

[d] All meals served on Day 1 were scheduled and standardized. Only the first meal after drug administration is cited.

ANALYTICAL

RIS-P01-103: STU=7
DATE STUDY INITIATED:
21 June 2003
DATE STUDY COMPLETED:
21 July 2003

	Starting date	Completion date
Sample receipt:	(b) (4)	
Analytical Protocol:		
Experiment (sample analysis):		

(b) (4)

STUDY RSA-5-(STUDY 8)- ADULTS

OBJECTIVE:

The primary objective of this study was to demonstrate the bioequivalence with respect to risperidone and active moiety between a single oral dose of 4 mg risperidone given as a 4 mg tablet manufactured (b) (4) and as a 4 mg RISPERDAL currently marketed tablet.

Study Design

This was a Phase I, open, randomized, 2-way cross-over bioequivalence study in 36 subjects with schizophrenia or schizoaffective disorder.
The subjects received in a randomized manner a single oral dose of 4 mg risperidone on two occasions:
- Treatment A: RISPERDAL marketed tablet;
- Treatment B: tablet manufactured (b) (4). The pharmacokinetics of risperidone were assessed up to 96 hours post dosing. The wash-out period between treatments was at least 10 days.
The duration of the study was approximately 6 weeks

DOSING AND PK SAMPLING

Table 1a. Time and event schedule for study RIS-RSA-5

(Protocol: RIS-RSA-5)

Study day	Time	Drug intake	Blood sample for pharmacokinetics	Other
Pre-study day (screening)				Screening[a)]
In both study periods				
Day –3				Admission to the study center.
Day –1 or Day 1 predose				Drug and alcohol screen and urine pregnancy test.
Day 1	predose		X	Start of semi-recumbent position.
	0 hour	X[b)]		
	0.25 hour		X	
	0.5 hour		X	
	0.75 hour		X	
	1 hour		X	
	1.5 hours		X	
	2 hours		X	
	3 hours		X	
	4 hours		X	End of semi-recumbent position. Standard meal.
	5 hours		X	
	6 hours		X	
	8 hours		X	
	12 hours		X	
Day 2	16 hours		X	
	24 hours		X	
	36 hours		X	
Day 3	48 hours		X	
Day 4	72 hours		X	
Day 5	96 hours		X	
End of study				
End of study (Day 5, period 2 or premature discontinuation)				End of confinement, lab safety, ECG, BP/HR
Blood samples and blood volume				
Number of samples			19/period 38 total	2*lab safety, 1*HCG (females)
Total volume			190 mL	215.5 mL[1)]

a) Within 3 weeks of dosing. Subject characteristics, physical examination (including weight and height), medical history, cardiovascular safety (BP, HR, ECG), lab safety (blood: 4.5 mL [hematology] + 6 mL[1)] [biochemistry], urinalysis), pregnancy test (4.5 mL, screening only), urine drug screen, overall eligibility.

b) A single oral dose of 4 mg of risperidone.

RIS-RSA-5: STU=8

DATE STUDY INITIATED:
22 April 2002
DATE STUDY COMPLETED:
10 July 2002

Study dates

Starting date Completion date
Sample receipt: (b) (4)
Analytical Stud
Sample analysis

(b) (4)

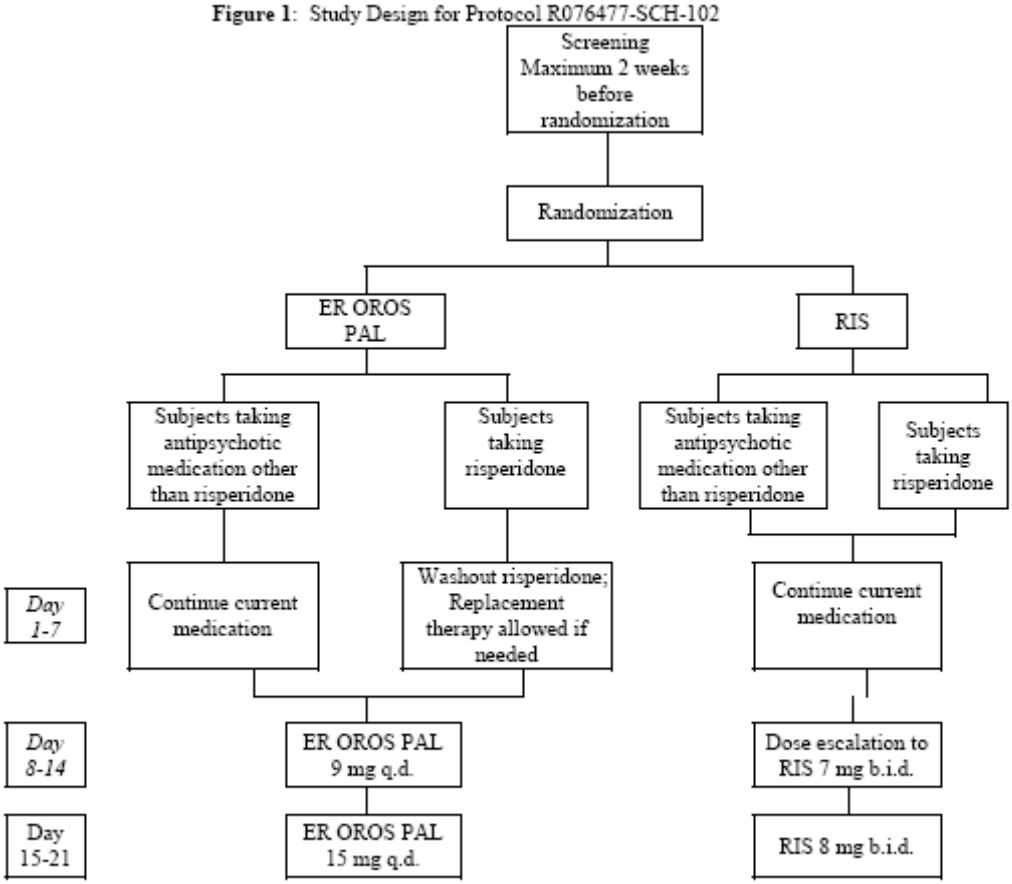
STUDY R076477-SCH-102 STUDY 9- ADULTS

OBJECTIVE:

The primary objectives of the study were to compare the steady-state pharmacokinetics of paliperidone after oral administration of 15 mg ER OROS paliperidone once daily with the steady-state pharmacokinetics of paliperidone after oral administration of 8 mg IR risperidone twice daily; and to explore the dose-proportionality of 9 mg and 15 mg ER OROS paliperidone.

Study Design

Figure 1: Study Design for Protocol R076477-SCH-102



A dose of 15 mg ER OROS paliperidone once daily was chosen because this is the highest dose of ER OROS paliperidone that is proposed for use in the Phase 3 studies. The dose of risperidone was chosen because 8 mg twice daily is the highest registered dose of risperidone. Study medication was administered after a (high-fat) breakfast as in a previous study the exposure to paliperidone increased by circa 10% after intake of food.[1] Food does not affect the pharmacokinetics of risperidone. The study was done in 17 subjects (17 M/2F)

DOSING AND PK SAMPLING

- Subjects randomly assigned to the risperidone treatment group who were taking prestudy antipsychotics other than risperidone received a 1-mg risperidone tablet every 12 hours on Day 8. On Days 9 through 14, doses of risperidone were increased by 1 mg every 12 hours daily, so that on Day 14, subjects received 7 mg every 12 hours as shown in Table 2.

