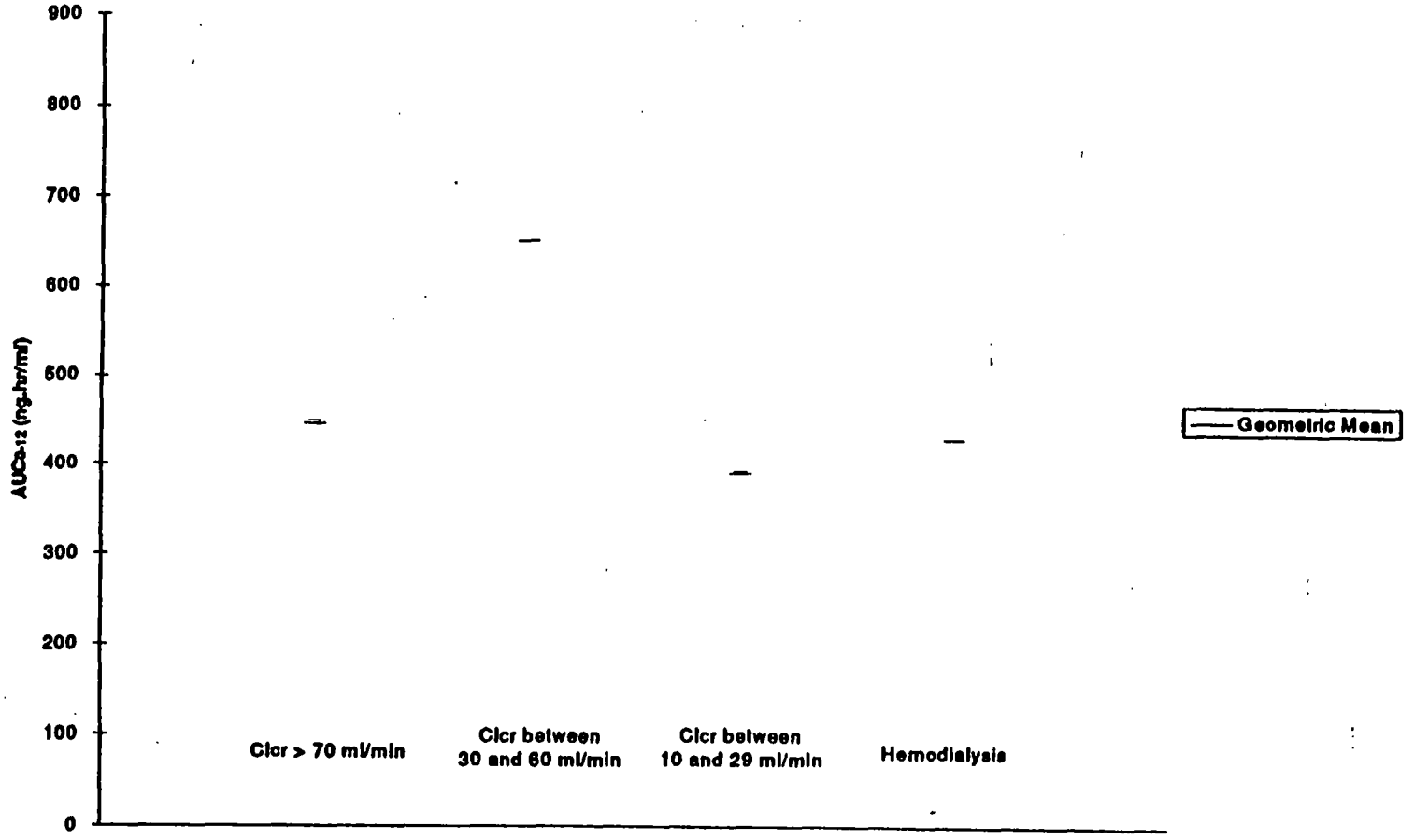
Attachment 9

8

Figure 1.7 Comparison of Individual AUC_{0-12} Values on Day 8 by Renal Function
Ziprasidone 026

