The model takes into account polymorphic biotransformation of risperidone into 9-hydroxy-risperidone, which is mediated by CYP2D6. The existence of three phenotypes, EMs, IMs and PMs, the latter known to be the least frequent in the population, was confirmed earlier. The phenotypic differences between patients were implemented using the mixture model option of NONMEM. Patients having different phenotypes may differ in typical values of FP and CLPM. The probabilities of being PM or IM [P(1), P(2)] were estimated as fixed-effect parameters. The probability P(3) of being EM was $1 - P(1) - P(2)$.

The absorption process was modeled as a sequential zero- and first order process, with a lag time. Zero-order input was implemented by assigning the value of –2 to the RATE data item of the NONMEM data set and by making the duration of the input into the depot compartment (D1) a parameter. In the structural model, there were absorption rate constants (K12 and K14) describing the input of risperidone and 9-hydroxy-risperidone, respectively, into their central compartments. More specifically, risperidone was the absorbed compound, and 9-hydroxy-risperidone was formed during the first-pass through the liver. Hence, the mechanistically more plausible parameterization was used with just one absorption rate constant, KA, and an apparent fraction of the ultimately absorbed dose converted into 9-hydroxy-risperidone during the first-pass (FP). At steady-state, FP is equivalent to the ratio of 9-hydroxy-risperidone AUC to the sum of risperidone and 9-hydroxy-risperidone AUCs.

Visual inspection of individual plasma concentration-time profiles suggested that the parameters D1, KA and F1 be subject to IOV. The F1 parameter itself could not be estimated, however, its IOV was estimable since patients had variable AUCs after repeated doses administered at different days.

The estimates of parameters obtained after fitting the base model to the index data set (identified outliers excluded) are presented in the following Table. The reference value of the minimum objective function (MOF) was -512.365.

Parameter	Central tendency	IIV (%CV)	IOV (%CV)
F1	1	-	45.6 (26.6)
FP (%)		108 (18.9)	-
PM	9.33 (39.7)		
IM	11.3 (37.5)		
EM	39.7 (10.6)		
ALAG1 (h)	0.181 (10.9)	32.1 (79.0)	-
D1 (h)	0.470 (8.0)	94.0 (74.1)	178 (28.8)
KA (1/h)	2.23 (16.5)	142 (34.6)	109 (34.7)
QP (L/h)	3.50 (21.3)	278 (113)	-
CLP (L/h)	3.23 (21.5)	194 (59.7)	-
CLPM (L/h)		36.2 (33.7)	-

|			
PM	1.07 (16.7)		
IM	5.44 (25.2)		
EM	18.7 (8.3)		
V2 (L)	139 (8.1)	26.7 (68.2)	-
V3 (L)	100 (37.1)	55.0 (137)	-
QM (L/h)	1.40 (16.1)	0, fix	-
CLM (L/h)	5.96 (4.4)	14.5 (85.6)	-
V4 (L)	139 (8.1)	26.7 (68.2)	-
V5 (L)	107 (23.8)	49.4 (131)	-
PM (%) – P(1)	7.93 (22.4)	-	-
IM (%) – P(2)		-	-
Single dose trials	32.6 (35.6)		
All other trials	4.00 (69.0)		
EM (%) – P(3)		-	-
Single dose trials	59.5		
All other trials	88.1		
As add-on to CBZ (L/h)		-	-
CLP, +CARB	7.63 (31.3)		
CLM, +CARB	6.32 (12.0)		
Residual variability (%SD)			
RIS	30.8 (21.3)		
9OH	37.9 (14.0)		

3. Covariate model

The graphical analysis of the empirical Bayes estimates vs. patient characteristics was the primary tool in the covariate model development. Also, prior pharmacokinetic and other relevant information was taken into consideration. The following figures show the results of the graphical exploration of clearance values in patients with and without carbamazepine comedication.

The following box plots demonstrate effects of carbamazepine on the clearance of risperidone (left) and of 9-hydroxy-risperidone (right).
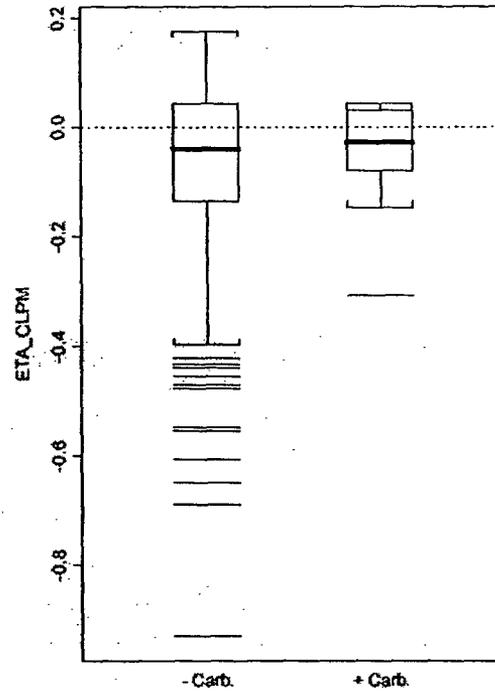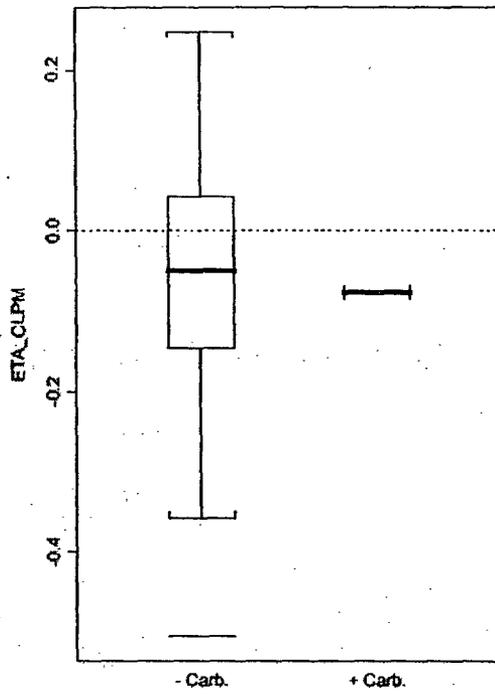
Risperidone
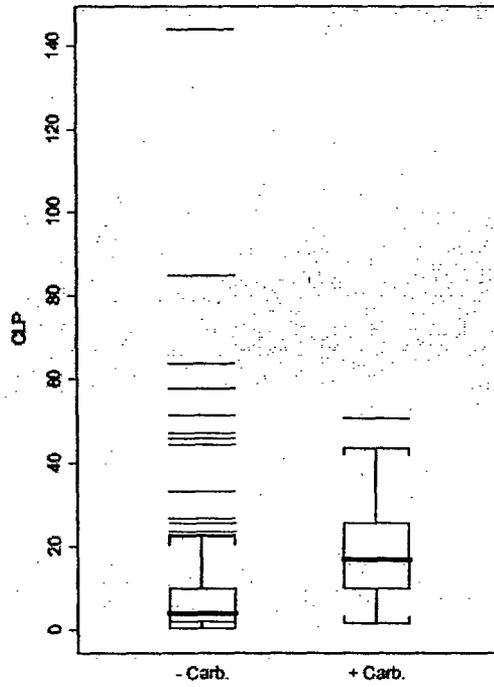
9-OH-Risperidone
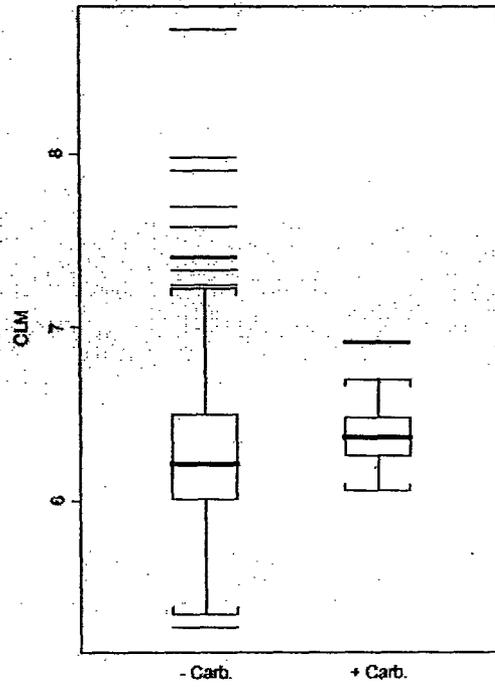
The following box plots demonstrate absence of effect of the carbamazepine on the clearance (CLPM) of risperidone to 9-hydroxy-risperidone (left panel: IMs, right panel: EMs)

The following plots of etas versus study (stu) for the model show the study effect on risperidone and 9-hydroxy-risperidone pharmacokinetic parameters. It appears that study has no significant effects on the pharmacokinetic parameters although some studies may have appreciable effect, such as study 4 on QP.
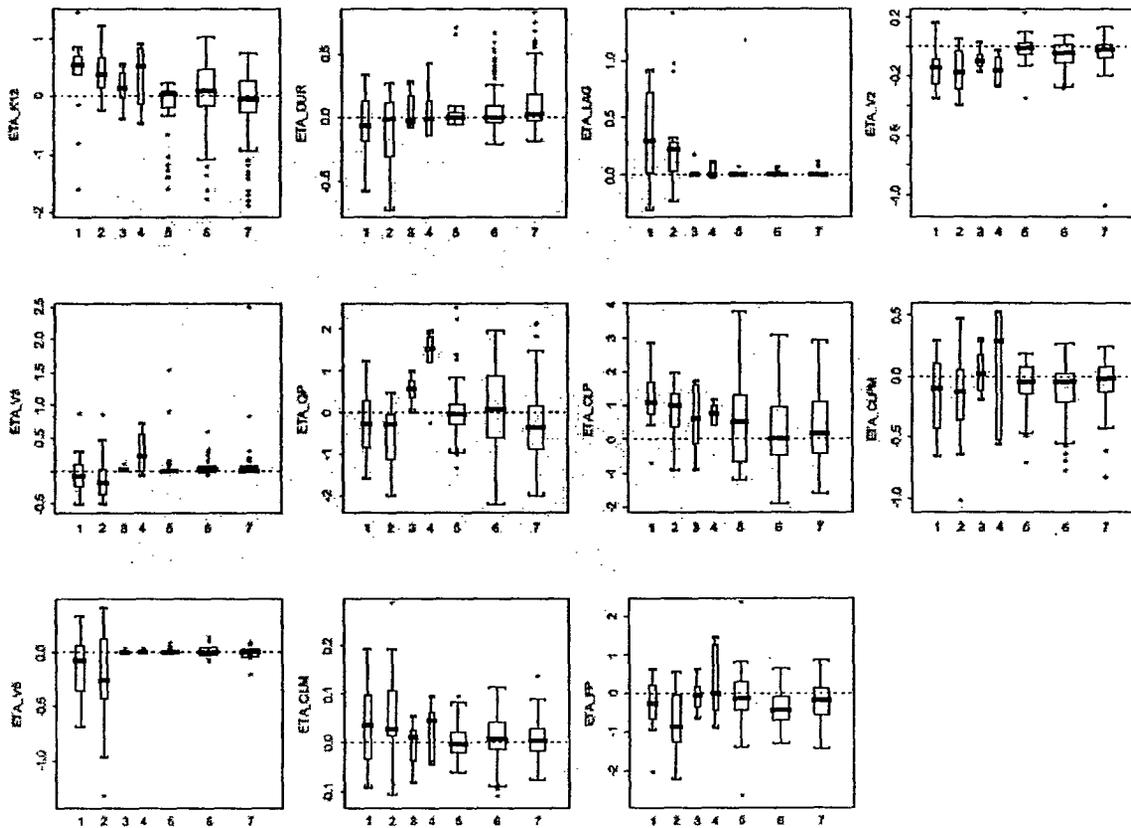
The following figure shows the study effect on the proportion of various phenotypes.

68
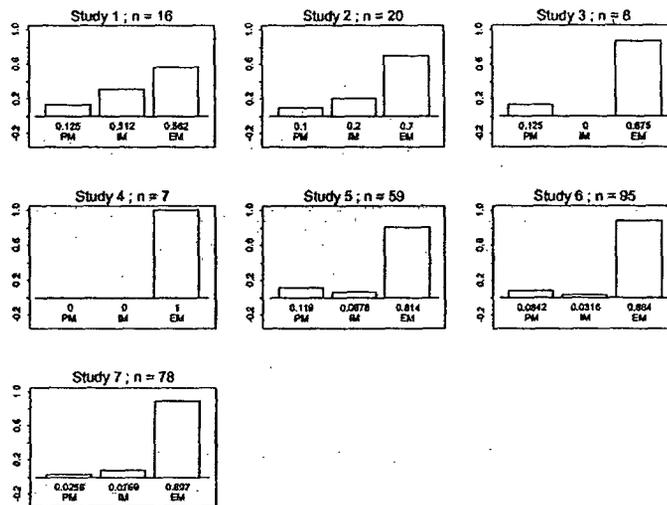
In the above figures, Study 1: JRD0001, Study 2: JRD0002, Study 3: RIS-GER-9, Study 4: RIS-FRA-4, Study 5: RIS-INT-46, Study 6: RIS-IND-2, Study 7: RIS-USA-239. Frequency distributions demonstrate the difference in percentage IMs and EMs in the single dose versus the repeated dosing trials.

The proportion of IMs was lower (while the proportion of EMs was higher) in multiple-dose trials (both Phase 1 and Phase 3) compared to single-dose trials.

The effect of carbamazepine was implemented in the model via a binary index variable. Carbamazepine comedication affected the risperidone clearance not mediated by CYP2D6 (CLP) and the 9-hydroxy-risperidone clearance (CLM). The effect was highly significant and was kept in the model. The effect of multiple dosing on P(2) (proportion of IMs) was implemented. Fitting this model to the index data set resulted in a significant decrease in MOF, and the effect was kept in the model. The effect of multiple dosing on the clearance of parent risperidone was insignificant.

The patient characteristics (WT, LBM, BMI, AGE and RACE) were selected for testing by inclusion in the model and fitting to the data. Laboratory variables were also tested by including in the model. None of the these variables improved the fit, and they were not included in the model. The correlation between interindividual random effects was tested including CLPM versus FP, CLPM versus CLM, K12 versus D1. None of these correlations was found to be significant. These tests are summarized in the following table.