Table 2: Dosage Escalation (Prestudy Other Antipsychotics) (Study R076477-SCH-102)

Day	Dosing Regimen	Total Daily Dose
8	1 mg b.i.d.	2 mg
9	2 mg b.i.d.	4 mg
10	3 mg b.i.d.	6 mg
11	4 mg b.i.d.	8 mg
12	5 mg b.i.d.	10 mg
13	6 mg b.i.d.	12 mg
14	7 mg b.i.d.	14 mg

- For subjects randomly assigned to the risperidone treatment group taking prestudy risperidone, the dose was divided into twice daily doses (every 12 hours) starting on Day 8. Subjects received escalating doses of risperidone (according to Table 3) from at least 3 mg every 12 hours on Day 8 up to 7 mg every 12 hours on Day 14. Study drug was given in equal doses every 12 hours, as 1-mg tablets.

Table 3: Dosage Escalation (Prestudy Risperidone) (Study R076477-SCH-102)

Day	Dosing Regimen	Total Daily Dose
8	3 mg b.i.d.	6 mg
9	3 mg b.i.d.	6 mg
10	3 mg b.i.d.	6 mg
11	4 mg b.i.d.	8 mg
12	5 mg b.i.d.	10 mg
13	6 mg b.i.d.	12 mg
14	7 mg b.i.d.	14 mg

(e.g., a subject is on a prestudy risperidone daily dose of 6 mg; subject will receive doses, as above, from Days 8 through 14.)

- All subjects randomly assigned to the risperidone treatment group received 8 mg risperidone (2 tablets of 4 mg) every 12 hours on Days 15 to 21.

Drug Sampling

Immediately before dosing on Day 8 (baseline), Days 11 to 14, and Days 18 to 21; at 2, 4, 6, 9, 12, 16, 19, 22, and 24 hours after dosing on Day 14; and at 2, 4, 6, 9, 12, 16, 19, 22, 24, 27, 30, 34, 40, 48, 72, 96, and 120 hours after dosing on Day 21 for subjects receiving ER OROS paliperidone; immediately before the morning dose on Day 8 (baseline) and Days 18 to 21; and at 1, 2, 3, 4, 6, 8, 12, 13, 14, 15, 16, 24, 36, 48, 72, 96, and 120 hours after the morning dose on Day 21 for subjects receiving risperidone.

R076477-SCH-102: STUDY=9

Study dates:

	starting date	completion date
Sample receipt:	(b) (4)	
Sample analysis:		

(b) (4)

PHARMACOKINETIC ANALYSIS

At this stage, the full dataset was split into an index dataset and a qualification dataset: 70% of the subjects of each study were randomly selected for the

index dataset, and the remaining 30% constituted the qualification dataset.

When concomitant medication was present one day before the PK sampling day, the flag for concomitant medication was set to 1 (present) on the PK day even though the concomitant medication was stopped the day before.

Planned Analysis for Risperidone and the Active Moiety

The analysis consisted of two separate population PK analyses, one for risperidone and one for the active moiety in the pool of children, adolescent and adult subjects after oral administration of risperidone. For both risperidone and the active moiety (i.e., sum of the risperidone + 9 hydroxy risperidone plasma levels), the population PK analysis consisted of the following steps:

- An exploratory analysis of concentration-time data and covariates; identification of potential outliers. At this stage, prior PK and other relevant information to support the structural model selection was used, particularly, the results of previous modeling activities.
- Using the index dataset, evaluation of a base and a covariate model (demographics, body size variables, and study).
- Model qualification and model adjustment if needed.
- Estimation of the model on the full dataset and exploration of the effect of concomitant medications.
- Estimation of the final model, with the effect of concomitant medications.

IDENTIFICATION OF OUTLIERS

Data points were considered as potential outliers if they substantially deviated from adjacent points in the concentration-time profiles.
Final outlier identification was performed after selecting a structural model and was based on the graphical exploration of individual and population residuals (weighted and non-weighted). After the model development was complete, the final model was fitted to the entire data set with all excluded outliers in, and the results were compared.

Outlier identification in the sparse data set was performed through a different approach. Initially, posterior predictions were generated for each individual by fitting the structural model to the sparse data. Individual and population residuals (weighted and non-weighted) were analyzed graphically and potential outliers were identified. For individuals with outliers, the observations were plotted against the time since the last dose (one subject per panel) and were superimposed with the corresponding individual and population predictions. The outliers that deviated both in terms of residuals

and observations were finally identified and excluded unless other factors (like co-administration of other drugs) caused the deviation of the concentration from predicted levels.

DERIVED, TRANSFORMED AND MISSING DATA

If a given covariate, either categorical or continuous, was missing in more than 15% of patients, it was omitted from the analysis. If necessary, an analysis of subpopulations was performed. In the current dataset, weight and height were missing for two subjects in Study RIS-USA-239: the missing values were replaced by the median, by sex, in the study population.
For the exploratory data analysis, the creatinine clearance (CRCL) in the populations derivation used the Cockroft-Gault equation for all subjects, pediatric and adults. The influence of CRCL on the active moiety and risperidone PK was explored in NONMEM using several different values using the Schwartz equation for the pediatric population or the Cockroft-Gault equation for the adult population. Creatinine clearance (CRCL in mL/min) was derived within the NMTRAN control file.

(b) (4)

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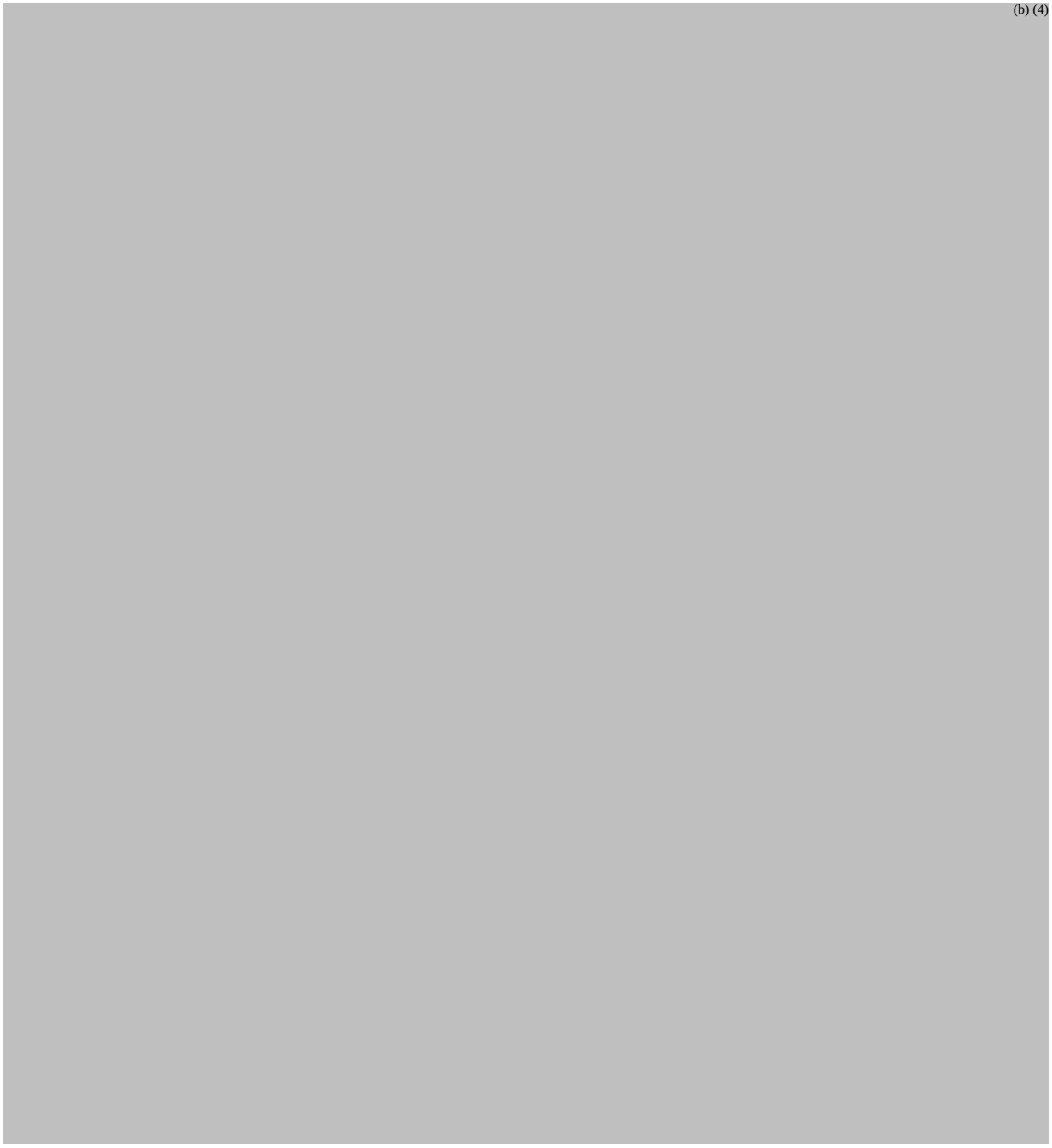