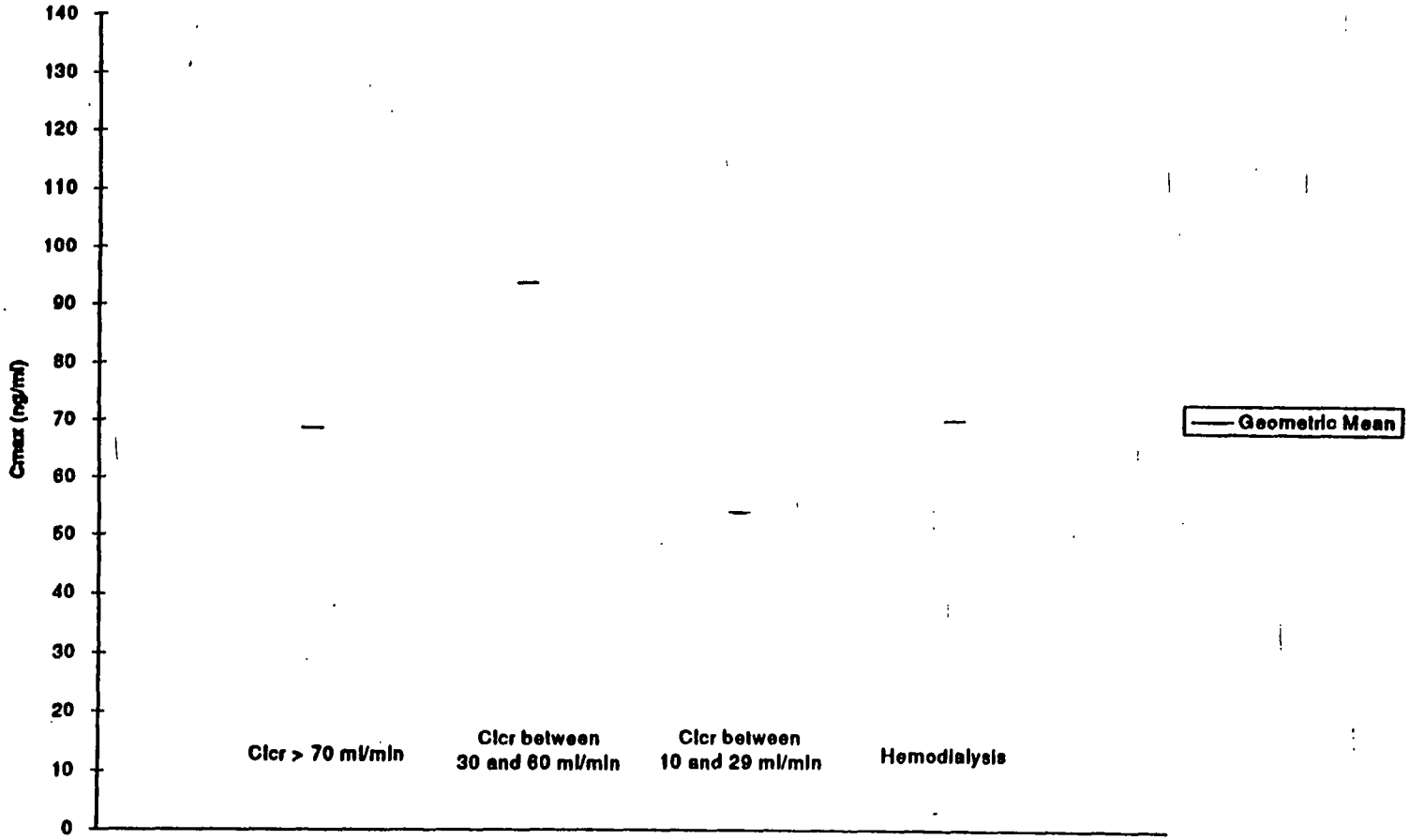


Source Data: Appendix IV, Table 2

Attachment 10

9

Figure 1.8 Comparison of Individual Cmax Values on Day 8 by Renal Function Ziprasidone 026