#	Model description	MOF	ΔMOF	P-value	Comments
1	Base model, no covariate effects	-512.365	-	-	-
2	**Effect of CARB on CLP and CLM**	**-536.284**	**-23.919**	**P<0.0001**	**Accepted**
3	**Effect of STU on proportion IMs**	**-550.83**	**-14.5**	**P<0.0001**	**Accepted**
4	Effect of STU on CLP	-550.83	0	NS	Not accepted
5	Effect of WT on FP	-554.979	-4.15	NS	Not accepted
6	Effect of WT on KA	-535.829	+15.001	NS	Not accepted
7	Effect of WT on CLPM	-538.578	+12.252	NS	Not accepted
8	Effect of WT on CLP	-539.298	+11.532	NS	Not accepted
9	Effect of LBM on CLP	-538.108	+12.722	NS	Not accepted
10	Effect of LBM on CLM	-536.818	+14.012	NS	Not accepted
11	Effect of LBM on CLPM	-535.991	+14.839	NS	Not accepted
12	Effect of BMI on CLP	-542.124	+8.706	NS	Not accepted
13	Effect of BMI on CLM	-535.989	+14.841	NS	Not accepted
14	Effect of AGE on QP	-553.272	-2.472	NS	Not accepted
15	Effect of AGE on CLP	-551.998	-1.17	NS	Not accepted
16	Effect of AGE on CLM	-550.933	-0.103	NS	Not accepted
17	Effect of AGE on CLPM	-550.958	-0.128	NS	Not accepted
18	Effect of RACE on CLP	-537.096	+13.734	NS	Not accepted

#	Model description	MOF	ΔMOF	P-value	Comments
19	**Initial model for effects of LAB variables**	**338.912**	-	-	-
20	Effect of CLCR on CLM	338.112	-0.8	NS	Not accepted
21	Effect of CLCR on CLP	338.912	+0	NS	Not accepted
22	Effect of CLCR on CLPM	336.515	-2.397	NS	Not accepted
23	Effect of ALB on CLP	337.485	-1.427	NS	Not accepted
24	Effect of ALB on CLM	335.925	-2.987	NS	Not accepted
25	Effect of ALB on CLPM	338.224	-0.688	NS	Not accepted
26	Effect of AST on CLP	337.106	-1.806	NS	Not accepted
27	Effect of AST on CLM	338.872	-0.04	NS	Not accepted
28	Effect of AST on CLPM	335.221	-3.691	NS	Not accepted
29	Correlation between ETA_DUR and ETA_K12	-543.718	+7.112 [4]	NS	Not accepted
30	Correlation between ETA_FP and ETA_CLPM	-545.87	+4.96 [4]	NS	Not accepted
31	Correlation between ETA_CLM and ETA_CLPM	-547.539	+3.291 [4]	NS	Not accepted

4. Model Qualification

The final model was used to generate population and posterior individual predictions. Parameter estimates obtained with the index data set were used as initial values for THETAs, OMEGAs and SIGMAs, and the estimation step of NONMEM was suppressed by setting the MAXEVAL option equal to 0.

The following figure shows the plots of measured risperidone and 9-hydroxy-risperidone concentrations in the qualificati'·   .s population an'   ·ividual predictions.
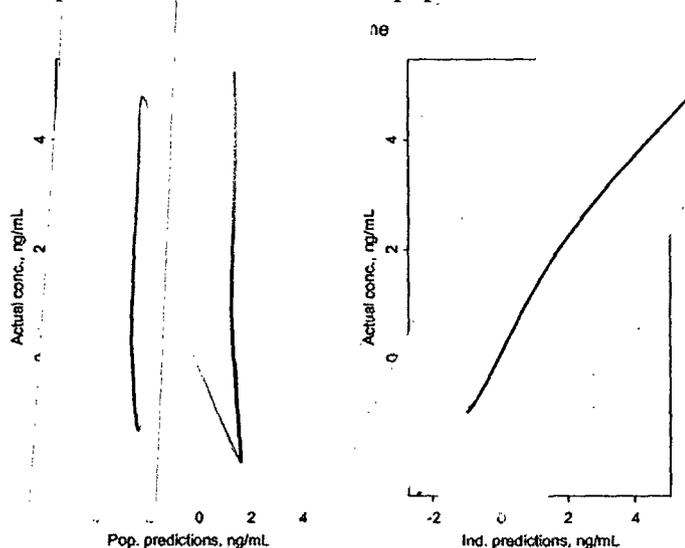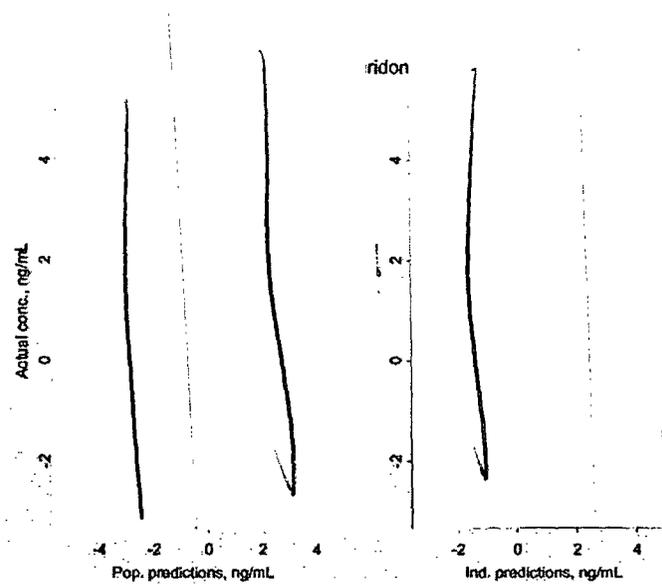
The identity and smoothing lines drawn through the data points almost coincided. No bias could be observed.

The following figure exhibits histograms of mean population prediction error (left panel) and root mean squared prediction error (right panel) obtained by randomly simulating plasma concentrations and calculating the prediction errors. Dashed lines represent the 2.5 and 97.5 percentiles and the thick line represents the median value.
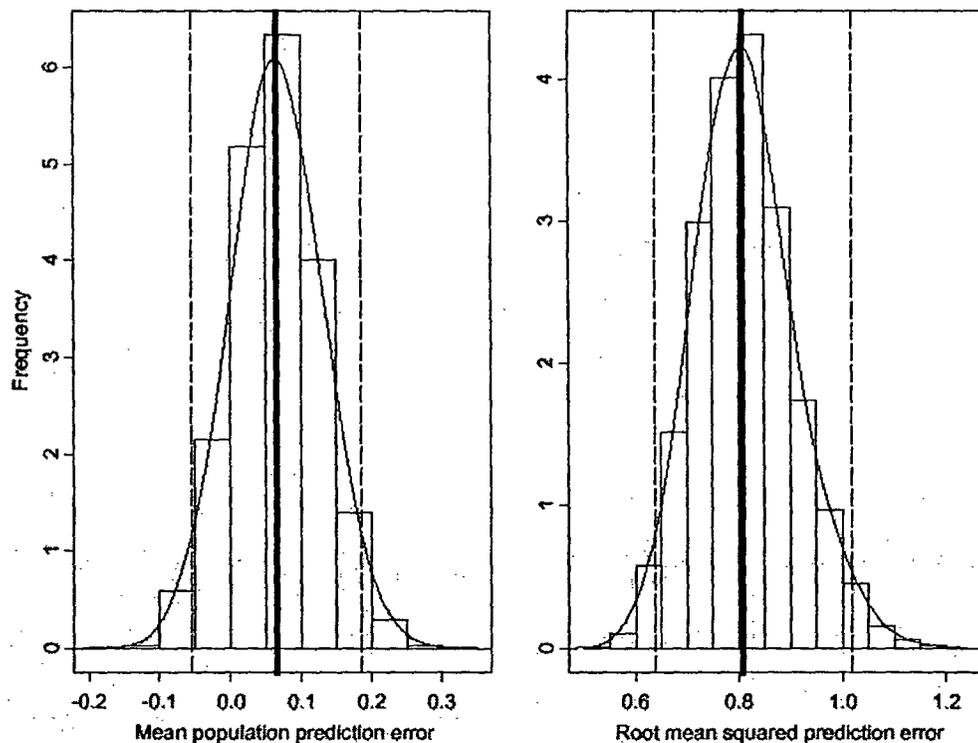
Median MPE deviates from zero by 0.065. The 95% confidence interval (-0.055, 0.186) includes zero. Median RMSE is 0.809 (0.639, 1.02).

5. Final Model

The final population pharmacokinetic model was fitted to the complete data set. The covariance step was implemented to check the significance of the estimates. Final values (model with exclusion of outliers) are summarized in the following Table.

| Parameter	Central tendency	IIV (%CV)	IOV (%CV)
F1	1	-	46.5 (24.4)
FP (%)		117 [1](17.9)	-
PM	1.75 (47.3)		
IM	10.9 (38.0)		
EM	41.3 (7.0)		
ALAG1 (h)	0.165 (9.4)	41.0 (69.0)	-
D1 (h)	0.458 (7.9)	113 (38.3)	158 (25.9)
KA (1/h)	2.34 (16.9)	149 (32.5)	108 (33.6)
QP (L/h)	3.65 (14.8)	215 (131)	-
CLP (L/h)	2.84 (28.1)	184 (72.0)	-
CLPM (L/h)		33.3 (27.7)	-
PM	1.18 (16.5)		
IM	4.37 (22.4)		
EM	19.6 (10.8)		
V2 (L)	137 (8.3)	30.0 (61.5)	-
V3 (L)	100 (23.6)	53.9 (91.8)	-
QM (L/h)	1.67 (20.3)	0, fix	-
CLM (L/h)	5.99 (5.4)	20.4 (65.5)	-
V4 (L)	137 (8.3)	30.0 (61.5)	-
V5 (L)	91.8 (16.0)	80.7 (68.0)	-
PM (%) – P(1)	4.93 (34.5)	-	-
IM (%) – P(2)		-	-
Single dose trials	23.5 (32.3)		
All other trials	8.26 (30.5)		
EM (%) – P(3)		-	-
Single dose trials	71.6		
All other trials	86.8		
As add-on to CBZ (L/h)		-	-
CLP, +CARB	6.49 (33.0)		
CLM, +CARB	6.22 (10.2)		
Residual variability (%SD)			
RIS	30.5 (18.4)		
9OH	36.2 (13.4)		

The following figure shows the plots of measured risperidone and 9-hydroxy-risperidone concentrations versus population (left panel) and individual (right panel) predictions. Full lines are identity lines, dashed lines represent local smoothers.
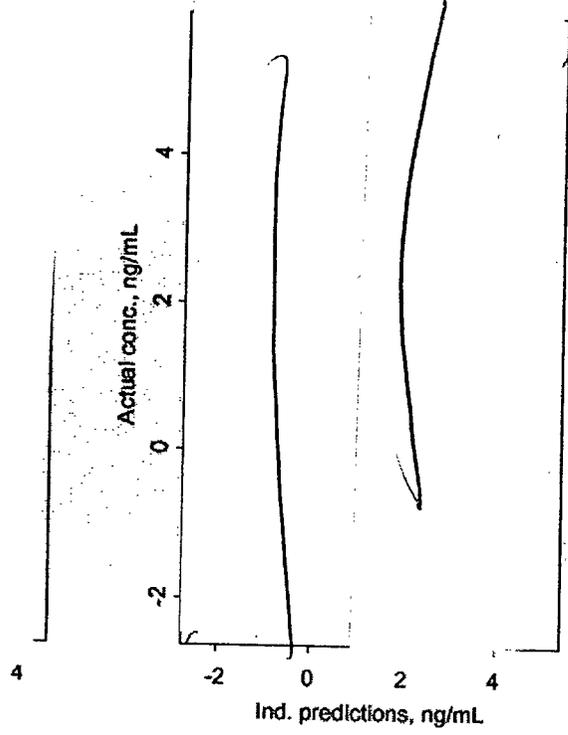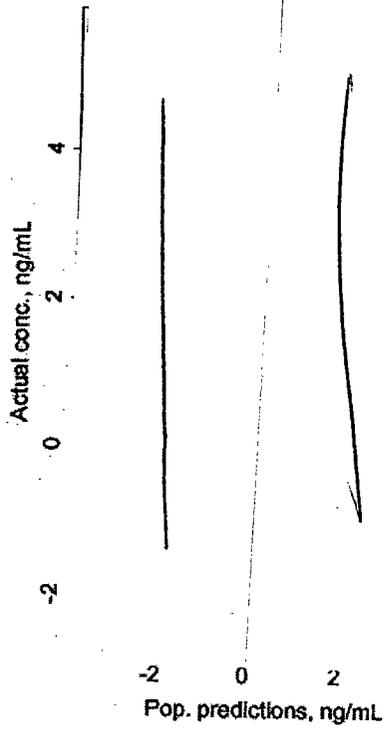
Risperidone
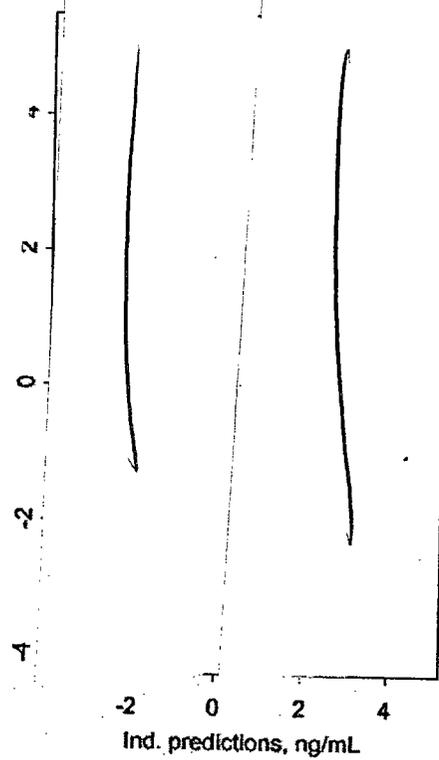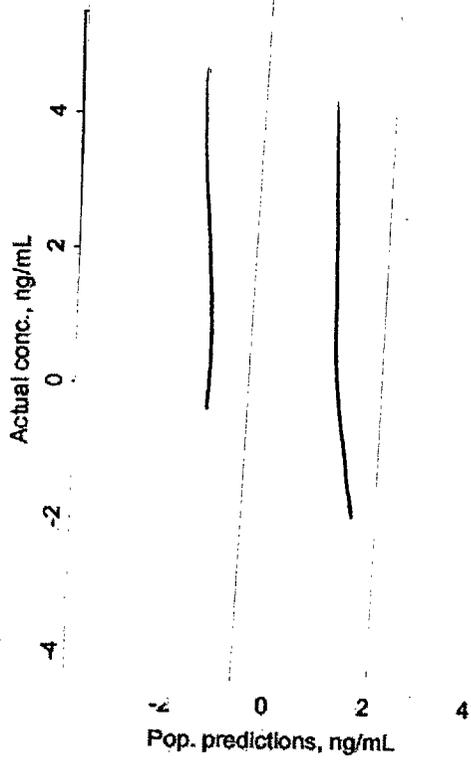
Model diagnostics includes the plots of weighted residuals versus population predictions, individual residuals versus individual predictions, and the normal quantile plots (qq plots) for both risperidone and 9-hydroxy-risperidone as shown in the following figures. Weighted Residuals Outside the Range of (+6, -6) Are Potential Outliers and Are Indicated With Their ID and STU Numbers. Dashed Lines Represent Supersmoothers and Full Lines Loess Smoothers.