RESULTS

Demographic and Baseline Characteristics

Table 4 Summary statistics of demographic and baseline characteristics

		Children (<12)	Adolescents (12 17)	Adults (>17)	All
Age (y)	N	52	252	476	780
	Mean	10.41	15.11	33.78	26.19
	SD	1.48	1.30	13.04	14.00
	Median	10.70	15.20	32.85	18.10
	Min	6.20	12.10	17.10	6.20
	Max	12.00	17.00	70.80	70.80
Weight (kg)	N	52	252	476	780
	Mean	38.66	60.84	68.62	64.11
	SD	9.92	12.74	18.49	18.07
	Median	38.65	59.75	65.00	62.00
	Min	20.30	30.50	35.00	20.30
	Max	68.49	102.51	152.70	152.70
Height (cm)	N	52	252	476	780
	Mean	140.38	166.12	167.72	165.38
	SD	9.82	9.69	9.99	11.94
	Median	140.34	166.00	167.60	166.00
	Min	113.00	139.70	134.60	113.00
	Max	156.20	187.96	196.00	196.00

Age Class

		Children (<12)	Adolescents (12 17)	Adults (>17)	All
Body Surface Area (m^2)	N	52	252	476	780
	Mean	1.22	1.67	1.78	1.71
	SD	0.19	0.21	0.28	0.29
	Median	1.22	1.67	1.74	1.70
	Min	0.80	1.09	1.17	0.80
	Max	1.71	2.27	2.75	2.75
Serum Creat (µmol/L)	N	52	252	476	780
	Mean	49.04	63.80	76.73	70.71
	SD	8.01	13.14	17.13	17.54
	Median	53.00	62.00	76.00	71.00
	Min	35.00	35.00	35.00	35.00
	Max	62.00	106.00	177.00	177.00
CRCL (mL/min) using Schwartz formula for actual BSA	N	52	252	476	780
	Mean	101.08	137.59	115.33	121.57
	SD	23.99	33.09	33.67	34.88
	Median	100.58	133.01	112.60	117.60
	Min	53.73	55.05	51.87	51.87
	Max	162.40	254.36	312.24	312.24

		Children (<12)	Adolescents (12 17)	Adults (>17)	All
Sex					
Male	N	34	141	294	469
	%	65.38	55.95	61.76	60.13
Female	N	18	111	182	311
	%	34.62	44.05	38.24	39.87
Race					
Caucasian	N	35	198	213	446
	%	67.31	78.57	44.75	57.18
Black	N	14	43	106	163
	%	26.92	17.06	22.27	20.90
Oriental	N	0	2	0	2
	%	0	0.79	0	0.26
Other	N	3	9	157	169
	%	5.77	3.57	32.98	21.67

Table 5 The number of subjects (%) taking the selected concomitant medications included in the population PK analysis.

Concomitant medications	Number of subject (%)
Anticholinergics	56 (7.18)
CYP2D6 inhibitor	22 (2.82)
CYP3A4 inhibitor	16 (2.05)
PGP inhibitor	16 (2.05)
RISPERDAL®	8 (1.03)
PGP inducer	7 (0.90)
CYP3A4 inducer	3 (0.38)
CYP2D6 inducer	1 (0.13)
Methylphenidate	1 (0.13)
Mood stabilizer	1 (0.13)

Due to the small numbers of subjects receiving concomitant CYP3A4 inducers, CYP2D6 inducers, methylphenidate or mood stabilizers was too small to allow analysis.

FIRM'S ANALYSIS

ACTIVE MOIETY INDEX DATA SET

The best model to describe the concentrations of the active moiety was a two-compartment model, with first order input and a lag time.

Allometric scaling factors for clearance and volume and the effect of creatinine clearance (derived with the Schwartz formula for the actual CRCL) were included *a priori* in the model.

To correct for the underprediction at the beginning of the distribution phase observed in the data rich studies, a study effect was tested on the volume of the central compartment. The volume of the central compartment was shown to be lower in Studies RIS-USA-160, RIS-NED-25, RIS-P01-103 and RIS-RSA-5.

Interindividual variability (IIV) was estimated for apparent clearance (CL/F), apparent central volume (V2/F), Ka and relative bioavailability (F1). Two separate additive models described the residual error: one for the single dose studies and the other one for the repeated dosing studies. The firm's base model control stream for the active moiety is presented in Appendix I

The population estimates for the base model (using the FO method) are reported in Table 6.

Table 6. Base Model Parameters for Active Moiety After Oral Administration of Risperidone. Results were obtained With the Index Dataset, Using the FO Method

Parameter	Estimates (SE) (b) (4)	95% CI	%CV
CL/F(L/h)=θ_1*(Weight/70)$^{0.75}$+θ_6*CRCL			
θ_1		[2.91; 4.81]	
θ_6		[0.007; 0.0214]	
V2/F (L)=(θ_2 + STU3*θ_8 + FLAG*θ_9) *(Weight/70)			
θ_2		[135; 171]	
θ_8		[-88.4; -45]	
θ_9		[-70.8; -36.6]	
V3/F (L)=θ_3*(Weight/70)			
θ_3		[72.9; 97.9]	
Q/F (L/h)			
θ_4		[1.24; 1.70]	
Ka (h^{-1})			
θ_5		[4.20; 6.76]	
ALAG1 (h)			
θ_7		[0.236; 0.244]	
F1		-	
IIV on CL: ω^2_1		[0.0379; 0.0917]	25.5
IIV on V2: ω^2_2		[-0.0181; 0.0391]	10.2
IIV on Ka: ω^2_3		[3.64; 8.90]	250.4
IIV on F1: ω^2_4		[0.127; 0.267]	44.4
Residual variability on log(conc)			
Study 6,7, 8 : σ^2_1		[0.0472; 0.0912]	Sd 0.263
Study 1, 2, 3, 4, 5, 9: σ^2_2		[0.18; 0.305]	Sd 0.490

Study: 1=RIS-BIM-301, 2=RIS-USA-231, 3=RIS-USA-160, 4=RIS-USA-239, 5=RIS-IND-2, 6=RIS-NED-25, 7=RIS-P01-103, 8=RIS-RSA5, 9=R076477-SCH-102.
CRCL: Creatinine clearance derived using Schwartz' formula for actual BSA
FLAG=1 if study 6, 7 or 8; FLAG=0 otherwise
STU3=1 if study 3; STU3=0 otherwise
IIV is Inter-Individual variability

The population absorption rate constant (i.e., the formation rate constant) is 5.48 h-1; the lag-time is 0.24 h. The IIV estimated for Ka is large, 250% CV. This is likely the result of insufficient information to estimate Ka in sparse sampling studies and may not reflect the true value of between subjects' variability in rate of absorption and/or conversion

COVARIATE SELECTION-INDEX DATA SET
Most of the covariates did not significantly affect the PK:

The following covariates were selected to be evaluated further:
• on apparent clearance:

effect of Study 9 (Study R076477-SCH-102), age and race (Black) and

• on F1: effect of Study 7 (Study RIS-P01-103) and age.