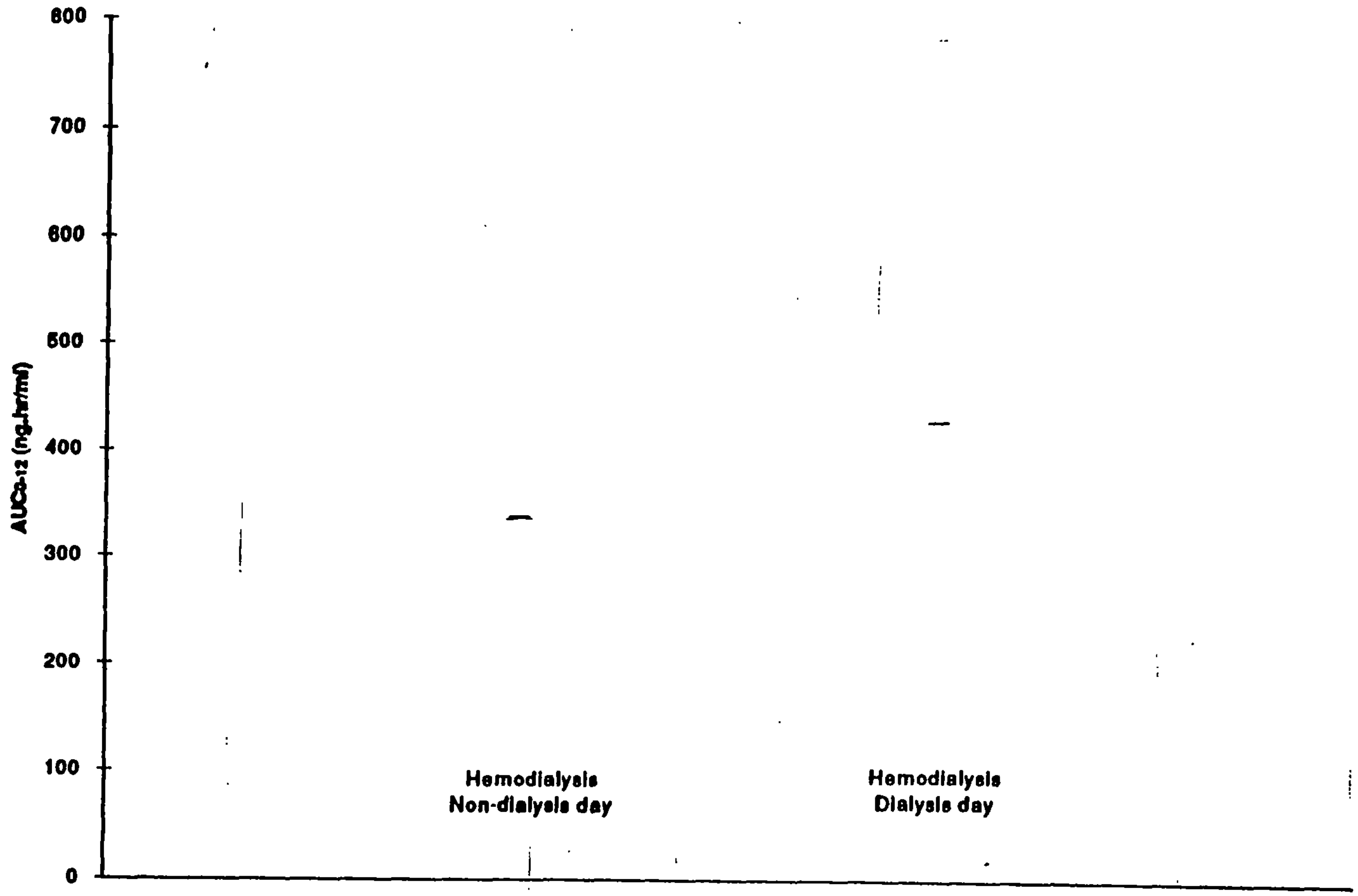


Source Data: Appendix IV, Table 2

10

Attachment 11

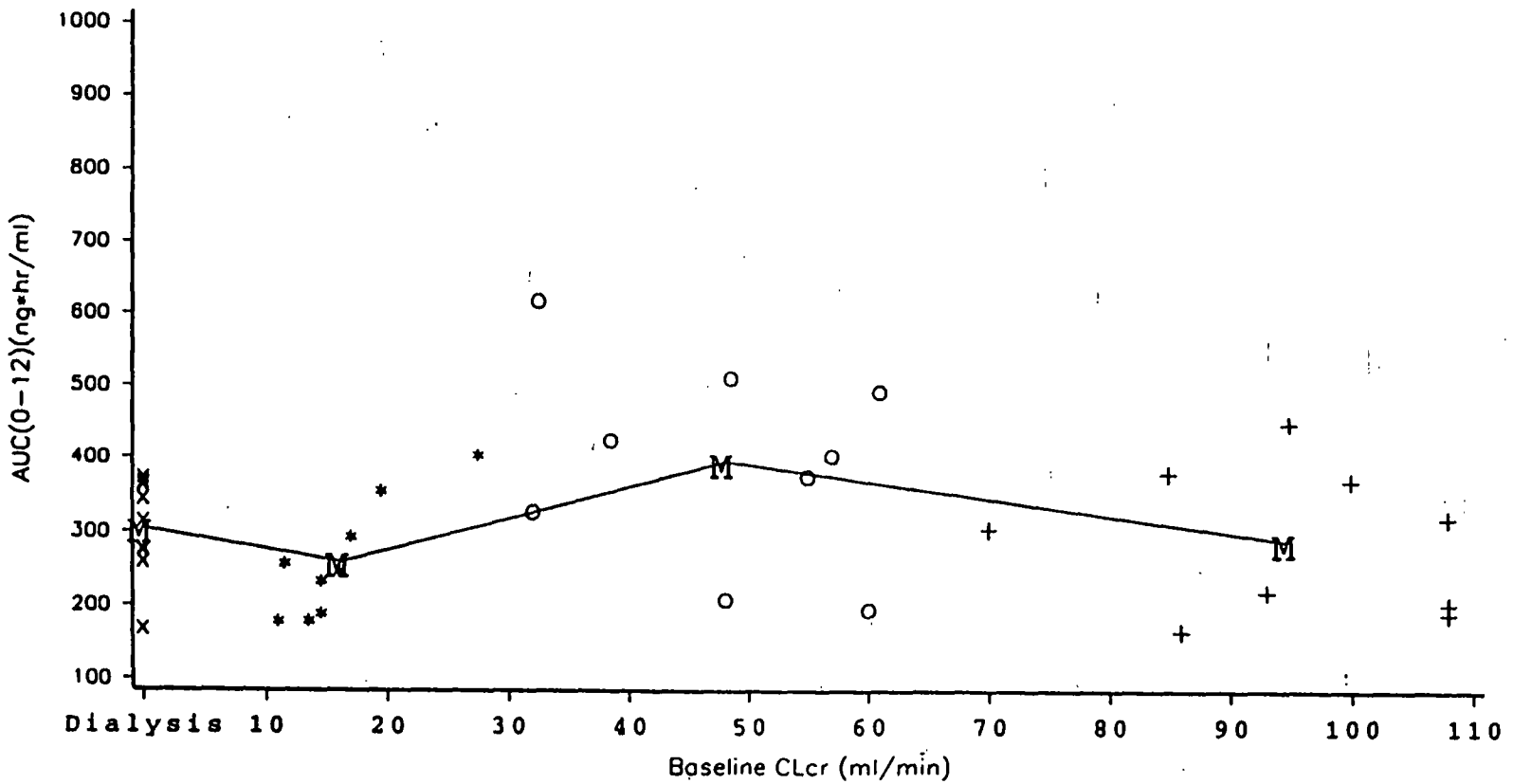
Figure 1.9 Comparison of Individual AUC0-12 Values; Dialysis (Day 8) vs Non-Dialysis (Day 7) Days Ziprasidone 026