Risperidone
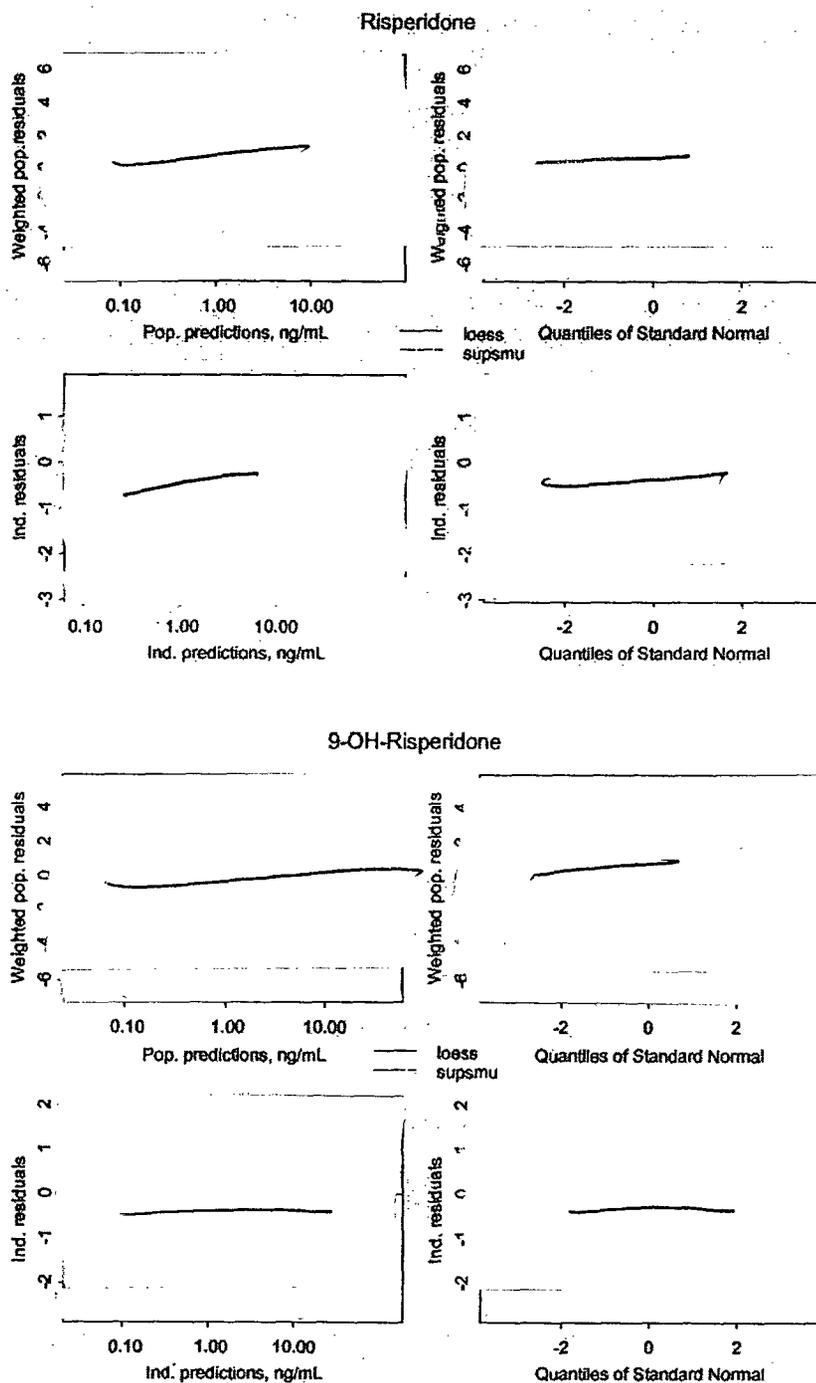
9-OH-Risperidone

Following figure shows the plots of weighted population (left panel) and individual (right panel) residuals versus time for risperidone (upper panel) and 9-OH-risperidone (lower panel). Lines are local smoothers.
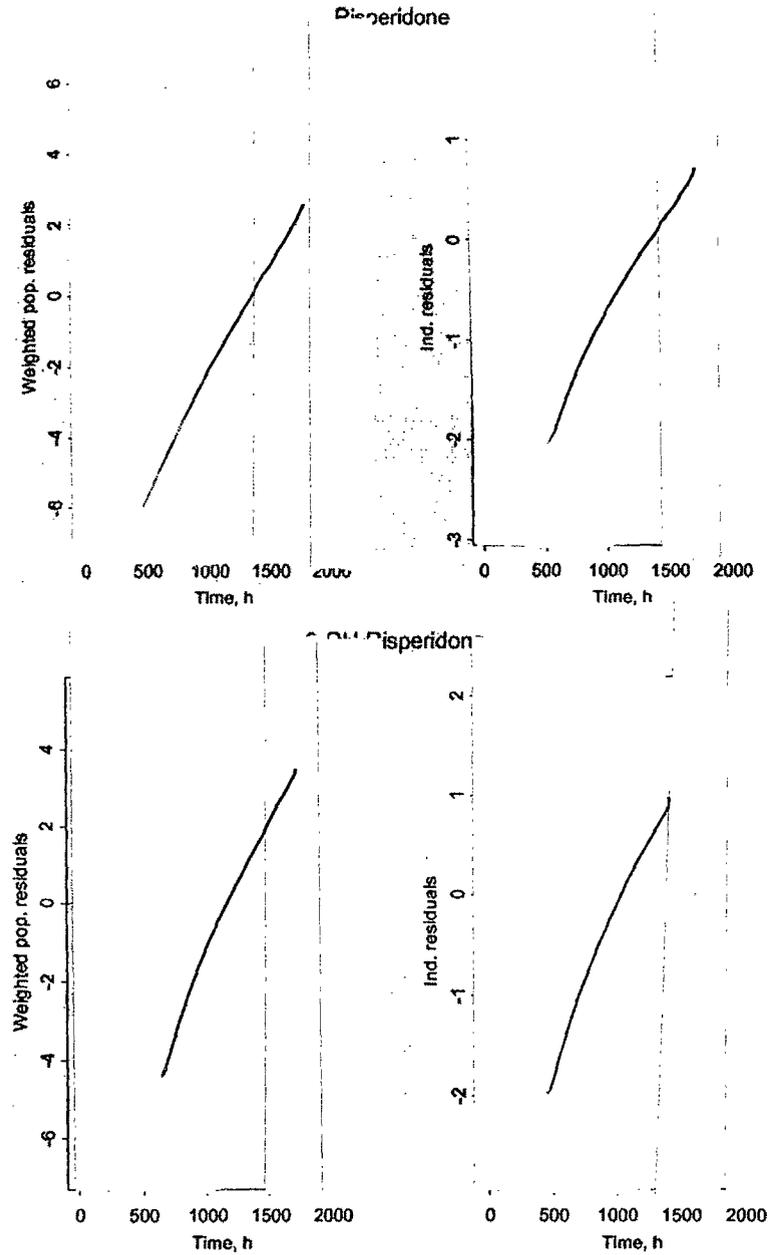
6. Simulation

A simulation for the concentrations of risperidone and 9-hydroxy-risperidone needed for the calculation of the active moiety quasi-clearance was performed. The so-called quasi-clearance refers to the apparent clearance for the active moiety (total of risperidone and 9-hydroxy-risperidone).

The following figures present plots of the active moiety quasi-clearance versus the important patient characteristics.