After inclusion of those covariates in a full model, a backward deletion procedure was applied as summarized in Table 7.

Table 7 . Backward Deletion of Covariates - Active Moiety, Index Dataset

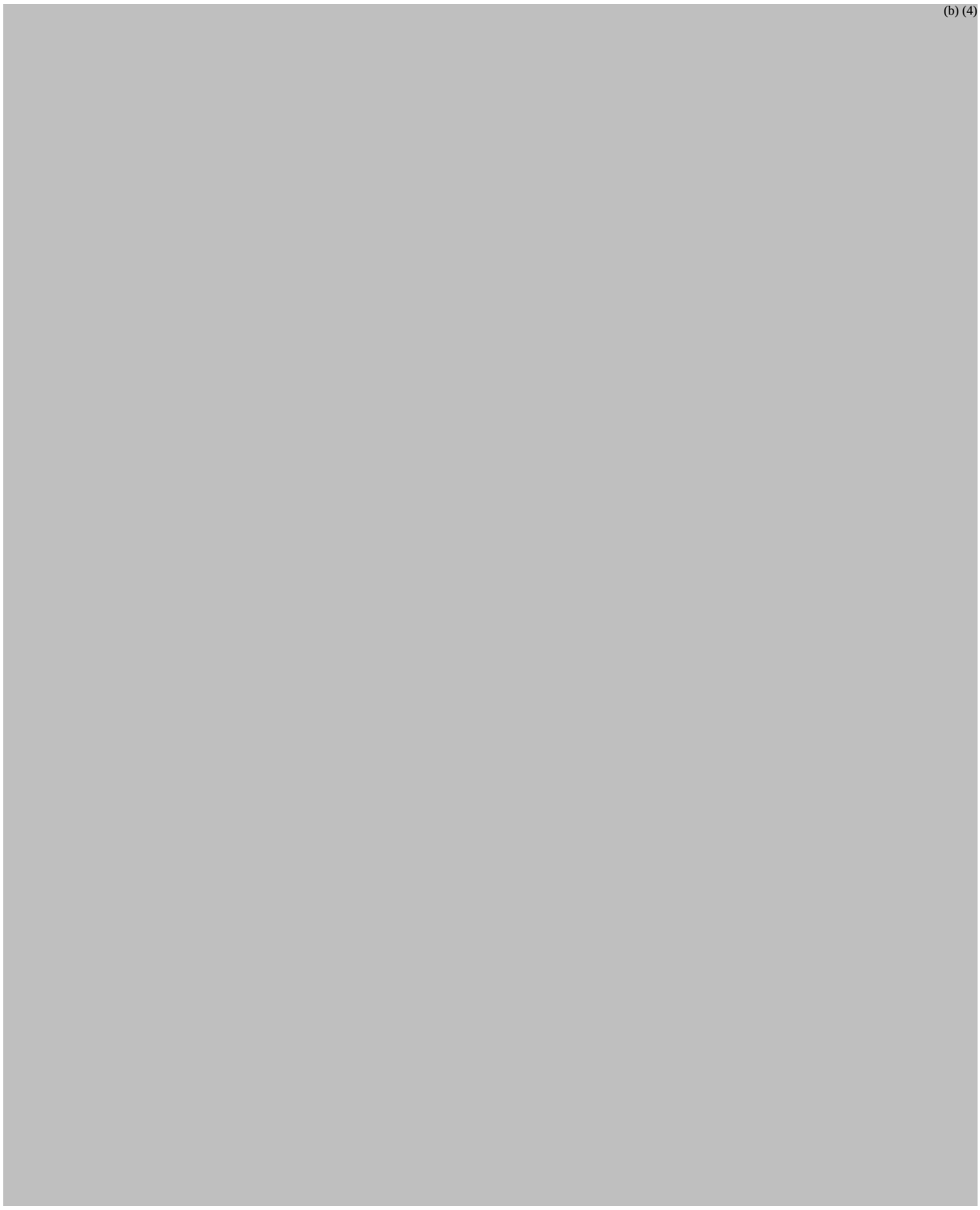
Run	Feature removed	MOF	ΔMOF	Conclusion
RUN181	Full model	-1441.013	NA[a]	
RUN182	Study 9 on CL	-1440.729	-0.284	NS[b], run182: new reference
RUN183	Study 7 on F1	-1432.461	-8.268	p<0.005
RUN184	Age on F1	-1439.701	-1.028	NS, run184: new reference
RUN185	Age on CL	-1431.805	-7.896	p<0.005
RUN186	Race (black) on CL	-1422.706	-16.995	p<0.005
RUN187	Final model	-1439.701		Eta on V2 close to zero, remove from run188
RUN188	Final_model_1	-1439.701		

NA[a]: Not Applicable
NS[b]: Not Significant

MODEL QUALIFICATION

Figure 2 presents the diagnostic plots of the model qualification, PRED vs. DV, IPRED vs. DV, WRES vs. PRED and IRES vs. IPRED.

Figure 3. External Qualification of the Active Moiety Final Model – Qualification Dataset
a. PRED Versus DV


(b) (4)

EFFECT OF CO-MEDICATIONS

The effect of co-medication was assessed using the full dataset. A summary of the univariate analyses of DDI is reported in Table

Table 8. Drug drug interactions –Active moiety

Run	Feature tested	MOF	ΔMOF	Conclusion
RUN221	Reference	-1955.993	NA[a]	Final model on full dataset
RUN222	D6IH on CL	-1957.102	-1.109	NS[b]
RUN223	A4IH on CL	-1957.301	-1.308	NS
RUN224	GPID on CL	-1962.792	-6.799	NS
RUN225	GPIH on CL	-1957.936	-1.943	NS
RUN226	CHOL on CL	-1960.597	-4.604	NS
RUN228	D6IH on F1	-1956.771	-0.778	NS
RUN229	A4IH on F1	-1956.003	-0.01	NS
RUN230	GPID on F1	-1964.679	-8.686	p<0.005
RUN231	GPIH on F1	-1956.103	-0.11	NS
RUN232	CHOL on F1	-1961.003	-5.01	NS
RUN233	RIS on F1	-1957.3	-1.307	NS

[a]Not Applicable
[b]NS: Not Significant

There were no significant drug drug interactions indicated except for GPID (PGP inducers) however, this PGP inducers effect should be interpreted with caution since only 7 out of 780 patients took this medication.