Source Data: Appendix IV, Tables 2 and 3

Attachment 12

Figure 2.1
Day 1 Ziprasidone AUC(0–12) vs Baseline CLcr
Ziprasidone Protocol 026



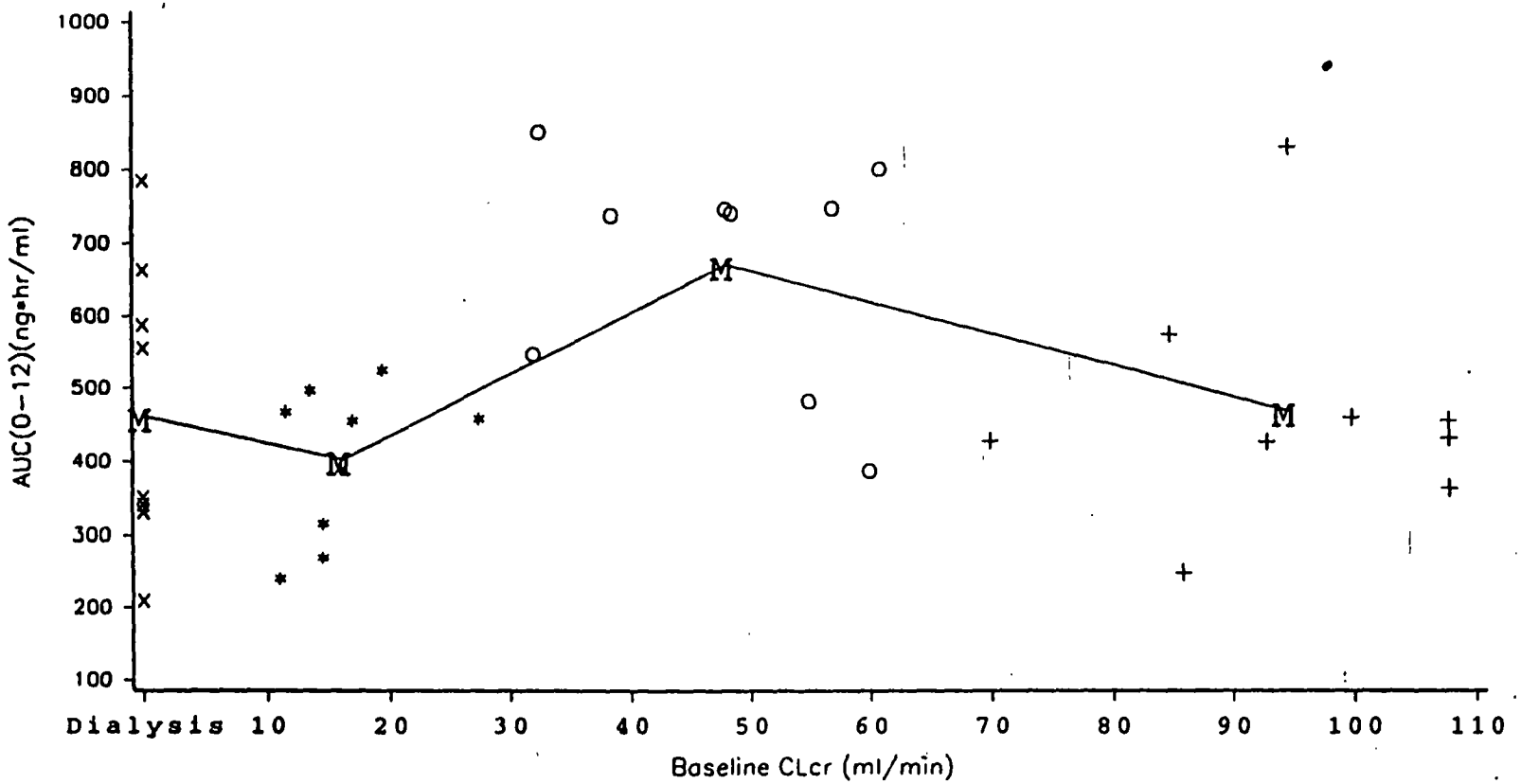
Creatinine Clearance +++ Group 1: CLcr >70 ml/min ooo Group 2: CLcr 30–69 ml/min ••• Group 3: CLcr 10–29 ml/min xxx Group 4: Hemodialysis

Solid line connects the mean values for each renal function group.
Source Data: Appendix III Tables 1 and 9, Appendix IV Table 1 and Appendix V Table 11 Date of Data Extraction: 21NOV96 Date of Figure Generation: 20DEC96

(d)