ive moiety

Active moiety

CL, L/h

100
50
10
5

Male   Female

CL, L/h

100
50
10
5

Caucasian   Black   Orl   His

CL, L/h

100
50
10
5

40   60   80   100   120   140
WT

CL, L/h

100
50
10
5

30   40   50   60   70   80
LBM

CL, L/h

100
50
10
5

20   30   40   50   60
BMI

CL, L/h

100

5

1.5   2.0   2.5
BSA

77
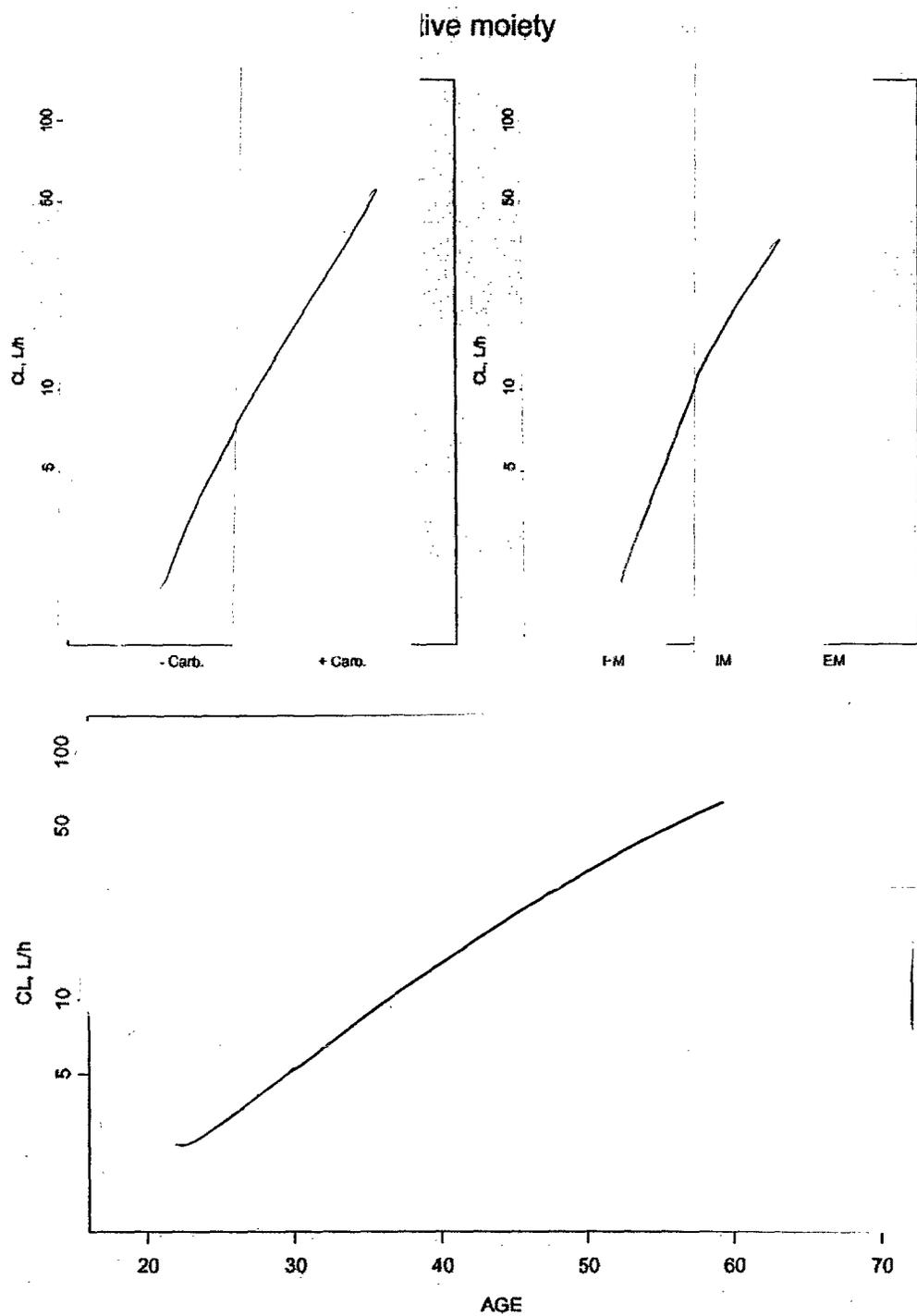
Active moiety

Active moiety

CL, L/h vs CLCR, mL/min
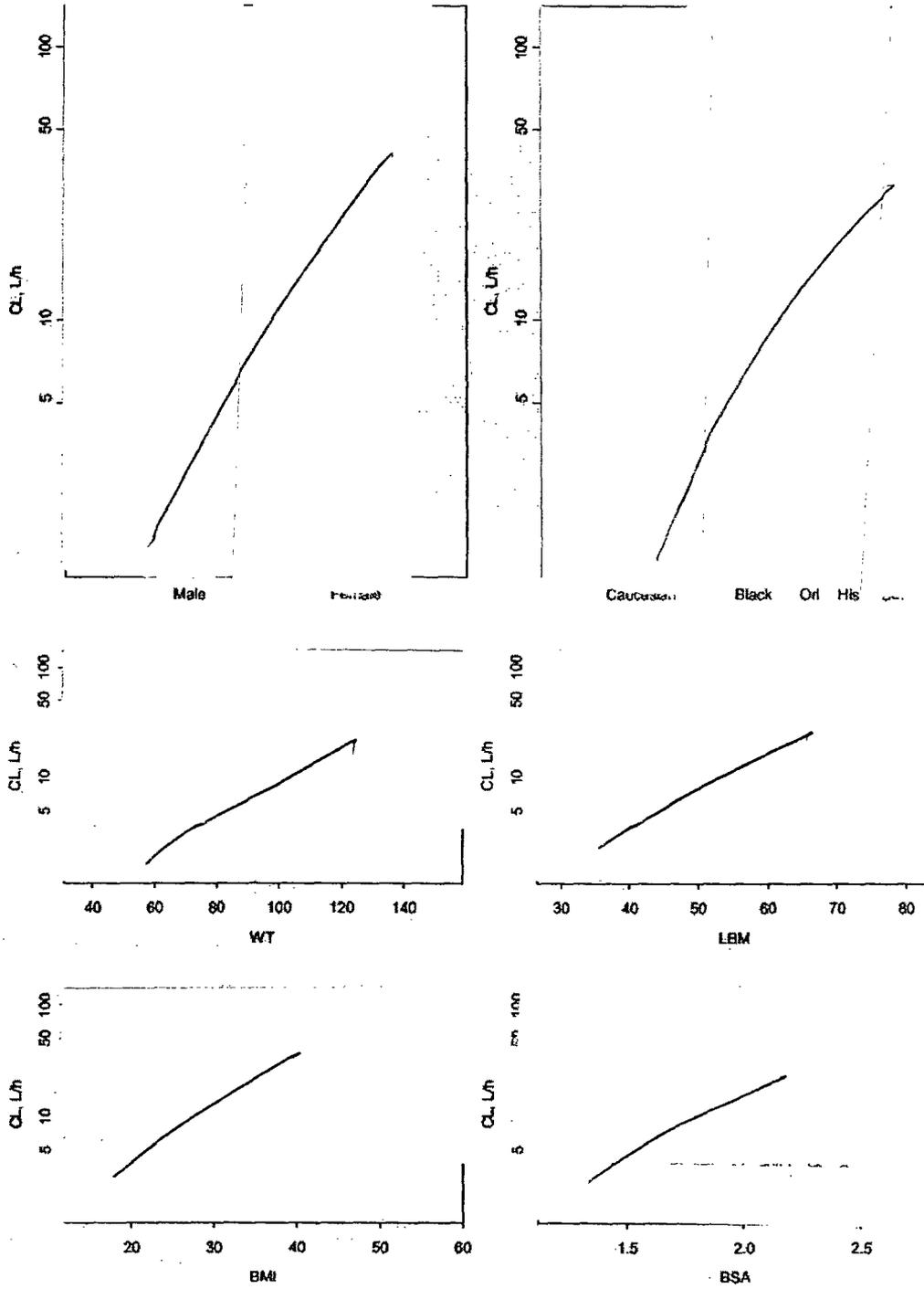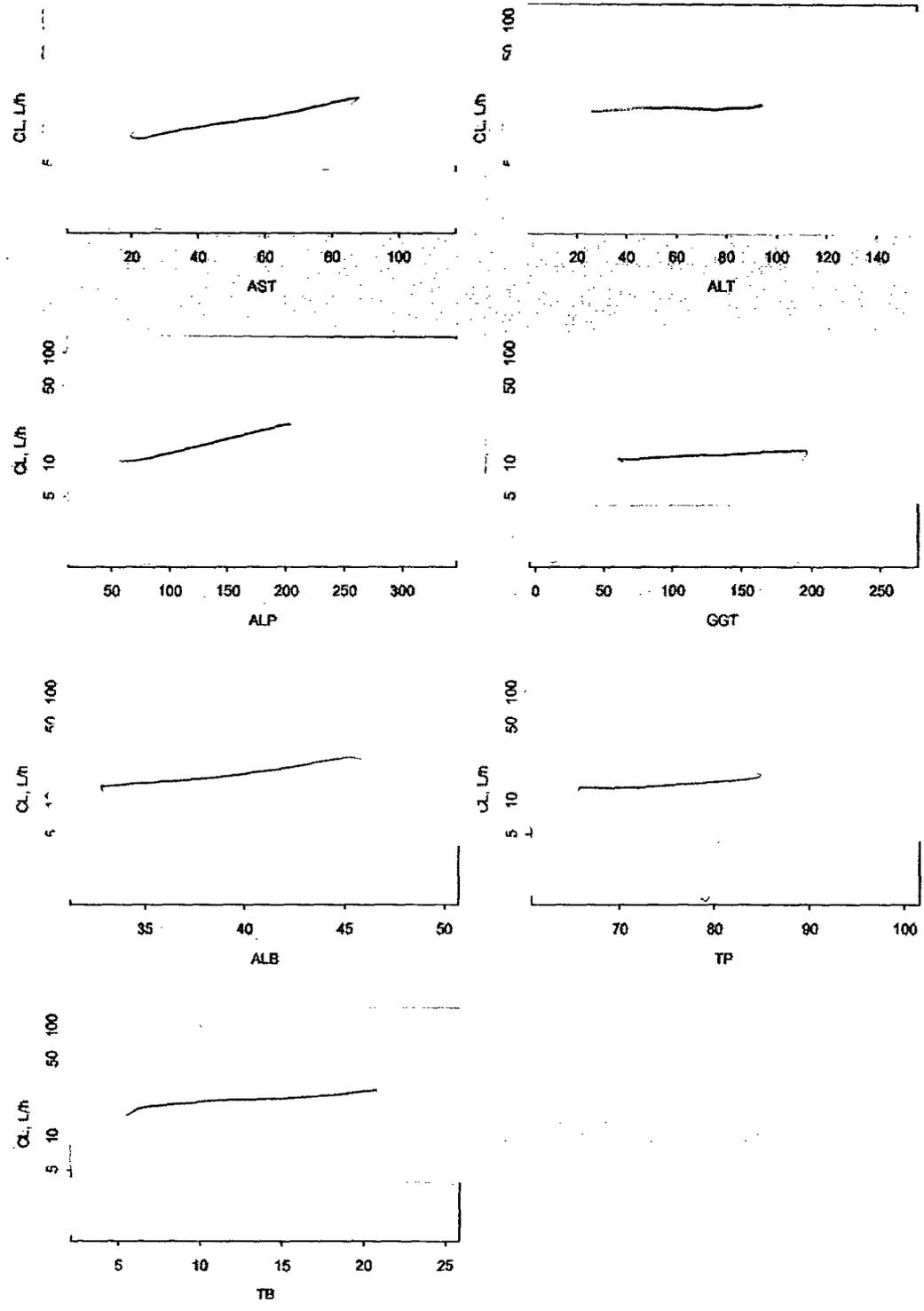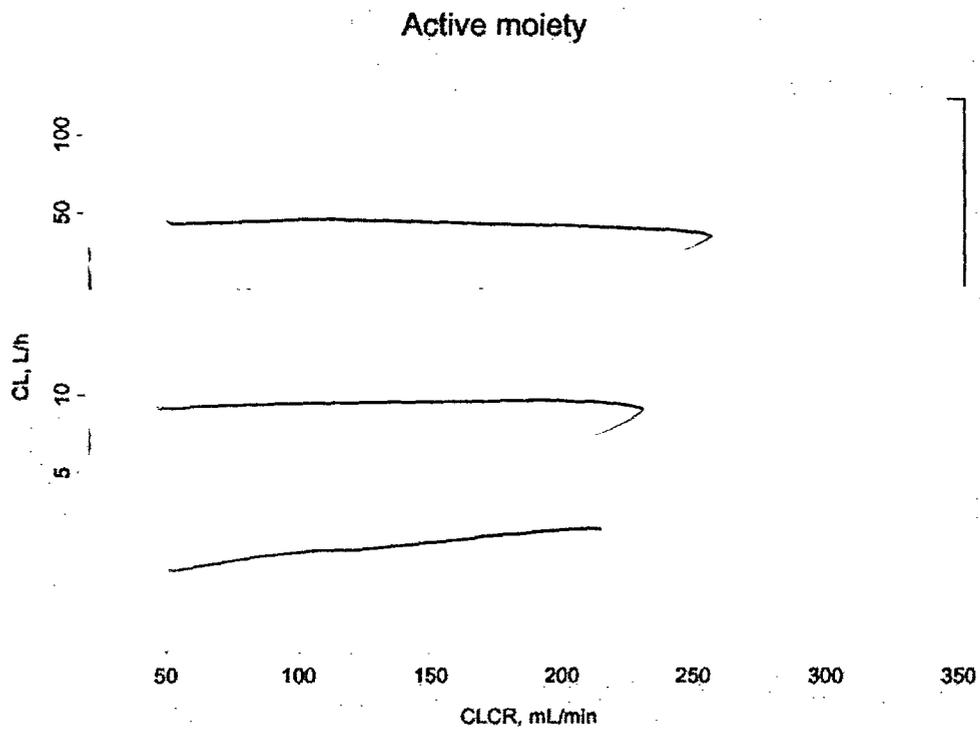
Regression analysis revealed a few significant correlations as shown in the following Table

Covariate	Intercept	Slope	P-value	Comments
AGE	7.5344	-0.0287	0.293	NS
WT	6.0680	0.0055	0.7057	NS
LBM	5.1458	0.0253	0.3529	NS
BMI	6.3990	0.0027	0.9529	NS
BSA	5.4919	0.5298	0.5898	NS
AST	6.5657	-0.0064	0.8536	NS
ALT	6.7840	-0.0130	0.5716	NS
ALP	6.6913	-0.0028	0.6923	NS
GGT	6.2324	0.0072	0.6388	NS
ALB	3.3941	0.0601	0.5538	NS
TP	-5.4487	0.1609	0.0063	Statistically significant
TB	6.9347	-0.0682	0.4844	NS
CLCR	6.6165	-0.0019	0.8234	NS
CARB	7.4681	1.1129	0.1127	NS
SEX	6.4596	-0.0490	0.8776	NS
RACE	6.4943	1.1560	0.0097	Statistically significant
		-0.8941	0.3426	
		-0.0085	0.9887	
		0.1120	0.7749	
SUBP	7.3137	-2.4006	0.0033	Statistically significant
		-0.5037	0.0856	

The effect of total protein, which most probably is a coincidence, the effect of RACE, where black patients seem to have higher clearances, and the effect of phenotype (SUBP), with EMs showing the highest quasi-clearance. None of these findings is expected to be clinically significant.

COMMENTS

1. A deficiency of the analysis is that the model treated the pre-systemic conversion and systemic conversion of risperidone to 9-hydroxyrisperidone differently represented by K14 and K24, respectively. The conversion is catalyzed by the same enzyme system and should have the same conversion rate constant, i.e., K14 should be the same as K24.

2. FP is defined as apparent fraction of the bioavailable dose absorbed as 9-hydroxy-risperidone. As a bioavailability factor, it is related to dose. However, in the model, this was used as factor to partition the absorption constant KA (to K12 and K14). To clarify the confusion, FP should be regarded as a factor to direct different amount of drug in depot to central compartments of riperidone (compartment 2) and 9-hydroxyrisperidone.(compartment 4), respectively.

3. Carbamazepine, as a CYP3A inducer, affected the risperidone clearance (CLP) that mediated by CYP3A4. However, its effect on the 9-hydroxy-risperidone clearance (CLM) is not well understood. Although the effect was kept in the model, the parameter estimate for CLM had no big difference between that in the presence and that in the absence of carbamazepine.

4. Due to the NONMEM run time (about 4-5 days on a 1.5 GHz computer without the covariance step), following limitations were posed.

   • The number of covariate effects that could be tested through inclusion in the model may be limited.

   • The first-order estimation method was used throughout the analysis. The first order conditional estimation method may be a better choice.

5. None of the demographic and biochemical variables had any influence on the pharmacokinetic parameters, which contrasts to results of previous population pharmacokinetic analyses, although the fact that the patient population was quite homogeneous can explain some of the differences.

6. The previous population pharmacokinetic analysis of risperidone and active moiety in dementia patients revealed a decrease of the apparent active moiety clearance with creatinine clearance below 50 mL/min associated with advanced age. However, the current analysis showed a lack of creatinine clearance effect on CLM. The studies under the current analysis included patients with a range of serum creatinine concentrations ̦ ————————— ʰat was within the non-pathological range of ————————. Nevertheless, calculated creatinine clearances ranged from . ————————————————————. In the trials in bipolar mania patients, only a very small proportion of patients was older than 60 and had their

creatinine clearance below 50 mL/min. This precluded the identification of a creatinine clearance effect on 9-hydroxy-risperidone clearance and active moiety quasi-clearance.

7. The model reasonably described the data based on the following observations.

- The structural pharmacokinetic model for risperidone and 9-hydroxy-risperidone was selected based on the prior expectation listed below.

  ➢ Risperidone is extensively metabolized in the body, and 9-hydroxy-risperidone is its primary metabolite formed systemically and also during the first pass through the liver after oral intake. The CYP2D6 isozyme is the primary isozyme involved in 9-hydroxy-risperidone formation.

  ➢ There are alternative metabolic pathways for risperidone mediated by other cytochrome P-450 isozymes including CYP3A4.

  ➢ 9-hydroxy-risperidone is metabolized further and also excreted unchanged via kidneys.

  ➢ Both compounds are distributed in the body, and at least one peripheral compartment for each can be distinguished based on visual inspection of plasma concentration-time profiles after single-dose administration.

- The patient characteristics were tested as potential covariates affecting pharmacokinetic parameters including age, sex, race, body weight, lean body mass, body mass index, renal function (creatinine clearance), lab parameters as indicators for liver functioning, study and concurrent intake of carbamazepine.

- A mixture model was implemented to address the phenotypic differences. Due to the crucial role of CYP2D6, risperidone metabolism is polymorphic, and three phenotypes were identified previously based on risperidone/active moiety ratios. Phenotypic differences could affect two model parameters: FP and CLPM. The model was able to differentiate between the three phenotypes (PMs, IMs and EMs). After single dosing, the per cent PMs is estimated to account for 4.9% of the patient population, the per cent IMs to 23.5% and the per cent EMs to 71.6%.

- Total clearance for risperidone calculated as the sum of CLP and CLPM, matches reasonably well with data after oral administration of risperidone (this analysis versus RIS-HOL-9005 data). PM 4 versus 4 L/h, IM 7 versus 17 L/h and EM 22 versus 31 L/h. Note the RIS-HOL-9005 study included 12 subjects only (among them, 2 PMs and 1 IM).

- Interoccasion variability was implemented for the relative bioavailability parameter F1, which was needed to account for the variability inherent to cross-over design studies and repeated dosing studies with several observation periods. This was also implemented for the absorption parameters (D1 and KA) that account for the high variability of absorption profiles between occasions.

- The interindividual variability (IIV) was estimated for all pharmacokinetic parameters, but the intercompartmental exchange flow rate for 9-hydroxy-risperidone.

- The diagnostic plots for the final model support the goodness of fit.

8. The significance of the effects of patients' demographic characteristics and other covariates on risperidone, 9-hydroxy-risperidone and active moiety (i.e. the sum of risperidone and 9-hydroxy-risperidone) pharmacokinetics may be interpreted as follows.

- Risperidone conversion to other metabolites (CLP) is not phenotype-dependent, but is increased by carbamazepine coadministration with a factor of 2.3 (from 2.8 to 6.5 L/h). On the other hand, 9-hydroxy-risperidone clearance (CLM) is almost unaffected: 6 vs. 6.2 L/h. This may indicate a negligible role of CYP3A4 in the further metabolism of 9-hydroxy-risperidone. Concentrations of 9-hydroxy-risperidone are substantially lower on carbamazepine co-therapy. This is a consequence of the suppressed 9-hydroxy-risperidone production caused by significantly decreased risperidone levels. This result is in line with that of a formal drug interaction study between risperidone and carbamazepine. Therefore, it is recommended that the dose of risperidone need to be titrated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy or other known enzyme inducers. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin and phenobarbital) with risperidone may cause similar decreases in the plasma concentrations of active moiety, which could lead to decreased efficacy of risperidone treatment.

- Study as a covariate affected the proportion of phenotypes. Multiple dosing had a lower proportion of IMs compared to single dose study (8.3% vs. 23.5%) and a higher proportion of EMs accordingly (86.8% vs. 71.6%). However, this does not impact the plasma concentrations of the active moiety. No differences between the Phase 3 trials could be observed.

- High IIV was observed for the absorption parameters KA and DUR. Also, the fraction metabolized during first pass was subject to a substantial interindividual variability. High interindividual variability was also observed for the clearance of risperidone and for its intercompartmental exchange flow rate.

In summary, this review answers the questions raised.

1. Is the pharmacokinetics of risperidone similar between patients with schizophrenia and bipolar mania?

The population pharmacokinetic model supports the similarity of pharmacokinetics between patients with schizophrenia and bipolar disorder.

2. Is there a need for dose adjustment when risperidone is given with carbamazepine? If yes, how should it be done?

The population pharmacokinetic model supports the dosing recommendation that the dose of risperidone may need to be titrated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy.

RECOMMENDATIONS

1. The population pharmacokinetic model supports the similarity of PK between patients with schizophrenia and bipolar disorder.

2. The population pharmacokinetic model supports the dosing recommendation that the dose of risperidone may need to be titrated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy.

Appendix III. Individual study synopsis

1. Study RIS-CAN-27. Drug interaction with valproate.

Study title: Observational, open, parallel-group trial to document the steady-state pharmacokinetics and safety of valproate in combination with risperidone or placebo in 24 adult bipolar patients. (Trial No.: RIS-CAN-27)

This study was reviewed previously under NDA 21-346.

2. Study RIS-FRA-4 . Drug interaction with carbamazepine.

Study title: Study of the effect of carbamazepine on the pharmacokinetics of risperidone in schizophrenic patients. (Trial No.: RIS-FRA-4)

This study was reviewed previously under NDA : ————

3. Study RIS-GER-9 . Drug interaction with lithium.

Study title: A study of the steady-state pharmacokinetics and safety of lithium in adult psychotic patients taking lithium in combination with risperidone or with other antipsychotic agents. (Trial No.: RIS-GER-9)

This study was reviewed previously under NDA 21-346.

4. Study RIS-SUI-5. Drug interaction with fluoxetine.

Study title: The effect of fluoxetine on the pharmacokinetics and safety of risperidone in adult psychotic patients (Trial No.: RIS-SUI-5).

This study was reviewed previously.

5. Study RIS-RSA-1. Drug interaction with amitriptyline.

Study title: Study of the effect of amitriptyline on the pharmacokinetics of risperidone in schizophrenic patients (Trial No.: RIS-RSA-1).

Investigator: Prof. De K. Sommers, Dept. of Pharmacology, University of Pretoria, P.O. Box 2034, Pretoria 0001, South Africa.

Study period: May 14, 1994 –June 10, 1994

Study Objectives: To assess the effect of repeated amitriptyline doses on risperidone steady-state pharmacokinetics.

Study Design:
This was an open-label, single center, 28-day treatment study conducted in 12 schizophrenic patients. The patients were titrated to a dose of 3 mg risperidone b.i.d. over a two-day period. The 3 mg b.i.d. dose was then maintained from Day 3 till Day 28. Amitryptiline was administered 2 weeks after the start of the risperidone treatment, when risperidone and the active moiety were at steady state. The dosage of amitriptyline was 25 mg b.i.d. on Day 15 and 50 mg b.i.d. from Day 16 to Day 21.