FINAL PK MODEL OF THE ACTIVE MOIETY – FULL DATASET

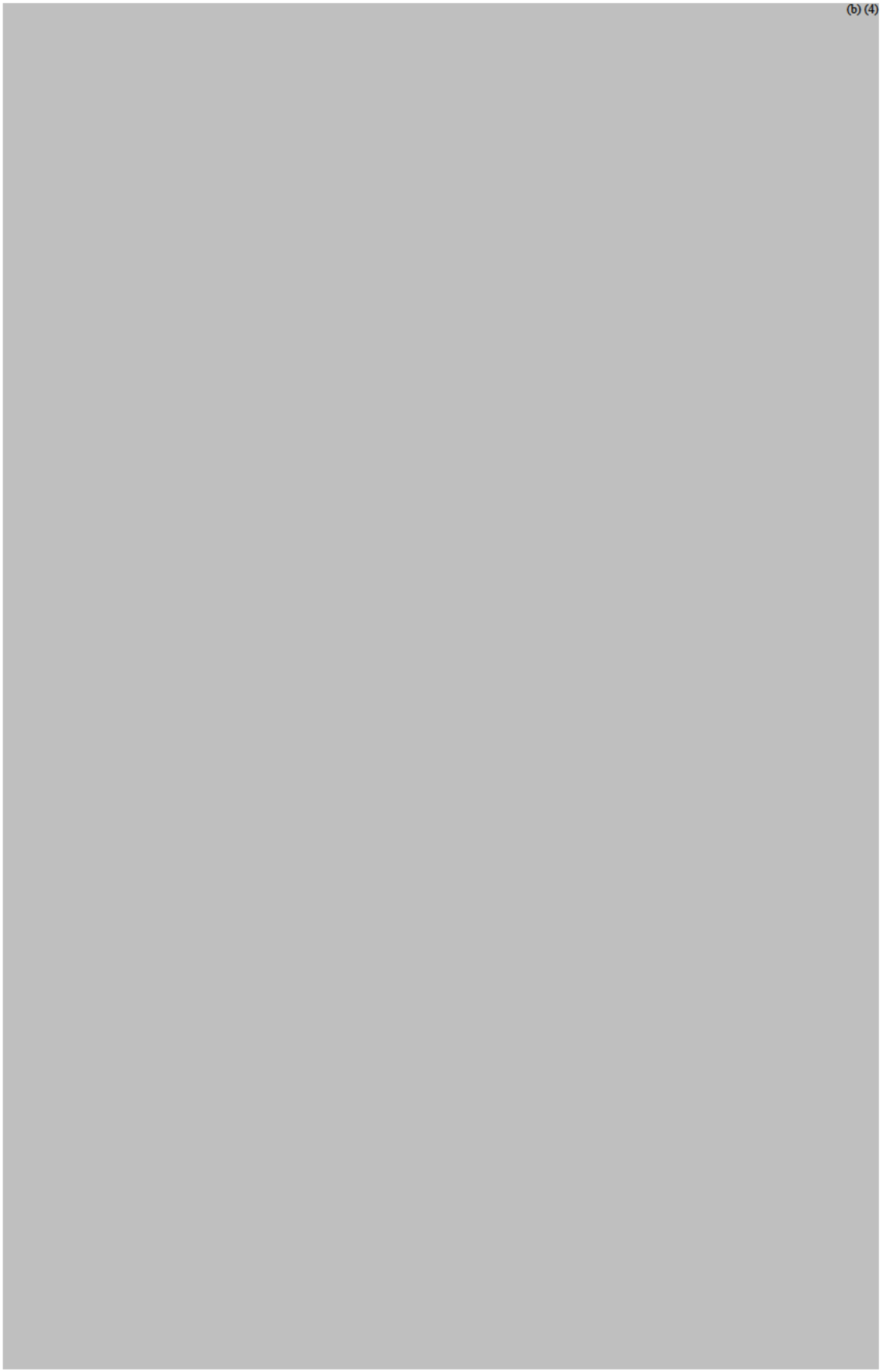
After including all significant effects, the final PK parameters of the active moiety were estimated using the FOCE method. To obtain a minimization with a successful covariance step, the model had to be further simplified: the covariance between CL/F and F1 was removed and the random effect on Ka was deleted.

Table 9. Final Model Parameters for Active Moiety After Oral Administration of Risperidone. Results are Obtained With the Full Dataset, Using the FOCE Method

Parameter	Estimates (SE)	95% CI	%CV
CL/F(L/h)=(θ_1*(Weight/70)$^{0.75}$+θ_6*CRCL + θ_9*BLAC)*(Age/18.1)**θ_{10}	(b) (4)		
θ_1		[3.77; 5.57]	
θ_6		[0.00172; 0.01454]	
θ_9		[0.521; 1.231]	
θ_{10}		[-0.242; -0.122]	
V2/F (L)=(θ_2 + FLAG*θ_8) *(Weight/70)			
θ_2		[122; 150]	
θ_8		[-53.7; -27.1]	
V3/F (L)=θ_3*(Weight/70)			
θ_3		[70.7; 102.1]	
Q/F (L/h)			
θ_4		[1.15; 1.53]	
Ka (h^{-1})			
θ_5		[1.91; 2.87]	
ALAG1 (h)			
θ_7		[0.230; 0.240]	
F1=1 + θ_{11}*GPID			
θ_{11}		[-0.751; -0.183]	
IIV on CL: ω^2_1		[0.0273; 0.0897]	24.2
IIV on F1: ω^2_2		[0.042; 0.168]	32.4
IOV on F		[0.069; 0.243]	39.5
Residual variability on log(conc)			
Study 6, 7 or 8 : σ^2_1		[0.22; 0.32]	Sd 0.520
Study 1, 2, 3, 4, 5 or 9: σ^2_2		[0.114; 0.258]	Sd 0.431

Study: 1=RIS-BIM-301, 2=RIS-USA-231, 3=RIS-USA-160, 4=RIS-USA-239, 5=RIS-IND-2, 6=RIS-NED-25, 7=RIS-P01-103, 8=RIS-RSA5, 9=R076477-SCH-102.
CRCL: Creatinine clearance derived using Schwartz' formula for actual BSA
BLAC=1 if race is black; BLAC=0 otherwise
FLAG=1 if study 3, 6, 7 or 8; FLAG=0 otherwise
GPID=1 if concomitant treatment with PGP Inducer; GPID=0 otherwise
IIV is Inter-Individual variability
IOV is Inter-occasion variability defined by weeks of treatment (at WEEK=0; WEEK=1; WEEK=2; WEEK=3; WEEK=4; WEEK>5)

Figure 4. Goodness-of-Fits Plots for the Active Moiety Final Model – Full Dataset, Adolescent Only


(b) (4)

The equation to predict the apparent clearance of the active moiety is:

(b) (4)

For a non-Black (BLAC=0) typical patient, with weight 62 kg, aged 18.1 years, with a creatinine clearance 117.6 mL/min, the apparent clearance is equal to 5.22 L/h.

The apparent clearance was slightly higher in Black patients, by 0.9 L/h, or approximately 17% for a typical adult.

SIMULATIONS

The firm conducted simulations to establish exposure as a function of age. Two different dosing regimens administration (3 mg/day, either q.d. or b.i.d. with a split dose) were simulated at steady state.
Depending on the number of different patients in each of the original datasets, simulations were replicated up to approximately 1000 patients.