Attachment 13

Figure 2.2
Day 8 Ziprasidone AUC(0-12) vs Baseline CLcr
Ziprasidone Protocol 026



Creatinine Clearance +++ Group 1: CLcr >70 ml/min ooo Group 2: CLcr 30-69 ml/min ••• Group 3: CLcr 10-29 ml/min xxx Group 4: Hemodialysis

Solid line connects the mean values for each renal function group.
Source Data: Appendix III Table 4, Appendix IV Table 2 and Appendix V Table 11 Date of Data Extraction: 21NOV96 Date of Figure Generation: 20DEC96

Study 030: (Hepatic Impairment)

Study Design and Summary:

(see attachments 1-3)

Results:

(See attachments 4-9)

Reviewer's Comment:

1. From the data shown in attachment 4, it does not seem there is any PK difference of clinical significance in both groups. However, as expected, there is a trend for higher AUCs in liver failure (~26% in day 5) compared to normals, but not for Cmax (attachments 4-8).

2. Drug accumulation at steady-state (day 5) is about 30-40% which is consistent with the previous studies. However, accumulation may be greater after chronic use in subjects with liver failure, particularly at higher doses.

3. The half life is slightly longer in liver impairment compared to normal subjects (5h vs 7h). Again, this does not seem to be of clinical significance.

4. The drug is highly bound to plasma protein (~99.9%) and clearly there is no difference between the groups.

5. The lack of correlation between the antipyrine and ziprasidone elimination rate in subjects with liver impairment is probably due to the small sample size in this group compared to normal subjects who showed better correlation, possibly, to a larger sample size (attachment 9)

Conclusions:

1. The PK of this drug is not significantly affected by liver impairment in this group of subjects.

2. Based on this study, there is no significant drug accumulation. However, this could be a problem at higher doses after chronic use.

PROTOCOL 128-030: PHASE I MULTIPLE DOSE OPEN STUDY DESIGNED TO COMPARE THE SAFETY AND DISPOSITION OF ZIPRASIDONE IN SUBJECTS WITH NORMAL HEPATIC FUNCTION TO SUBJECTS WITH HEPATIC IMPAIRMENT

Principal Investigator: L. Bauer, Pharm.D., G. Everson, M.D., K. Anderson, M.D., K. Lasseter, M.D.

Study Publication: None

Study Dates: 20 September 1995 - 21 October 1996

Study Objective: To compare the disposition of oral ziprasidone HCl (CP-88-059-1) at steady-state in subjects with hepatic dysfunction to matching subjects with normal hepatic function.

Study Design: This was an open, multi-center, multiple dose study of ziprasidone (20 mg BID) administered orally with food for 4 days (days 1-4) with a single morning dose on day 5. All doses are expressed as mg equivalents of ziprasidone free base. Two groups of subjects were studied:

Group 1: Normal subjects without hepatic impairment with sex, age, and weight of this group being matched as closely as possible to subjects in Group 2.

Group 2: Subjects with chronic stable hepatic impairment. Subjects in this group had cirrhosis as evidenced by either a previous liver biopsy or liver/spleen scan consistent with cirrhosis, together with laboratory and clinical findings that support the diagnosis of cirrhosis.

For the purpose of matching age and weight, a range of $\pm$5 years and $\pm$20 pounds, respectively, was used.

Evaluation Groups:

	Normal Hepatic Function	Hepatic Impairment
Entered Study	14	16
Completed Study	13	14
Evaluated for Pharmacokinetics		
Ziprasidone	13	13
Antipyrine	13	13
Assessed for Safety		
Adverse Events	14	16
Laboratory Tests	13	16

Subjects: Male and female subjects with normal hepatic function or chronic stable hepatic impairment, ranging in age from 30 to 67 years.

Drug Administration:

Dosage Form 20 mg research capsule CP-88,059-1 (FID #CS-90-031)

Dosing: Subjects received ziprasidone 20 mg twice daily for 4 days (days 1-4) with a single 20 mg dose on day 5. For morning dosing, breakfast was consumed over a 20 minute period and study medication was then immediately administered with 50 ml of water. For evening dosing, dinner was consumed over a 20 minute period and study medication was then immediately administered with 50 ml of water. The interval between morning and evening dosing was approximately 12 hours. An identical breakfast was consumed on days 1 and 5.