Blood samples for risperidone were taken pre-dose on Days 12-14, 19-21, 27 and 28 with serial sampling on Days 14 and 21. Blood samples for amitriptyline were taken pre-dose on Days 12, 19-21, 27 and 28 with serial sampling on Day 21.

Results

Assay performance

Radioimmunoassay procedures (RIA) were used to determine the plasma concentrations of risperidone (RIA I) and the active moiety (RIA II). The following table shows the assay performance.

Assay	Quan limit	Range (ng/mL)	Precision (CV%)	Accuracy (%)
RIA I			6.2 to 14.4	
RIA II			3.5 to 15.4	

Amitriptyline and nortriptyline plasma levels were determined using the GC-NPD. The following table shows the assay performance.

Assay	Quan limit	Range (ng/mL)	Precision (CV%)	Accuracy (%)
Amitriptyline			2.1 to 6.9	
Nortriptyline			3.1 to 4.2	

The assays are acceptable based on current standard.

Pharmacokinetics

The pharmacokinetic parameters of the active moiety, risperidone and 9-hydroxy-risperidone are summarized in the following table.

Parameters (mean ± SD; N=12)	Risperidone + Amitriptyline	Risperidone Alone	AUC ratio ± SD Risperidone + amitriptyline / Risperidone alone
Active moiety			
tmax, h	2.3 ± 0.5	1.9 ± 0.7	-
Cmax, ng/mL	74.6 ± 27.3	71.0 ± 27.5	-
AUC12h, ng.h/mL	650 ± 245	584 ± 245	1.16 ± 0.34
Risperidone			
tmax, h	2.0 ± 0.7	1.8 ± 0.6	-
Cmax, ng/mL	28.4 ± 24.0	25.0 ± 21.5	-
AUC12h, ng.h/mL	183 ± 189	152 ± 157	1.21 ± 0.35
9-hydroxy-risperidone			
tmax, h	3.2 ± 1.4	3.1 ± 2.4	-
Cmax, ng/mL	49.9 ± 18.5	48.1 ± 19.2	-
AUC12h, ng.h/mL	475 ± 186	432 ± 187	1.15 ± 0.36

No statistically significant differences in mean pharmacokinetic parameters (AUC12h, tmax and Cmax) were found between risperidone monotherapy and the 1-week co-treatment with amitriptyline. The AUC12h ratio of 9-hydroxy-risperidone to risperidone was unchanged between the two trial periods (4.1 at Day 14 versus 3.9 at Day 21).

The pharmacokinetic parameters of amitriptyline and the active metabolite nortriptyline are summarized in the following table.

Parameters (mean ± SD; N=12)	Amitriptyline	Nortriptyline
tmax, h	2.6 ± 0.5	4.3 ± 4.9
Cmax, ng/mL	79.9 ± 26.1	43.6 ± 16.5
AUC12h, ng.h/mL	725 ± 250	460 ± 176

The steady-state plasma concentrations of amitriptyline after one week of treatment ranged between ——————— corresponding to values reported in the literature. These data do not suggest an effect of risperidone co-administration on the pharmacokinetics of amitriptyline.

Comments

1. The conclusion should be drawn after the 90% confidence interval is calculated
2. amitriptyline exerts no inhibitory action on the metabolism of risperidone or 9-hydroxy-risperidone.

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6. Study RIS-USA-122. Drug interaction with donepezil.

Study title: Determination of the pharmacokinetics and safety of steady-state risperidone and donepezil administration in healthy male volunteers. (Trial No.: RIS-USA-122)

Investigator: Jerry Herron, MD, Little Rock, Arkansas, USA

Study period: September 16, 1998 to December 16, 1998

Study Objectives: The primary objective of the trial was to compare the pharmacokinetic profiles of risperidone and donepezil when taken alone and taken together at steady-state. A secondary objective was to monitor the safety of the combination of risperidone and donepezil at steady-state in healthy male volunteers.

Study Design:
This is a single center, open label, randomized, 3-way crossover study that evaluated the pharmacokinetic (PK) profiles of steady-state risperidone (RIS), donepezil (DON), and their combination in 24 healthy male volunteers. Each subject received RIS 0.5 mg twice daily (b.i.d.) plus placebo (PLA), DON 5 mg once daily (o.d.) plus PLA, and RIS 0.5 mg b.i.d. plus DON 5 mg o.d. for 14 days in each treatment period. The treatment periods were separated by 21-day washout periods. Blood samples for PK determinations were taken immediately before 8 AM dosing on Days 1, 7, 11, 12, and 13 (Period I); Days 36, 42, 46, 47, and 48 (Period II); and Days 71, 77, 81, 82, and 83 (Period III). Additional PK blood samples were taken at the end of each period (Days 14, 49, and 84) immediately before 8 AM dosing (Hour 0) and at 0.5, 1, 2, 3, 4, 8, 12, 16, and 24 hours post-dose.

Results
Assay performance

Radioimmunoassay procedures (RIA) were used to determine the plasma concentrations of risperidone (RIA I) and the active moiety (RIA II). The following table shows the assay performance.

Assay	LOQ (ng/mL)	Range (ng/mL)	QC sample		Calibration	
			Precision (CV%)	Accuracy (%)	Precision (CV%)	Accuracy (%)
RIA I			5.5 to 10.7		2.5 to 6.9	
RIA II			4.3 to 9.4		2.4 to 5.6	

The determination of donepezil in plasma employed an HPLC-UV method.

Assay	LOQ (ng/mL)	Range (ng/mL)	QC sample		Calibration	
			Precision (CV%)	Accuracy (%)	Precision (CV%)	Accuracy (%)
RIA I			4.0 to 2.6		1.5 to 8.1	

The assays are acceptable based on the current standard.

Pharmacokinetics

Risperidone-donepezil interaction analysis was conducted similarly to analysis of average bioequivalence. The pharmacokinetic parameters of the active moiety, risperidone, 9-hydroxy-risperidone and donepezil, as well as summary statistics are included in the following table.

Parameters (N=24)	Mean ± SD		Treatment ratio (90% CI)
	Risperidone + Donepezil	Risperidone alone	Risperidone + Donepezil / Risperidone alone*
Active moiety			
AUCτ, ng.h/mL	109 ± 33	100 ± 36	110.36 (103.93 - 117.20)
Cmax, ng/mL	12.7 ± 4.2	11.1 ± 3.8	114.61 (107.46 - 122.24)
Cmin, ng/mL	6.38 ± 1.91	6.01 ± 2.38	108.22 (100.53 - 116.49)
Cavg, ng/mL	9.10 ± 2.74	8.33 ± 3.02	110.44 (104.00 - 117.28)
Fluctuation Index	0.69 ± 0.16	0.62 ± 0.13	110.97 (99.49 - 122.46)
Risperidone			
AUCτ, ng.h/mL	31.3 ± 30.9	28.3 ± 32.9	114.54 (103.06 - 127.31)
Cmax, ng/mL	4.84 ± 3.09	4.12 ± 3.29	120.67 (107.42 - 135.56)
Cmin, ng/mL	1.23 ± 1.93	1.16 ± 1.94	108.74 (95.41 - 123.93)
Cavg, ng/mL	2.61 ± 2.58	2.37 ± 2.76	114.50 (103.05 - 127.23)
Fluctuation Index	1.80 ± 0.68	1.65 ± 0.60	108.73 (100.61 - 116.86)
9-hydroxy-risperidone			
AUCτ, ng.h/mL	77.8 ± 18.7	71.6 ± 21.6	109.83 (103.86 - 116.14)
Cmax, ng/mL	8.52 ± 2.69	7.42 ± 2.41	114.90 (106.91 - 123.49)
Cmin, ng/mL	5.14 ± 1.39	4.85 ± 1.48	106.43 (97.63 - 116.04)
Cavg, ng/mL	6.49 ± 1.56	5.97 ± 1.80	109.83 (103.89 - 116.12)
Fluctuation Index	0.51 ± 0.25	0.43 ± 0.15	120.60 (94.72 - 146.48)
Donepezil			
	Risperidone + Donepezil	Donepezil	Treatment ratio (90% CI) Risperidone + Donepezil / Donepezil alone*
AUCτ, ng.h/mL	437 ± 113	444 ± 93	97.03 (91.11 - 103.33)
Cmax, ng/mL	22.3 ± 5.6	23.0 ± 4.7	96.06 (90.14 - 102.37)
Cmin, ng/mL	14.9 ± 4.2	15.0 ± 3.4	97.92 (90.15 - 106.36)
Cavg, ng/mL	18.2 ± 4.7	18.5 ± 3.9	96.96 (91.06 - 103.24)
Fluctuation Index	0.41 ± 0.09	0.43 ± 0.08	95.53 (89.82 - 101.24)

Relative bioavailability and associated 90% CI of logarithmic transformed AUCτ, Cmax, Cmin, and Cavg were contained in the equivalence range of 80% to 125% for active moiety, 9-hydroxy-risperidone, and donepezil. For risperidone, all upper limits exceeded 125%, except that of Cmin (90% CI 95.41-123.93%). These results suggest a minor interaction between donepezil and the parent drug risperidone, which is unlikely to be clinically significant.

Safety

Twenty subjects (83.3%) reported at least one adverse event (AE). Of 13 types (preferred terms) of AE reported, the most frequent were headache, nervousness, and somnolence. No AE was severe, serious, or related to treatment with the study medication. No AE resulted in subject

discontinuation from the trial. There were no clinically relevant changes in laboratory or vital signs. There were no clinically relevant changes in ECG measurements during treatment with risperidone. On Day 14 of donepezil treatment, one subject with normal baseline QTc values had prolonged (QT 452 ms).

Comments

1. The results of this study indicated a minor increase in some pharmacokinetic parameters of the parent drug risperidone upon co-administration of donepezil. These increases are unlikely to be clinically relevant, while no effects of donepezil on the pharmacokinetic parameters of 9-hydroxy-risperidone and the active moiety were observed.

2. The study showed no effect of risperidone on donepezil pharmacokinetics.

7. Study GAL-USA-19. Drug interaction with galantamine.

Study title: Drug interaction trial to explore the pharmacokinetic effects of coadministration of REMINYL (galantamine) and RISPERDAL (risperidone) at steady state in normal, healthy, elderly volunteers. (Trial No.: GAL-USA-19)

Investigator: K. Lasseter, M.D

Study period: July 18, 2000 to October 2, 2000

Study Objectives: To assess the potential mutual pharmacokinetic interaction of REMINYL (galantamine) and RISPERDAL (risperidone) and the safety of the combination versus the safety profile of the drugs when administered as monotherapy in healthy elderly subjects.

Study Design: This was an open-label, randomized, 2-way crossover, single-center, Phase I trial. Sixteen elderly healthy subjects were randomized to 2 treatment sequences. Each subject received both treatments in a randomized, crossover order. The 2 periods were separated by a 14-day washout period.

Treatment A:
RISPERDAL® (risperidone): 0.5 mg b.i.d. for 6 days (Days 1-6 or Days 44-49), then 0.5 mg q.d. for 1 day (Day 7 or Day 50).

Treatment B:
REMINYL® (galantamine): 4 mg b.i.d. for 7 days (Days 1-7 or Days 23-29), 8 mg b.i.d. for 7 days (Days 8-14 or Days 30-36), 12 mg b.i.d. for 7 days (Days 15-21 or Days 37-43), 12 mg b.i.d. for 6 days (Days 22-27 or Days 44-49) and 12 mg q.d. for 1 day (Day 28 or Day 50) each coadministered with risperidone.

RISPERDAL® (risperidone) → 0.5 mg b.i.d. for 6 days (Days 22-27 or Days 44-49) and 0.5 mg q.d. for 1 day (Day 28 or Day 50) each coadministered with galantamine.

The treatment sequences were:
Group 1: Treatment A then B (or Group RIS/GAL+RIS).
Group 2: Treatment B then A (or Group GAL+RIS/RIS).

A total of 16 elderly subjects (with a minimum of 8 female subjects) were to be enrolled to ensure complete data from the 2 treatment periods from 12 subjects. Additional subjects were to be enrolled if necessary to ensure complete data from a minimum of 12 subjects total and 4 subjects for each treatment sequence. However, all valid data including data from any dropout subject were to be reported and incorporated in the final analysis when appropriate.

Sampling for treatment A: On Days 5 and 6 (or Days 48 and 49), one 5-mL blood sample was collected at 0 hour (prior to morning dosing). On Day 7 (or Day 50), one 5-mL blood sample was collected at 0 hour (prior to morning dosing), and at 0.5, 1, 2, 3, 4, 5, 7, 9, 12, 24, 48, 72, and 96 hours postdosing.

Sampling for treatment B: On Days 19 and 20 (or Days 41 and 42), one 5-mL blood sample was collected at 0 hour (prior to morning dosing). On Day 21 (or Day 43), one 5-mL blood sample was collected at 0 hour (prior to morning dosing), and at 0.5, 1, 2, 3, 4, 5, 7, 9, and 12 hours postdosing. On Days 26 and 27 (or Days 48 and 49), two 5-mL blood samples were collected at 0 hour (prior morning dosing). On Day 28 (or Day 50), two 5-mL blood samples were collected at 0 hour (prior to morning dosing), and at 0.5, 1, 2, 3, 4, 5, 7, 9, 12, 24, 48, 72, and 96 hours postdosing.

Results:
Assay performance

A LC/MS/MS method was used for the determination of risperidone and its metabolite 9-hydroxyrisperidone in 496 human plasma samples. The following table shows the assay performance in this study.

Assay	Quan limit	Range (ng/mL)	Precision (CV%)	Accuracy (%)
Risperidone			3.1 to 9.6	
9-OH-Risperidone			4.4 to 5.7	

The determination of galantamine used an HPLC-fluorescence method. The assay performance are shown in the following table.

| Quan limit	Range (ng/mL)	Precision (CV%)	Accuracy (%)
		1.4 to 3.8	

The assays are acceptable based on current standard.

Pharmacokinetics

The mean values of PK parameters of galantamine for both Single and Combination Treatments are summarized in the following Table.