Figure 5. Simulated Concentrations of Active Moiety in NonBlack Subjects Treated With 3 mg/day (Split b.i.d Dose) of Risperidone (5th, 25th, 50th, 75th and 95th percentile

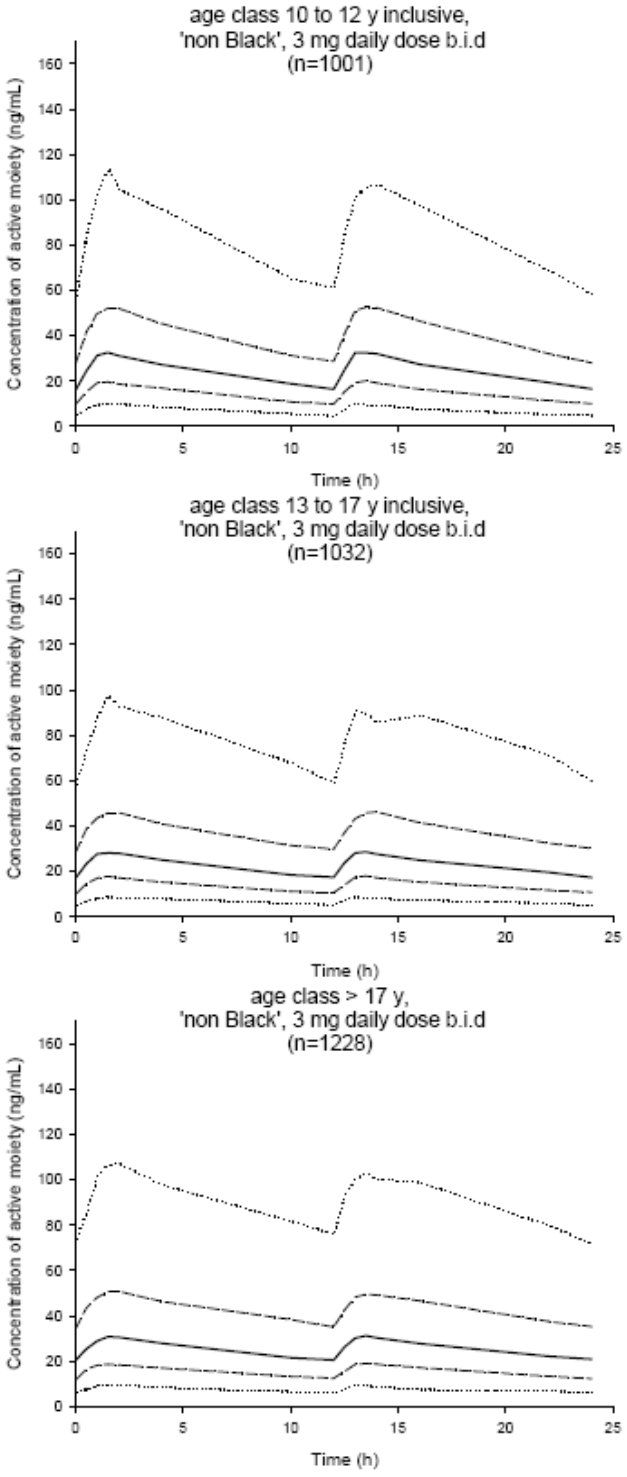
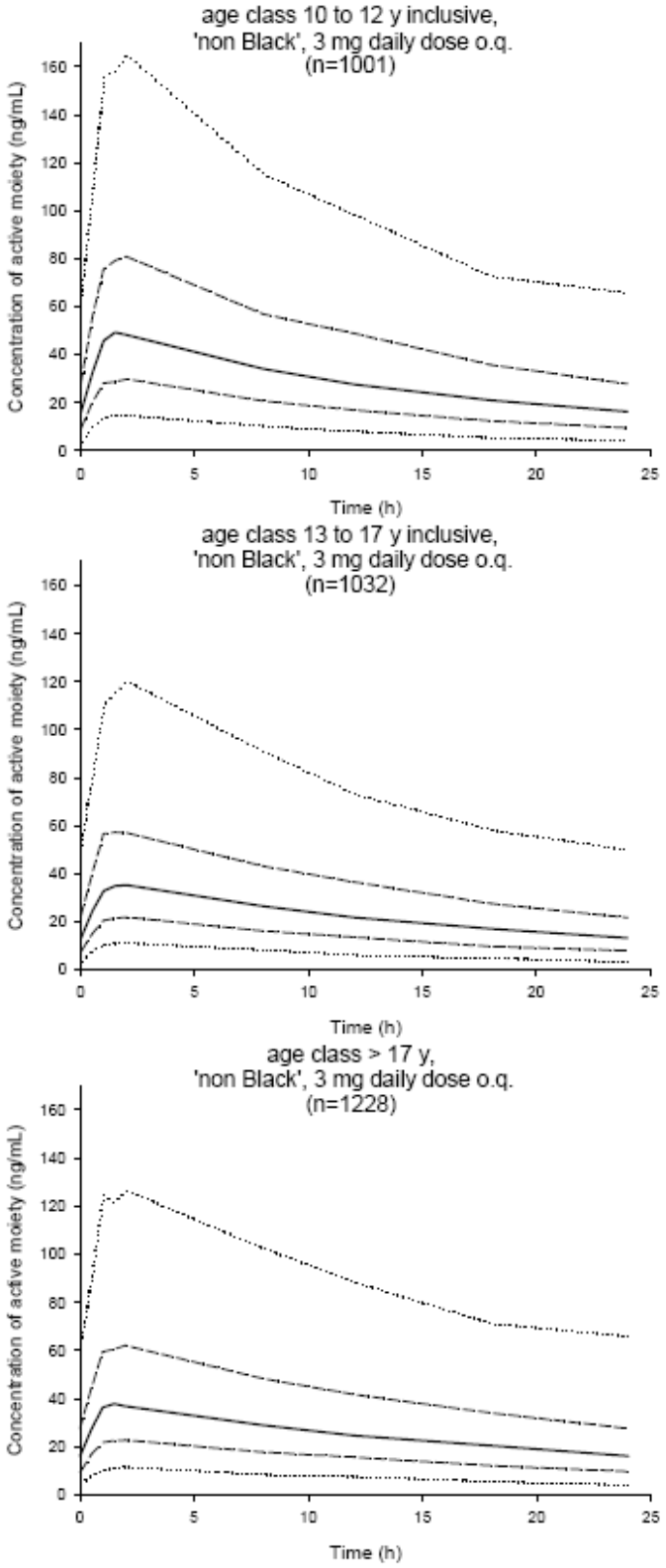
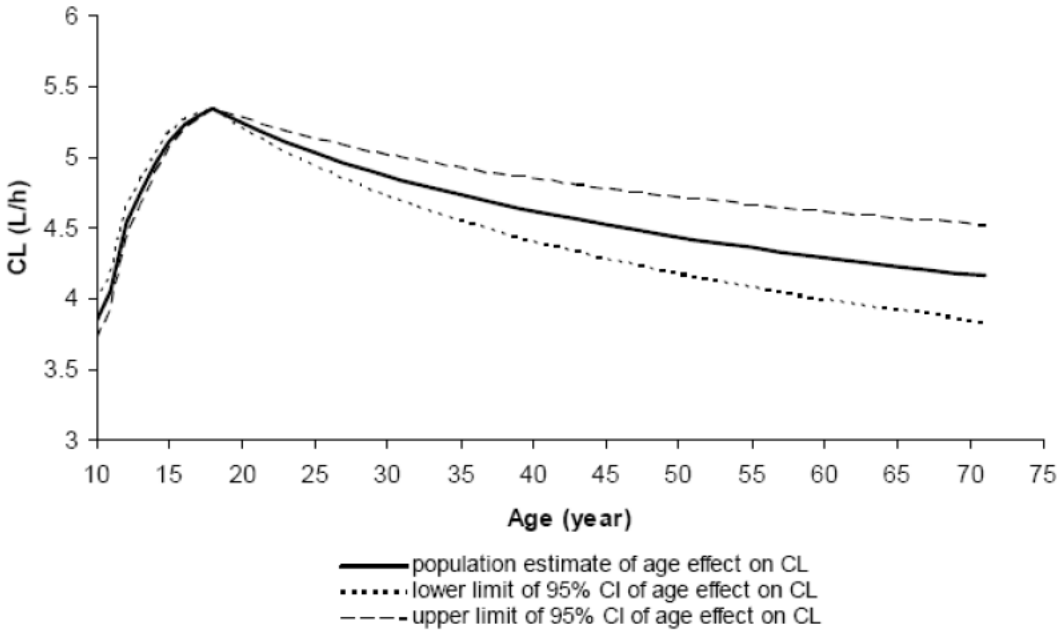


Figure 5. Simulated Concentrations of Active Moiety in NonBlack Subjects Treated With 3 mg/day (qd Dose) of Risperidone (5^{th}, 25^{th}, 50^{th}, 75^{th} and 95^{th} percentile.