Pharmacokinetic and Safety Evaluations: On day 1, blood samples for determination of serum ziprasidone concentrations were collected prior to and up to 12 hours postdose, and on day 5, collected prior to and up to 120 hours postdose. Serum samples were collected prior to ziprasidone morning dosing on days 2 through 4. Serum concentrations on days 1 and 5 were used to estimate the pharmacokinetic parameters of AUC_{0-12}, C_{max}, and T_{max}, and serum concentrations on day 5 only were used to estimate K_{el}, and $T_{1/2}$. On day 5, blood samples for protein binding determinations (Fb) were collected in heparinized tubes from each subject just prior to the morning dose. In addition, each subject received antipyrine to further evaluate hepatic function. Subjects were monitored for adverse events, abnormal laboratory test results, and changes in vital signs and ECGs.

Analytical Methods:

Statistical Methods: An analysis of variance was used to test for a hepatic group effect by using PROC GLM in SAS. Twelve completed subjects from each group were required in order to have at least 80% power of detection at least a 75% difference in the area under the serum concentration time-curve (AUC) using a 5% significance level on day 5 between Groups 1 and 2. The LSMEANS statement in SAS was used to estimate the means and their variances.

Pharmacokinetic Results:

Means and Coefficients of Variation (CV%) of Pharmacokinetic Parameters

	Normal Hepatic Function				Hepatic Impairment			
	Day 1		Day 5		Day 1		Day 5	
	mean	CV%	mean	CV%	mean	CV%	mean	CV%
$AUC_{(0-12)}$ (ng•hr/ml)[a]	317	18	467	24	338	22	590	31
C_{max} (ng/ml)[a]	52	27	68	25	50	23	71	28
T_{max} (hour)	5	34	4	24	6	36	4	43
K_{el} (1/hr)	--	--	0.145	18	--	--	0.1	26
$T_{1/2}$ (hr)[b]	--	--	4.8	--	--	--	7.1	--
Fb (% bound)	--	--	99.92	<1	--	--	99.88	<1

[a]=Geometric means b=Calculated as ln 2/mean K_{el}

Safety Results:

Findings	Number of Subjects [With/Evaluated (Discontinued)] Normal Hepatic Function	Hepatic Impairment
Adverse Events (All Causality)	13/14(1)	13/16(2)
Adverse Events (Treatment-emergent, Treatment-related)	13/14(1)	12/16(2)
Clinically Significant Laboratory Test Abnormalities	9/13(0)	11/16(0)

Summary and Conclusions: Steady state systemic exposures were attained by the third day of dosing. Based upon AUC_{0-12}, C_{max}, and T_{max} on day 1, there were no statistically significant differences in the pharmacokinetics of ziprasidone between the hepatically impaired subjects and the normal subjects. By day 5, there was a statistically significant difference between the two groups regarding AUC; however the difference was only a 26% increase in AUC_{0-12} for the hepatically impaired group compared to the subjects with normal hepatic function. There were no statistically significant differences in C_{max} and T_{max} between the two groups on day 5. There was a statistically significant difference in K_{el} on day 5, however this corresponded to only a mean increase of 2.3 hours in the half-life of the hepatically impaired subjects. There was no statistically significant difference in percent plasma protein binding among the two treatment groups. There was a statistically significant difference between normal subjects and those with hepatic impairment with regard to antipyrine elimination rate and antipyrine clearance, but no difference was detected regarding antipyrine volume of distribution. There was no correlation between antipyrine and ziprasidone elimination rates and antipyrine clearances when compared between the subjects with normal hepatic function and those with hepatic impairment.

Three subjects were discontinued from the study due to treatment-related adverse events. One subject with normal hepatic function was discontinued for anxiety and restlessness; one subject with hepatic impairment was discontinued for dizziness, fatigue, and a panic attack, and the other hepatically impaired subject was discontinued for somnolence. No serious adverse events were reported. All adverse events were of mild to moderate severity except for one incidence of severe migraine, not considered treatment-related, in a subject with normal hepatic function. The most frequently reported adverse event in both treatment groups was somnolence. Most of the clinically significant laboratory test abnormalities seen in the hepatically impaired subjects, including elevations in SGOT and total bilirubin in particular, were a result of the subjects' underlying medical conditions.