	Single Treatment		Combination Treatment	
	Mean	SD	Mean	SD
$AUC\tau$, ss , ng.h/mL	729.7	230.4	696.1	186.2
Tmax, ss, h	2.56	1.03	2.19	1.05
Cmax, ss, ng/mL	96.15	28.51	95.91	21.21
Cmin, ss, ng/mL	34.02	16.23	32.99	12.52
Cavg,ss , ng/mL	60.81	19.20	58.01	15.51
FI	1.09	0.32	1.12	0.26
CL/F, L/h	18.47	7.36	18.35	4.58

The mean plasma concentration-time profiles of galantamine for both Single and Combination Treatments are presented in the following Figure. The mean profiles were essentially superimposed for the Single and Combination Treatments. This suggested that that risperidone did not influence the plasma concentration profiles of galantamine at the steady state.
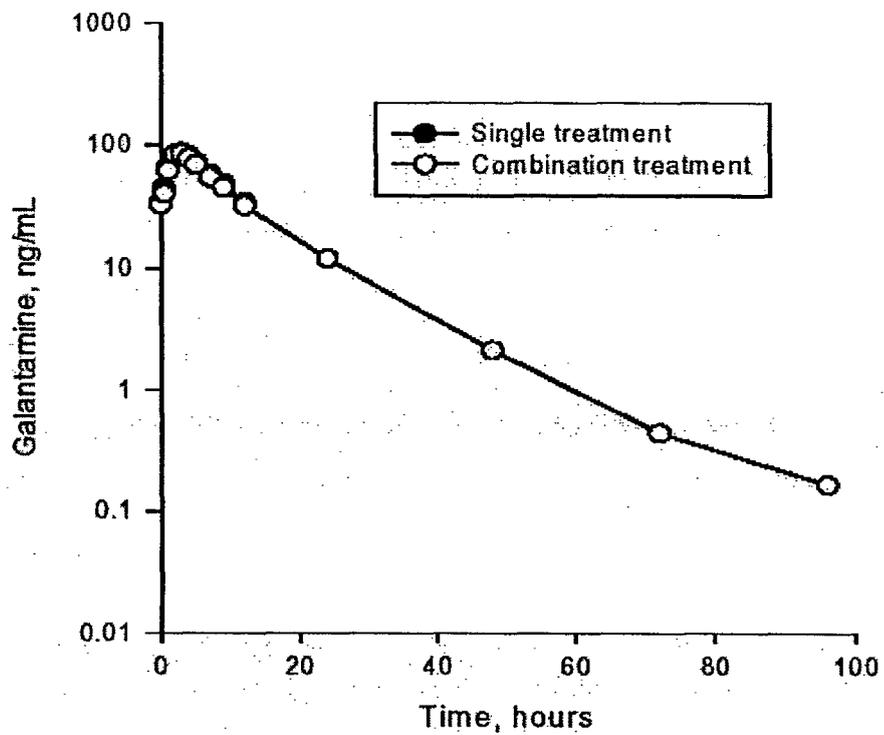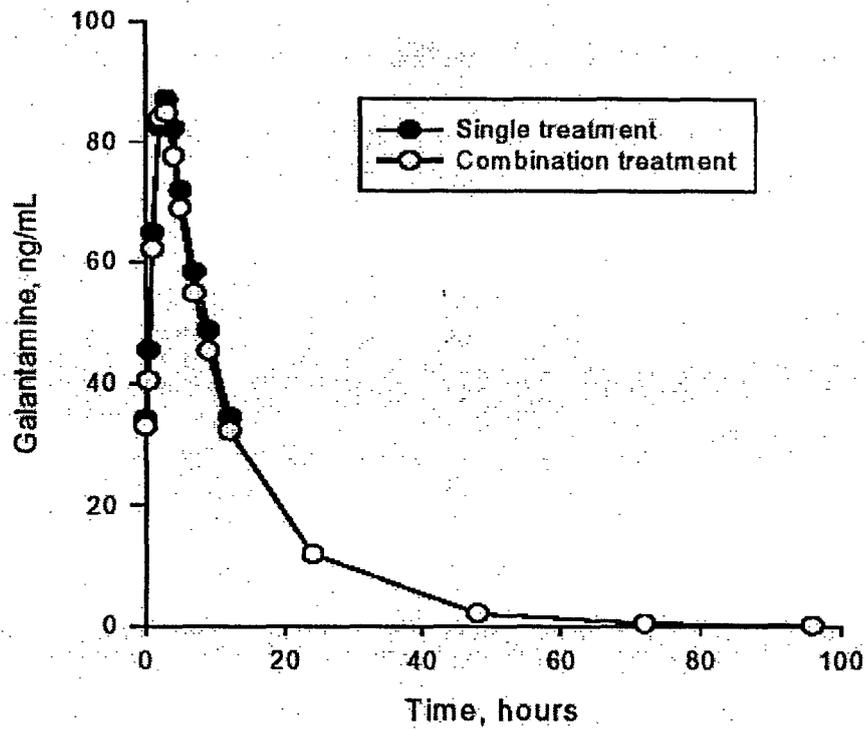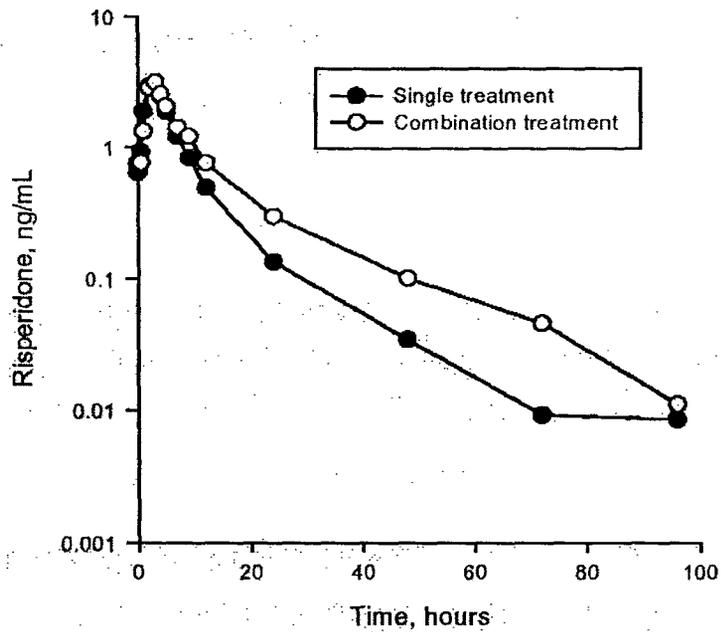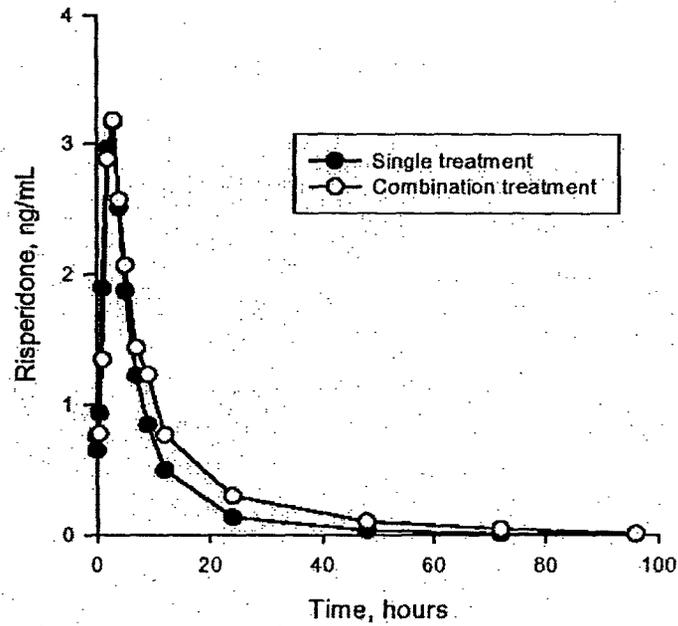
The treatment ratio (RIS+GAL/GAL) and associated 90% CI of AUCσ,ss* and Cmax,ss are summarized in the following Table. As shown in the table, the mean treatment ratios and associated 90% confidence intervals of Cmax,ss and AUCσ,ss were both contained within the range of 80-125%, indicating the steady state bioavailability of galantamine was not altered by coadministration with risperidone.

PK Parameters	Combination Treatment (C)		Single Treatment (S)			Mean Ratio (C/S, %)	90%CI
	N	LS Mean	N	LS Mean	MSE		
AUCτ, ss, ng.h/mL	16	674.3	16	691.7	5063.11	97.5	91.4-104.0
Cmax,ss, ng/mL	16	93.79	16	92.18	84.55	101.7	95.7-108.2

The mean values of PK parameters of risperidone active moiety, risperidone, and 9-hydroxyrisperidone are summarized in the following Table.

	Single Treatment		Combination Treatment	
	Mean	SD	Mean	SD
Active moiety				
AUCτ, ss , ng.h/mL	110.6	39.0	106.5	41.1
Cmax, ss, ng/mL	13.28	5.25	12.01	4.25
Tmax, ss, h	2.53	0.83	3.56	1.86
Cmin, ss, ng/mL	7.57	3.12	7.48	3.38
Cavg,ss , ng/mL	9.22	3.25	8.87	3.43
FI	0.64	0.35	0.55	0.18
λz, 1/h	0.02	0.00	0.02	0.00
t1/2, term, h	30.82	4.24	30.79	4.98
Risperidone				
AUCτ, ss , ng.h/mL	18.9	13.3	21.4	17.0
Cmax, ss, ng/mL	3.96	2.41	3.61	2.08
Tmax, ss, h	2.14	0.74	2.63	0.96
Cmin, ss, ng/mL	0.65	0.68	0.76	0.95
Cavg,ss , ng/mL	1.57	1.11	1.78	1.42
FI	2.39	0.81	2.19	1.09
λz, 1/h	0.21	0.11	0.20	0.12
T1/2, term, h	5.39	5.26	7.27	7.89
CL/F, L/h	41.39	28.21	39.73	26.60
9-hydroxyrisperidone				
AUCτ, ss , ng.h/mL	91.8	30.3	86.0	32.7
Cmax, ss, ng/mL	9.72	3.44	8.73	3.16
Tmax, ss, h	3.47	0.92	4.19	2.14
Cmin, ss, ng/mL	6.93	2.69	6.72	2.98
Cavg,ss , ng/mL	7.65	2.53	7.17	2.73
FI	0.39	0.27	0.31	0.17
λz, 1/h	0.02	0.00	0.02	0.00
t1/2term, h	32.56	4.46	33.08	5.85

The mean plasma concentration-time profiles of risperidone active moiety, risperidone, and 9-hydroxyrisperidone are presented by treatment in the following Figure.

The treatment ratios (RIS+GAL/RIS) and associated 90% CI of $AUC\tau,ss$ and $Cmax,ss$ are summarized in the following Table. For risperidone active moiety, the treatments ratio (93.6%) and associated 90% CI (86.6%, 101.1%) were within the range of 80-125, indicating that the total exposures of the active moiety were essentially the same after Single and Combination

Treatments; The 90% CI of treatment ratio (89.9%) for Cmax,ss were 77.0% to 105.0% and outside the lower boundary of the range of 80-125.

PK Parameters	Combination Treatment (C)		Single Treatment (S)			LS Mean Ratio (C/S,%)	90%CI
	N	LS Mean[a]	N	LS Mean[a]	MSE		
Active moiety							
AUCτ, ss, ng.h/mL	16	99.3	15	106.1	147.55	93.6	86.6-101.1
Cmax,ss, ng/mL	16	11.30	15	12.57	7.99	89.9	77.0-105.0
Risperidone							
AUCτ, ss, ng.h/mL	16	16.1	15	14.6	10.99	110.6	96.4-127.0
Cmax,ss, ng/mL	16	3.16	15	3.27	0.75	96.7	81.3-115.0
9-OH-risperidone							
AUCτ, ss, ng.h/mL	16	80.5	15	89.3	111.02	90.2	83.1-97.9

Adverse events

Overall, 13 (81.3%) subjects reported at least one adverse event (57 adverse events). Adverse events reported in at least 3 subjects overall were headache (n=9), dizziness (n=3), and fatigue (n=3). No difference in incidence was observed when comparing the Combination Treatment RIS+GAL (43.8%) versus RIS 0.5 mg b.i.d. and GAL 12 mg b.i.d. as monotherapy (43.8 and 50.0, respectively).

Comments:

1. Although the study showed that there were no significant drug interactions between risperidone and galantamine, the dose of risperidone used in the study (0.5 mg) was the initial dose for elderly, which may not show the maximum effects. However, based on the results of an in vitro trial on the interaction of galantamine on model substrates for different CYP 450 isoenzymes, the inhibition potential of galantamine towards the major forms of human CYP 450 is very low and probably not clinically relevant. In vivo data confirmed this finding.

2. While both of risperidone and galantamine are metabolized in the liver and at least partially by cytochrome CYP 2D6, neither are considered potent CYP 2D6 inhibitors. Therefore, the CYP 2D6 based effect on the metabolism of either drug with coadministration is expected to be limited.

8. Study RIS-NED-26. Drug interaction with erythromycin.

Study title: Investigation of the Potential Effect of Multiple-Dose Administration of the CYP3A4 Inhibitor Erythromycin on the Pharmacokinetics, the Tolerability and the Safety of a Single Dose of Risperidone in Healthy Volunteers. (Trial No.: RIS-NED-26)

Investigator: D. de Vries, M.D., Pharma Bio-Research Group B.V., Zuidlaren, The Netherlands

Study period: June 5, 2001 to September 24, 2001

Study Objectives: To explore possible effects of coadministration of the selective CYP3A4 inhibitor erythromycin on the single-dose pharmacokinetics of risperidone in healthy volunteers; To explore the tolerability and safety of the risperidone/erythromycin combination; To explore the differences in possible interaction effects between PMs and EMs of CYP2D6.

Study Design:

This is an open, randomized, 3-way cross-over, single-center study. Eighteen subjects were recruited. Among them, there were 12 extensive and 6 poor metabolizers of CYP2D6, as determined by dextromethorphan phenotyping. One subject discontinued the study due to adverse events in the third period of the study; all other subjects completed the study. The three treatment groups are as follows.

Treatment A: Co-treatment of risperidone and erythromycin. Erythromycin 500 mg q.i.d. from Day 1 to Day 6 and risperidone 1 mg single dose on Day 6.
Treatment B: Risperidone alone. Risperidone 1 mg was administrated single dose on Day 6.
Treatment C: Erythromycin alone. Erythromycin 500 mg q.i.d. was administrated from Day 1 to Day 6.

On Day 6, serial blood sampling was performed for risperidone and erythromycin measurement. Pre-dose samples for documentation of steady-state of erythromycin were taken on Days 4, 5 and 6. Separate LC-MS/MS methods were used for bioanalysis of risperidone and erythromycin.

Results

Assay performance

Plasma levels of risperidone (R064766) and 9-hydroxyrisperidone (R076477) were determined using LC-MS/MS methods. The following table shows the assay performance.

Assay	LOQ (ng/mL)	Range (ng/mL)	QC sample		Calibration	
			Precision (CV%)	Accuracy (%)	Precision (CV%)	Accuracy (%)
R064766			0.0 to 13.9		1.3 to 5.0	
R076477			0.0 to 8.8		1.2 to 4.7	

The determination of erythromycin in plasma employed an LC-MS/MS method. The following table shows the assay performance.

| LOQ (ng/mL)	Range (ng/mL)	QC sample		Calibration	
		Precision (CV%)	Accuracy (%)	Precision (CV%)	Accuracy (%)
		2.7 to 7.2		1.0 to 7.7	

The assays are acceptable based on the current standard.

Pharmacokinetics

Plasma concentration-time profiles of active moiety, risperidone and 9-hydroxy-risperidone for both treatments are shown in the following figure.