Similar simulated results were seen for the black subjects except the resulting levels were lower due to the increased clearance as previously discussed.

Figure 6. Effect of Age on Active Moiety Clearance in Different Age Groups.



This figure shows that the age effect on apparent clearance is moderate, the most rapid change in clearance is due to the change in median body weight during the child's growth.

(b) (4)

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There appeared to be underprediction at the higher concentrations and overprediction at the lower concentrations

Two different subpopulations of subjects were identified, that could be assumed to represent intermediate/poor metabolizers and extensive metabolizers, although no confirmation of such categorization could be done in the absence of complete genotype and/or phenotype data.

After allometric scaling, the PK of risperidone was similar between children, adolescents and adults. The risperidone apparent clearance and the volume of distribution at steady state for the three age classes and subpopulations are:

Parameter	Child, body weight: 39 Kg; age: 11 yr		Adolescent; body weight: 60 Kg, age: 15 yr		Adult; body weight: 70 Kg; age: 33 yr	
	Subpopulation 1	Subpopulation 2	Subpopulation 1	Subpopulation 2	Subpopulation 1	Subpopulation 2
CL/F (L/h)	5.47	20.8	7.56	28.7	8.48	32.2
Vd_{ss} (L)	143.6	176.6	220.9	271.7	257.7	317.0

(Subpopulation 1 is identified as the IM/PM population while subpopulation 2 represents the EM population)

FDA ANALYSIS

The data which the firm submitted did not have plasma stability data to cover the 5 yr storage period for some of the samples. Therefore an analysis was undertaken involving the deletion of Study 2 in adolescents for the active moiety and risperidone for the base model. (b) (4)

[redacted]

BASE MODEL -ACTIVE-MOIETY

Base model for Active moiety

Parameter	Firm's analysis Estimate(SE)	FDA analysis	FDA analysis without study 2
CL θ_1 θ_6	(b) (4) [redacted]	3.86(0.484) 0.0142(0.00365)	4.15(0.561) 0.0121(0.00435)
V2/F θ_2 θ_8 θ_9		153(9.25) -65.7(11.6) -53.7(8.7)	161(11.2) -72.9(13) -60.4(10)
V3/F θ_3		85.4(6.39)	85.2(6.35)

	(b) (4)		
Q/F θ_4		**1.47(0.119)**	**1.48(0.122)**
Ka θ_5		**5.48(0.654)**	**5.48(0.657)**
ALAG1 θ_7		**0.24(0.00189)**	**0.24(0.00189)**
F1		**1 Fixed**	**1 Fixed**
IIV on CL ω^2_1		**0.0648(0.0137)**	**0.068(0.0158)**
IIV on V2 ω^2_2		**0.0105(0.0146)**	**0.0076(0.0139)**
IIV on Ka ω^2_3		**6.27(1.34)**	**6.31(1.36)**
IIV on F1 ω^2_4		**0.197(0.0358)**	**0.225(0.048)**
Residual variability **Study 1,2,3,4,5,9:σ^2_1** **Study 6,7,8:σ^2_2**		 **0.0692(0.0112)** **0.24 (0.033)**	 **0.0692(0.0112)** **0.24 (0.044)**

FINAL MODEL ACTIVE MOIETY

FINAL MODEL WOULD NOT RUN ON MY COMPUTER BUT DID RUN ON YANING'S RESULTS WERE FOUND TO BE THE SAME AS FOR THE SPONSOR.

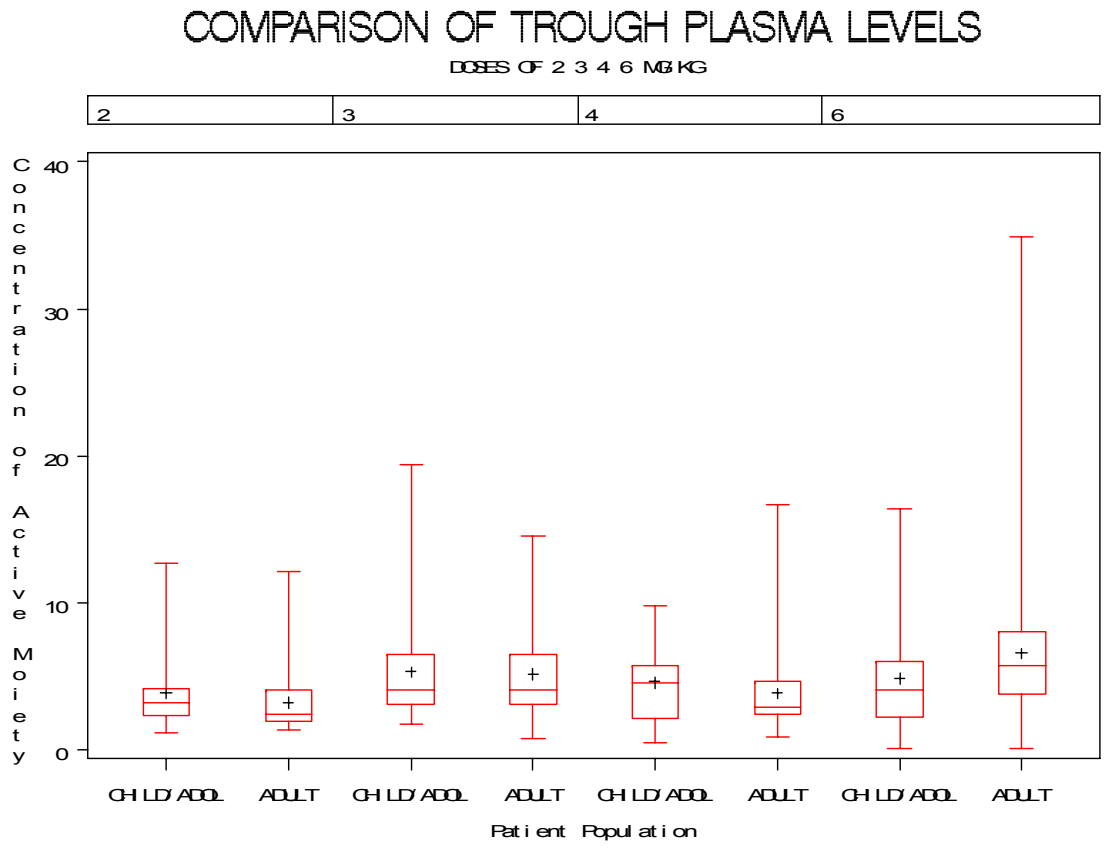
(b) (4)

COMMENT

1. There was minimal change in the base model results with study 2 deleted.
2. FDA results for the base and final models were identical to the firm's results

The firm's analysis was further checked by selecting times after dose for the observed data based upon the sampling schedules for studies 1, 2 and 3. These were used to make comparisons to the other adult studies at the same times after dose for the intensive sampling studies.
Trough samples were selected based upon time of last dose that were comparable between the studies. These were further sorted based upon dose with the final concentrations normalized to dose.:

Figure 9. Comparison of adolescent and adult data observed data as a function of normalized dose for Active moiety at trough.



Comment:

1. Mean values for the active moiety were similar for adults and children and adolescents at trough based upon mg/kg.

BASE MODEL - RISPERIDONE

Table 12 Comparative results were:

Parameter	Firm's analysis Estimate (Rel SE)	FDA analysis (Rel SE)	FDA analysis without study 2 (Rel SE)
Ka	(b) (4)	6.03(9.1)	6.03(9.0)
CL θ_2 θ_9		 49(12.9) 0.782(11.8)	 51(13.4) 0.782(11.8)
V2/F θ_3		323(13.6)	331(14.1)
V3/F θ_4		256(21.6)	255(23.3)
Q/F θ_5		6.96(16.2)	7.3(17.9)
ALAG1 θ_6		0.24(0.8)	0.24(0.8)
F1 Population 1: θ_7 Population 2		 3.5(12.3) 1(fixed)	 3.6(14.1) 1(fixed)
Proportion population 1: p(1)= θ_8		0.346(24.2)	0.35(20.3)
Proportion population 2: 1-p(1)		0.654	0.654
IIV on Ka ω^2_1		8.3(22.8)	8.3(22.8)
IIV on CL ω^2_2		0.332(17.3)	0.38(20.2)
IIV on V2 ω^2_3		0.261(22.1)	0.30(24.2)
Residual variability Study 1,2,3,4,5,9:σ^2_1 Study 6,7,8:σ^2_2		 0.073(19.1) 0.828 (11.5)	 0.073(19.1) 0.837 (11.5)

COMMENTS

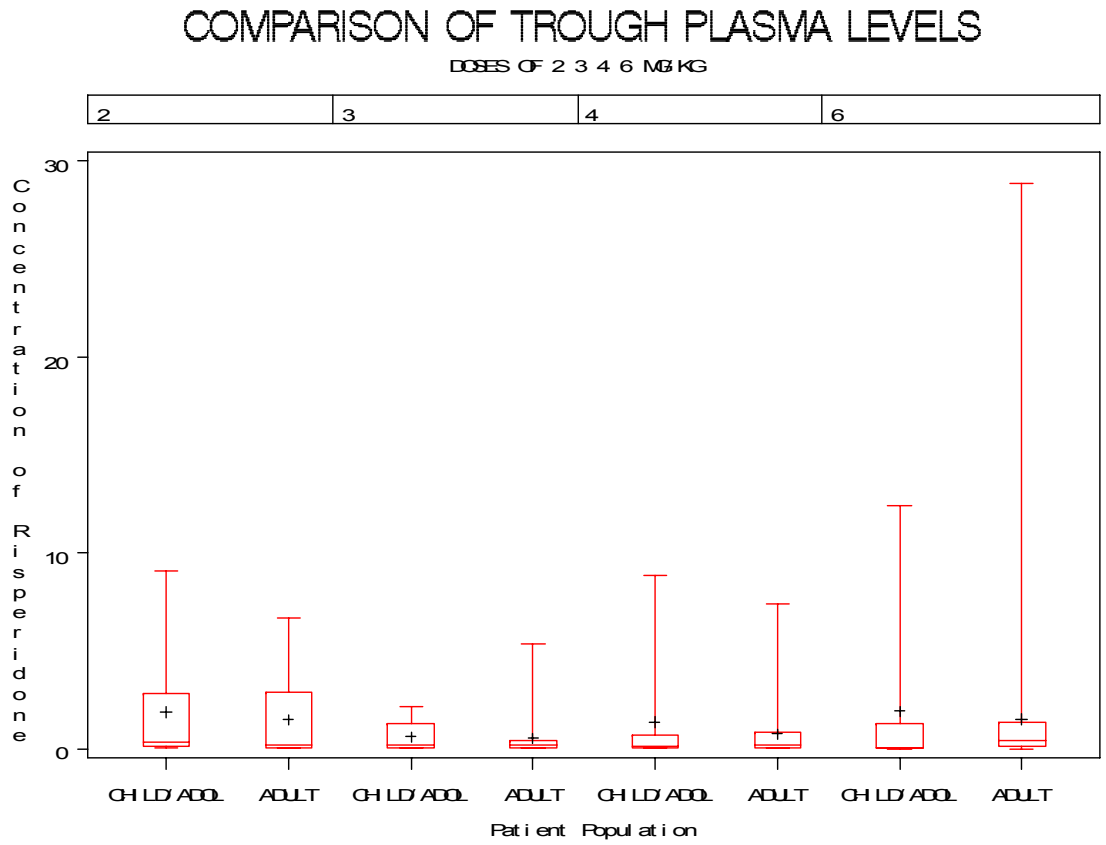
1.There was minimal change in the base model results with study 2 deleted.
2. FDA results for the base and final models were identical to the firm's results

Table 13. Final Model Parameters for Risperidone After Oral Administration. Results are Obtained With the Full Dataset, Using the FOCE Method.

Parameter	Firm's Estimates (SE)	FDA Estimates (SE)
Ka (h-1) Study 1,2,3,4,5,9: θ1 Study 6,7,8 : θ10	(b) (4)	
CL/F (L/h)=θ2*(Weight/70)0.75* θ9 POP1 θ2 θ9		
V2/F (L)=θ3*(Weight/70) θ3		
V3/F (L)=θ4*(Weight/70) θ4		
Q/F (L/h) θ5		
ALAG1 (h) θ6		
F1 Population 1: θ7 Population 2		
Proportion population 1: P(1)= θ8		
Proportion population 2: 1-P(1)		
IIV on CL: ω2 1		
IIV on V2: ω2 2		
IIV on F1: ω2 3		
Residual variability on log(conc) Study 1, 2, 3, 4, 5, 9: σ2 1 Study 6, 7, 8 : σ2 2		

An analysis of the trough times after dose concentrations were selected based upon the sampling schedules for studies 1, 2 and 3 and analyzed the same as those for the active moiety.

Figure 10. Comparison of adolescent and adult data observed data as a function of normalized dose for Risperidone at trough.



DISCUSSION

The results from this analysis indicates that based upon the model developed to describe risperidone and the active moiety that there are differences in clearance between adolescents, children, and adults.
Values for the standard errors indicated that the parameters were estimated with precisions usually less than 25%. The residual variability remained high suggesting that assumptions about dosing history may be incorrect or sampling date/time may not be accurate for some subjects at steady state.

The analysis of the raw trough data based upon time after dosing supports the model results indicating that weight normalized doses are comparable in children, adolescents and adults in the dose range 2,3,4,5 and 6 mg/kg. However based upon the lack of a clear dose response relationship for both indications dosing based upon body weight is not recommended. Recommended doses for schizophrenia is 3 mg QD while that for bipolar should be initiated at 0.5 mg QD with adjustment of 0.5-1 mg/day as tolerated.

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SIGNATURES

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RD/FTinitialized by Raman Baweja, Ph.D._____

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APPENDIX I
FIRM'S BASE MODEL FOR ACTIVE MOIETY

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