The bioequivalence analysis for all subjects showed that the treatments were bioequivalent for C_{max} and AUC for the active moiety and 9-hydroxy-risperidone and for AUC for risperidone. The 90% confidence interval of C_{max} for risperidone was 76-95%. The results of the analysis are shown in the following table.

| Parameter	Mean (SD)				Ratio RIS+ERY/RIS(%)	90% CI	N
	RIS	N	RIS + ERY	N			
Active moiety							
Cmax, ng/mL	9.41 (3.48)	18	8.37 (2.07)	17	94	84-105	17
tmax, h	1.6 (1.0)	18	2.3 (1.2)	17	-	-	-
AUClast, ng.h/mL	177 (69)	18	186 (53)	17	-	-	-
AUC∞, ng.h/mL	187 (73)	18	195 (57)	17	106	99-115	17
t1/2 term, h	22.6 (5.6)	18	22.2 (4.5)	18	-	-	-
Risperidone							
Cmax, ng/mL	6.78 (3.72)	18	5.64 (2.73)	18	85	76-95	18
tmax, h	1.5 (1.0)	18	1.7 (0.9)	18	-	-	-
AUClast, ng.h/mL	84.4 (85.9)	18	88.6 (85.3)	18	-	-	-
AUC∞, ng.h/mL	87.7 (88.6)	18	91.9 (88.3)	18	103	94-112	18
t1/2 term, h	10.4 (9.3)	18	9.8 (8.0)	18	-	-	-
9-hydroxy-risperidone							
Cmax, ng/mL	3.23 (2.75)	18	3.23 (3.00)	17	95	84-108	17
tmax, h	11.6 (10.5)	18	15.8 (15.7)	17	-	-	-
AUClast, ng.h/mL	91.3 (54.6)	18	90.6 (56.2)	17	-	-	-
AUC∞, ng.h/mL	106 (52)	17	110 (53)	15	101	93-110	15
t1/2 term, h	27.6 (7.9)	17	28.1 (9.9)	16	-	-	-
(+)-9-hydroxy-risperidone (R078543)							
Cmax, ng/mL	2.98 (2.50)	17	2.97 (2.34)	17	-	-	-
tmax, h	10.6 (10.4)	17	11.6 (12.8)	17	-	-	-
AUClast, ng.h/mL	64.1 (43.2)	17	66.2 (41.8)	17	-	-	-
Cmax ratio (R078543/R078544)	3.43 (1.65)	17	3.75 (2.04)	17	-	-	-
(-)-9-hydroxy-risperidone (R078544)							
Cmax, ng/mL	0.73 (0.46)	17	0.64 (0.36)	17	-	-	-
tmax, h	16.2 (7.7)	17	19.8 (10.6)	17	-	-	-
AUClast, ng.h/mL	26.1 (17.9)	17	26.3 (17.3)	16	-	-	-
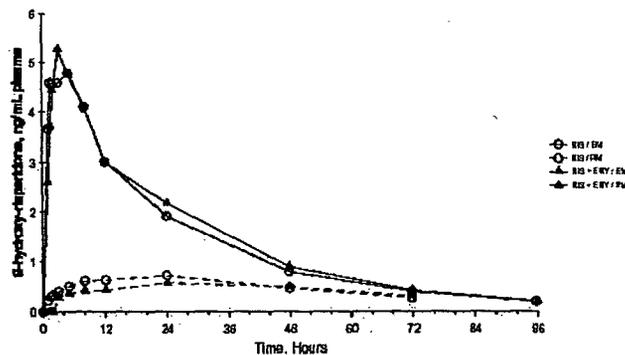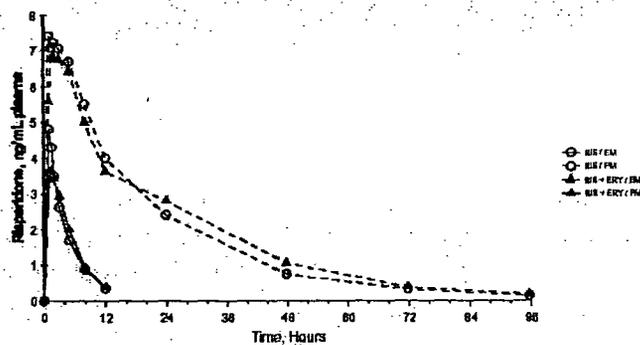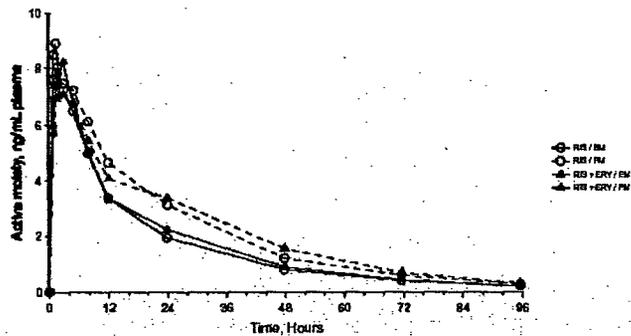
Per protocol, the CYP2D6 metabolic status of the subjects were determined by dextromethorphan phenotyping However, 2 subjects who were identified as extensive metabolizers of dextromethorphan, behaved as poor metabolizers of risperidone. Therefore, the risperidone metabolic characterization of the subjects was used, leading to a total of 10 extensive and 8 poor metabolizers of risperidone in this study.

The active moiety levels were comparable for EMs and PMs in both treatments. Exposure to RIS was higher in PMs than in EMs, while this was the opposite for 9-OH-RIS as shown in the figure above and the table below.

Parameter	Mean (SD)

	RIS		RIS + ERY	
	EM	PM	EM	PM
Active moiety				
Cmax, ng/mL	9.47 (2.95)	9.33 (4.28)	8.79 (2.32)	7.90 (1.77)
tmax, h	1.4 (0.3)	1.9 (1.4)	2.5 (1.2)	2.1 (1.2)
AUClast, ng.h/mL	155 (47)	205 (84)	163 (38)	211 (59)
AUC∞, ng.h/mL	163 (49)	217 (88)	172 (41)	221 (64)
t1/2 term, h	22.8 (5.2)	22.4 (6.5)	23.9 (4.3)	20.1 (4.1)
Risperidone				
Cmax, ng/mL	5.01 (2.14)	8.99 (4.20)	3.99 (2.22)	7.69 (1.76)
tmax, h	1.2 (0.2)	1.9 (1.4)	1.4 (0.4)	2.1 (1.2)
AUClast, ng.h/mL	21.6 (17.9)	163 (69)	21.8 (20.8)	172 (53)
AUC∞, ng.h/mL	22.8 (19.0)	169 (71)	23.2 (22.6)	178 (55)
t1/2 term, h	2.8 (1.2)	19.8 (5.0)	3.1 (1.5)	18.2 (2.9)
9-hydroxy-risperidone				
Cmax, ng/mL	5.22 (2.07)	0.73 (0.28)	5.58 (2.19)	0.59 (0.27)
tmax, h	2.8 (2.1)	22.5 (4.2)	3.2 (1.0)	30.0 (11.1)
AUClast, ng.h/mL	131 (37)	41.8 (19.5)	138 (25)	37.1 (18.0)
AUC∞, ng.h/mL	139 (39)	57.5 (18.4)	147 (28)	54.7 (24.7)
t1/2 term, h	23.0 (4.2)	34.1 (7.3)	22.7 (3.5)	37.1 (10.7)
(+)-9-hydroxy-risperidone (R078543)				
Cmax, ng/mL	4.70 (1.77)	0.53 (0.16)	4.76 (1.00)	0.40 (0.20)
tmax, h	2.8 (2.2)	21.7 (6.0)	3.7 (1.9)	22.9 (13.4)
AUClast, ng.h/mL	90.7 (36.2)	26.2 (12.2)	97.3 (18.3)	21.7 (15.6)
(-)-9-hydroxy-risperidone (R078544)				
Cmax, ng/mL	1.01 (0.41)	0.33 (0.06)	0.90 (0.21)	0.27 (0.07)
tmax, h	13.2 (7.6)	20.6 (5.9)	16.1 (8.5)	25.1 (11.7)
AUClast, ng.h/mL	36.7 (16.1)	11.1 (4.50)	37.2 (10.8)	8.13 (6.99)
Cmax ratio (R078543/R078544)	4.70 (0.56)	1.61 (0.48)	5.33 (0.67)	1.49 (0.54)

Cmax of (+)-9-hydroxy-risperidone was about 5 times higher than that of (-)-9-hydroxy-risperidone in extensive metabolizers and about 1.5 times higher in poor metabolizers, both during risperidone monotherapy and co-treatment with erythromycin. This could be explained by the following proposed metabolic scheme for risperidone.
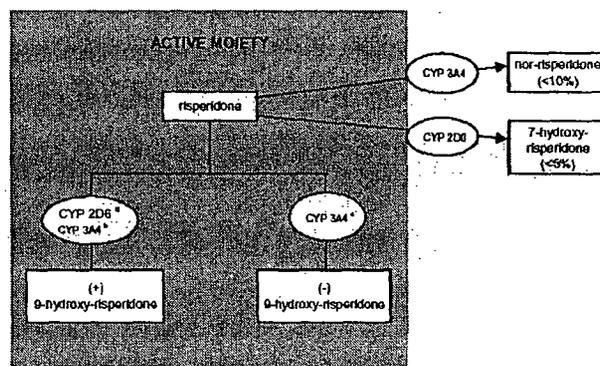
^{a} $K_m = 0.26 \pm 0.18\ \mu M$
^{b} $K_m = 42 \pm 14\ \mu M$
^{c} $K_m = 109 \pm 42.5\ \mu M$ (human liver microsomes, data from Furukori et al.[17])

The (+)/(-) ratio will be higher in extensive metabolizers of CYP2D6 than in poor metabolizers due to the large difference in Km between CYP2D6 and CYP3A4. In poor metabolizers, formation of both enantiomers will be mediated by CYP3A4. Furthermore, there is a difference in excretion rate between the enantiomers. The (-)-enantiomer will be cleared twice as fast as the (+)-enantiomer. In the literature, it was observed that the formation of (-)-hydroxy-risperidone by liver microsomes was strongly inhibited by ketoconazole, a CYP3A4 inhibitor, with less effect on the (+)-hydroxylation. This phenomenon is not apparent from the results of the present study.

Erythromycin had no clinically relevant effect on the pharmacokinetics of active moiety, risperidone and 9-hydroxy-risperidone when considering poor and extensive metabolizers of risperidone separately.

Plasma concentration-time profiles of erythromycin were analyzed for both treatments. Treatment ratios for Cmin, Cmax and AUC5h showed a shift upwards as shown in the following table.

| Treatment | Mean (SD) | | Ratio[a] | 90% |
Parameters	ERY (n=17)[b]	RIS + ERY (n=18)	RIS+ERY/ERY (%) (n=17)	Confidence Interval (n=17)
Cmin, ng/mL	236 (376)	216 (191)	114	93-140
Cmax, ng/mL	788 (478)	820 (454)	107	83-138
tmax, h	1.3 (0.6)	1.2 (0.4)	-	-
AUC5h, ng.h/mL	2548 (2144)	2521 (1682)	105	83-134

Comments

1. This study showed that there were no clinically significant interactions between risperidone and erythromycin.

2. The significance of this study is its thorough analysis. Not only were the PK parameters between two treatments compared, but the differences between different metabolic statuses were analyzed as well. Further, the differences between different enantiomers were investigated.

9. Phase III Monotherapy Studies RIS-USA-239, RIS-IND-2, and RIS-USA-240 (241)

The pharmacokinetics of risperidone in patients with acute manic episodes of Bipolar I disorder were studied in the Phase-3 monotherapy trials including RIS-USA-239 (pivotal), RIS-IND-2 (supportive), RIS-USA-240 (terminated for business reasons), and its open-label extension trial RIS-USA-241.

RIS-USA-239 was a 3-week, randomized, double-blind, parallel-group, multi-center trial with 2 treatment groups (risperidone or placebo, N=259 patients). Study medication was administered once daily in a flexible-dose range of 1 to 6 mg. The starting dose was 3 mg and could be de- or increased by 1 mg daily. Plasma samples for risperidone pharmacokinetics were scheduled to be drawn on Day 7 predose and postdose (at least 1 hour after the predose sample) and on Day 21 predose. In total, 598 samples were made available for bioanalysis. Taking into account the placebo samples which were not analyzed (N=284) and samples excluded from the pharmacokinetic analysis (N=65), the final pharmacokinetic analysis was based on data from 249 samples. Plasma concentrations of risperidone and 9-hydroxy-risperidone were determined by the LC-MS/MS method. The mean mode dose of risperidone in this flexible-dosing trial was 4.1 mg daily. For a majority of the patients, the dose escalation scheme was as follows: 3 mg on Day 1, 3 or 4 mg on Day 2, 3 to 5 mg on Day 3 and 3 to 6 mg from Day 4 onwards.

Descriptive statistics of the plasma concentrations of the active moiety, risperidone and 9-hydroxy-risperidone at each visit are shown in the following table.

Visit	N	Actual plasma concentrations (ng/mL)		Plasma concentrations normalized to a 4 mg dose (ng/mL)	
		Mean ± SD	Median (min – max)	Mean ± SD	Median (min – max)
Active moiety					
Day 7 predose	87	22.5 ± 14.1	18.2	20.8 ± 10.0	19.4
Day 7 postdose	89	44.3 ± 26.1	39.3	39.9 ± 20.1	37.1
Day 21 predose	73	27.2 ±18.4	23.6	27.4 ± 15.7	24.3
Risperidone					
Day 7 predose	87	2.66 ± 6.09	0.40	2.34 ± 5.04	0.37
Day 7 postdose	89	17.6 ± 16.3	13.2	15.7 ± 13.4	12.0
Day 21 predose	73	4.53 ± 7.83	0.89	4.99 ± 8.59	0.87
9-hydroxy-risperidone					
Day 7 predose	87	19.9 ± 11.7	16.9	18.4 ± 8.69	17.2
Day 7 postdose	89	26.7 ± 13.1	26.	24.2 ± 10.3	23.2
Day 21 predose	73	22.7 ± 15.7	19.	22.4 ± 13.0	19.6
Median time after last drug intake (min – max) (h)					
Day 7 predose	87	22.00			
Day 7 postdose	89	1.00			
Day 21 predose	73	17.58			

In general, the plasma concentrations of the active moiety, risperidone and 9-hydroxy-risperidone were within the expected concentration range (for a 4-mg dose of risperidone o.d.: 25.6 ng/mL for the active moiety and 1.84 ng/mL for risperidone, as shown in a previous population pharmacokinetic analysis). The predose plasma drug concentrations on Day 7 were

lower than those on Day 21. This is related to the fact that steady state was not yet reached after 6 days of treatment, due to dose adjustment in the first days of the study. In addition, the median sampling times after last drug intake were 22 hours on Day 7, and around 18 hours on Day 21.

The postdose samples on Day 7 were collected at a median time of 1 h after dosing, which corresponds to the expected tmax for risperidone. The postdose risperidone plasma concentrations were therefore much higher than the predose concentrations. This difference was less explicit for 9-hydroxy-risperidone, due to its later tmax as a result of its formation through metabolism of risperidone .

The supportive trial RIS-IND-2 had an identical dosing regimen (N=290 patients) as in RIS-USA-239. Plasma samples were scheduled to be drawn on Day 7 predose and postdose (at least 1 hour after the predose sample) and on Day 21 predose. In total, 760 samples were available for bioanalysis, from which 367 samples, subsequently determined to be placebo samples, were not analyzed. In addition, 32 samples were excluded from the pharmacokinetic analysis. The final pharmacokinetic analysis was therefore based on data from 361 samples. Plasma concentrations of risperidone and 9-hydroxy-risperidone were determined by the LC-MS/MS method. For a majority of the subjects, the dose escalation scheme was 3 mg on Day 1, 4 mg on Day 2, 5 mg on Day 3 and 6 mg from Day 4 onwards. The mean mode dose of risperidone, 5.6 mg daily, was close to the maximum dose permitted (6 mg).

Descriptive statistics of the plasma concentrations of the active moiety, risperidone and 9-hydroxy-risperidone at each visit are shown in the following table.

Visit	N	Actual plasma concentrations		Normalized to a 4-mg dose	
		Mean ± SD	Median (min–max)	Mean ± SD	Median (min–max)
Active moiety					
Day 7 predose	123	36.8 ± 26.7	31.4	26.4 ± 17.9	22.8
Day 7 postdose	117	81.3 ± 50.9	67.7	57.3 ± 33.7	51.5
Day 21 predose	121	47.1 ± 45.0	39.4	34.4 ± 32.8	27.4
Risperidone					
Day 7 predose	123	7.87 ± 13.64	2.18	5.51 ± 9.22	1.60
Day 7 postdose	117	40.2 ± 37.8	27.6	28.2 ± 25.7	19.3
Day 21 predose	121	11.1 ± 29.9	2.62	8.44 ± 24.48	1.81
9-hydroxy-risperidone					
Day 7 predose	123	28.9 ± 19.6	26.7	20.9 ± 13.3	19.6
Day 7 postdose	117	41.0 ± 23.4	36.4	29.1 ± 15.4	26.7
Day 21 predose	121	36.0 ± 25.3	32.2	25.9 ± 17.2	23.1
Median time after last drug intake (min – max) (h)					
Day 7 predose	123	21.00			
Day 7 postdose	117	1.00			
Day 21 predose	121	19.72			

The actual plasma concentrations in this trial were high as compared to the other trials (Day 21, mean predose active moiety concentration: 47.1 ng/mL versus 27.2 ng/mL in RIS-USA-239 and 28.2 ng/mL in RIS-INT-46). This is due to the higher doses given in RIS-IND-2 (mean mode dose: 5.6 mg versus 4.1 mg and 3.7 mg in RIS-USA-239 and RIS-INT-46, respectively). After

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dose-normalization, the average concentrations in RIS-IND-2 and RIS-INT-46 were comparable, while those in RIS-USA-239 were lower (Day 21, mean predose active moiety concentration: 34.4 ng/mL versus 27.4 ng/mL in RIS-USA-239 and 34.9 ng/mL in RIS-INT-46).

As observed in RIS-USA-239, the predose plasma drug concentrations on Day 7 were lower than those on Day 21 for a similar reason. The median times after last drug intake were comparable for both predose sampling visits.

RIS-USA-240 was a 3-week, randomized, double-blind, parallel-group multi-center trial in which approximately 432 patients were to be randomized to one of three groups (placebo, risperidone or divalproex sodium). Only 39 patients were randomized. Enrollment of the remaining patients was stopped and the trial was terminated by the sponsor due to business reasons. All patients were allowed to complete and if they wanted to enroll in RIS-USA-241. Only 17 subjects entered this 9-week, multi-center, open-label extension trial.

Plasma samples were scheduled to be taken on Day 7 predose and postdose and on Day 21 predose in RIS-USA-240, and on Day 63 (Week 9) predose and postdose in RIS-USA-241. For RIS-USA-240, only 28 samples from patients from the risperidone group were made available for bioanalysis, but further to the omission of excluded samples, only 22 samples were included in the descriptive statistics. For RIS-USA-241, only 14 samples were available, and 11 samples included. Plasma concentrations of risperidone and 9-hydroxy-risperidone were determined by the LC-MS/MS method. The mean mode dose of risperidone was 3.3 mg daily in RIS-USA-240. In RIS-USA-241, most of the patients received 2-3 mg/day.

Due to the small number of available samples, it was not possible to draw relevant conclusions from the data collected.

10. Phase III Adjunctive Therapy Study RIS-INT-46

RIS-INT-46 is a supportive adjunctive therapy trial. In the pivotal adjunctive therapy trial RIS-USA-102, no samples to assess the pharmacokinetics of risperidone were collected. The plasma concentrations of the active moiety, risperidone and 9-hydroxy-risperidone were only monitored in RIS-INT-46. Serum levels of the mood stabilizers were monitored in both RIS-USA-102 and RIS-INT-46.

Both adjunctive Phase-3 clinical trials in patients with Bipolar I disorder (RIS-USA-102 and RIS-INT-46) had a similar design, consisting of two phases. The first phase was a 3-week, double-blind treatment with parallel groups (placebo, risperidone and haloperidol for RIS-USA-102; placebo and risperidone for RIS-INT-46) during adjunctive mood stabilizer treatment (lithium and valproate in RIS-USA-102 and lithium, valproate or carbamazepine in RIS-INT-46). The second phase was a subsequent 10-week, open-label risperidone treatment.

Both trials used a flexible q.d. risperidone dosage regimen (1-6 mg/day). In both trials, serum concentrations of mood stabilizers were targeted to the following levels.

Valproate: trough serum concentration of 50-120 μg/mL (RIS-USA-102) or 50-125 μg/mL (RIS-INT-46);
Lithium: 0.6-1.4 mEq/L (12 hours after last dose);
Carbamazepine: trough serum concentration of 4-12 μg/mL (used in RIS-INT-46, and for one patient during the open-label phase of RIS-USA-102).

During the double-blind phase of study RIS-USA-102, patients received either lithium or valproate as a mood stabilizer. During the open-label phase, patients could continue the same mood stabilizer they received in the double-blind phase or switch to the other mood stabilizer (lithium or valproate), or to a third mood stabilizer, carbamazepine. However, only 1 patient used carbamazepine, which did not allow for a meaningful analysis.

Serum concentrations of lithium and valproate during the double-blind phase and the open-label phase are shown in the following table.

	Mood stabilizer + placebo		Mood stabilizer + risperidone		Mood stabilizer + haloperidol	
	N	Mean ± SE	N	Mean ± SE	N	Mean ± SE
Lithium (mEq/L)						
Double-blind Baseline	12	0.6 ± 0.09	14	0.7 ± 0.11	16	0.5 ± 0.06
Double-blind Week 3	6	0.8 ± 0.13	11	0.7 ± 0.08	8	0.7 ± 0.07
Open-Label Week 10	3	0.7 ± 0.20	6	0.6 ± 0.11	1	0.2
Valproate (μg/mL)						
Double-blind Baseline	35	52.9 ± 4.97	37	53.4 ± 4.92	36	50.1 ± 5.67
Double-blind Week 3	18	77.3 ± 6.43	26	65.4 ± 5.31	24	76.2 ± 5.22
Open-label Week 10	11	66.6 ± 8.92	10	52.8 ± 9.24	11	70.3 ± 11.51

Serum concentrations of lithium and valproate were similar between the three treatment groups for both treatment phases (double-blind and open-label). However, the doses of mood stabilizers

were titrated based on the targeted concentrations. Serum concentrations were lowest at baseline and remained similar or increased slightly during the trial in all three study groups. For both lithium and valproate, the actual serum levels were at the low end of the targeted range.

In study RIS-INT-46, plasma samples were drawn at baseline, at endpoint of the 3-week double-blind phase and endpoint of the 10-week open-label phase (all predose). A total of 374 samples were available for bioanalysis, and the final pharmacokinetic analysis was based on 139 samples, after exclusion of 221 samples (including samples from subjects randomized to the placebo group in the double-blind phase). Plasma concentrations of the active moiety and risperidone were determined by the RIA methods. The mean mode dose of risperidone was 3.7 mg o.d. in both the double-blind phase (risperidone treated patients only) and open-label phase (all patients).

The descriptive statistics of the actual and dose-normalized (4-mg dose) plasma concentrations of risperidone, 9-hydroxy-risperidone and the active moiety over the time interval of 8-15h are summarized per mood stabilizer in the following table. The 8-15h interval was chosen as an arbitrary time interval assuming that the plasma levels measured between this time interval fairly represent average steady-state levels.

	N	Actual plasma concentrations		Normalized to a 4-mg dose	
		Mean ± SD	Median (min – max)	Mean ± SD	Median (min – max)
Lithium treatment group					
Act					
Baseline	9	NQ*	NQ	NQ*	NQ
Endpoint DB	23	28.9 ± 20.9	25.3	38.5 ± 24.8	36.2
Endpoint OL	19	38.6 ± 30.4	39.9	42.7 ± 28.1	39.8
Ri					
Baseline	9	NQ	NQ	NQ	NQ
Endpoint DB	23	5.85 ± 9.02	1.12	7.93 ± 13.12	1.46
Endpoint OL	19	9.33 ± 12.94	4.87	11.1 ± 17.0	3.33
9-hydr(				*e*	
Baseline	9	NQ	NQ	NQ	NQ
Endpoint DB	23	23.1 ± 14.8	22.0	30.6 ± 17.2	32.2
Endpoint OL	19	29.2 ± 23.3	19.2	31.6 ± 22.5	31.4
Valproate tre					
A(					
Baseline	5	NQ	NQ	NQ	NQ
Endpoint DB	11	36.2 ± 20.3	30.2	40.4 ± 21.8	35.9
Endpoint OL	7	21.2 ± 6.2	19.8	37.8 ± 14.3	42.1
R					
Baseline	5	NQ	NQ	NQ	NQ
Endpoint DB	11	10.1 ± 10.0	8.38	15.0 ± 20.6	7.58
Endpoint OL	7	3.85 ± 6.01	1.41	7.76 ± 12.06	2.72
9-hydr				*ie*	
Baseline	5	NQ	NQ	NQ	NQ
Endpoint DB	11	26.1 ± 19.3	16.	25.5 ± 10.9	26.8
Endpoint OL	7	17.3 ± 7.9	18.	30.1 ± 14.8	36.7
Carbamazep...				t group	
Active moiety					

Baseline	3	NQ	NQ		NQ	NQ
Endpoint DB	9	16.7 ± 9.1	14.3		18.8 ± 10.5	18.8
Endpoint OL	3	7.58 ± 4.36	10.0		12.4 ± 7.1	10.2
R						
Baseline	3	NQ	NQ		NQ	NQ
Endpoint DB	9	2.87 ± 4.62	0.67		3.29 ± 4.83	0.56
Endpoint OL	3	2.00 ± 3.15	0.23		3.99 ± 6.33	0.52
9-hydr						
Baseline	3	NQ	NQ		NQ	NQ
Endpoint DB	9	13.8 ± 5.4	11.4		15.5 ± 7.0	17.5
Endpoint OL	3	5.58 ± 3.78	4.56		8.43 ± 1.68	9.10

The results show that the plasma concentrations of the active moiety, risperidone and 9-hydroxy-risperidone were within the expected concentration range, and were comparable at endpoint of the double-blind phase and at endpoint of the open-label phase. Also, the plasma drug concentrations were similar when lithium or valproate were taken as concurrent mood stabilizer. However, when risperidone was co-administered with carbamazepine, plasma concentrations of the active moiety, risperidone and 9-hydroxy-risperidone were on average 50% lower. This latter finding can be explained by the cytochrome P450-inducing properties of carbamazepine and is in line with previous findings.

During the double-blind and the open-label phase of trial, patients received either lithium, valproate or carbamazepine as mood stabilizer. During the open-label phase, patients could continue with the same mood stabilizer they received in the double-blind phase or switch to one of the other mood stabilizers (lithium, valproate or carbamazepine). Serum concentrations of the mood stabilizers are shown in the following tables.

	Mood stabilizer + placebo		Mood stabilizer + risperidone	
	N	Mean ± SE	N	Mean ± SE
Lithium (mEq/L)				
Baseline DB	41	0.55 ± 0.04	37	0.55 ± 0.05
Day 3	36	0.64 ± 0.05	31	0.56 ± 0.04
Week 1	37	0.70 ± 0.04	38	0.61 ± 0.03
Week 2	26	0.76 ± 0.05	35	0.61 ± 0.04
Week 3	19	0.75 ± 0.07	27	0.63 ± 0.04
Valproate (µg/mL)				
Baseline DB	17	49.76 ± 6.64	17	46.33 ± 7.34
Day 3	9	61.78 ± 7.78	14	67.95 ± 7.75
Week 1	14	82.21 ± 4.85	13	70.56 ± 7.49
Week 2	6	76.00 ± 14.64	13	64.18 ± 6.76
Week 3	5	97.00 ± 5.87	9	63.04 ± 7.54
Carbamazepine (µg/mL)				
Baseline DB	13	4.84 ± 0.65	12	4.98 ± 1.07
Day 3	9	6.36 ± 0.30	12	6.92 ± 0.83
Week 1	11	6.35 ± 0.74	14	6.41 ± 0.64
Week 2	11	6.34 ± 0.44	11	6.78 ± 0.45
Week 3	9	5.69 ± 0.29	7	6.31 ± 0.53

The table above shows the results for double blind phase and the table below shows the results during open-label phase.

	Placebo-treated in DB[*]		Risperidone-treated in DB	
	N	Mean ± SE	N	Mean ± SE
Lithium (mEq/L)				
Week 1	9	0.71 ± 0.05	11	0.63 ± 0.05
Week 10	22	0.79 ± 0.05	20	0.74 ± 0.05
Valproate (μg/mL)				
Week 1	4	42.75 ± 11.40	4	60.00 ± 7.69
Week 10	8	79.25 ± 5.86	9	80.78 ± 9.74
Carbamazepine (μg/mL)				
Week 1	5	6.93 ± 0.85	2	6.39 ± 2.55
Week 10	12	6.30 ± 0.31	7	6.13 ± 0.49

Comments

1. Plasma concentrations of the active moiety, risperidone and 9-hydroxy-risperidone in patients were similar to the previous observation in schizophrenia patients.

2. Serum concentrations of mood stabilizers were within the targeted therapeutic range and were fairly comparable between treatment groups (mood stabilizer plus placebo versus mood stabilizer plus adjunctive therapy), and between both phases of the studies (double-blind and open-label). However, the doses of mood stabilizers were changing based on the targeted concentrations.

3. When carbamazepine was coadministered as a mood stabilizer, the exposure to the active moiety, risperidone and 9-hydroxy-risperidone was on average 50% lower than when either lithium or valproate was co-administered.

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	20-272-S026/20-588-S017	Brand Name	Risperdal
OCPB Division (I, II, III)	I	Generic Name	Risperidone
Medical Division	HFD-120	Drug Class	Antipsychotics
OCPB Reviewer	John Duan	Indication(s)	Bipolar I/mania
OCPB Team Leader	Ramana Uppoor, Joga Gobburu	Dosage Form	Tablets, Oral solution
		Dosing Regimen	0.25, 0.5, 1, 2, 3, and 4 mg tablets, 1 mg/mL oral solution
Date of Submission	12/13/2002	Route of Administration	Oral
Estimated Due Date of OCPB Review	8/29/2003	Sponsor	Johnson & Johnson
PDUFA Due Date	10/13/2003	Priority Classification	Standard
Division Due Date	8/29/2003		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	4	4	
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	8	8	
In-vivo effects of primary drug:	X	8	8	
In-vitro:				
Subpopulation studies -				
Ethnicity:				
Gender:				
Pediatrics:				
Geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				

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	"X" if yes		
Data rich:	X	1	1	
Data sparse:	X	1	1	
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X	7	7	
Total Number of Studies		26	26	

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?	X	
QBR questions (key issues to be considered)		1. Is the pharmacokinetic behavior similar between schizophrenia and bipolar I patients 2. Are there any drug interactions between risperidone and commonly coadministered medications? What is the significance of these drug interactions?
Other comments or information not included above		
Primary reviewer Signature and Date	John Duan	
Secondary reviewer Signature and Date	Ramana Uppoor, Joga Gobburu	

CC: NDA 20-272/20-588, HFD-850 (Lee), HFD-120(Bates), HFD-860 (Duan, Uppoor, Mehta, Sahajwalla), CDR