In summary, as there was little difference in the pharmacokinetics of ziprasidone between subjects with clinically significant cirrhosis and subjects with normal hepatic function, liver function (Child-Pugh A and B) does not seem to affect the pharmacokinetic parameters of ziprasidone.

Attachment 1

(4)

Table 5.1.1 Summary of Ziprasidone Pharmacokinetic Parameters Following 20 mg BID Dosing Ziprasidone 030

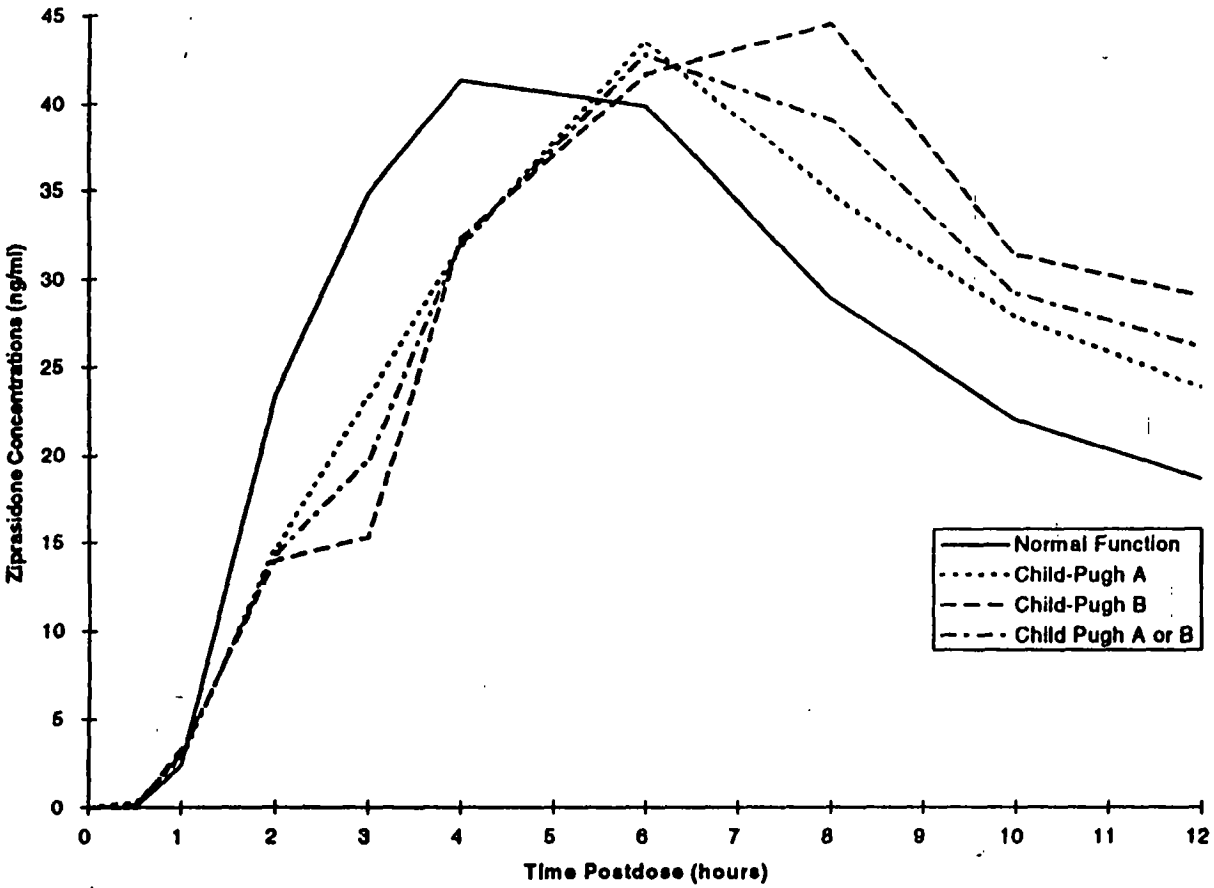
	Hepatic Function	Day	AUC0-12 (ng•hr/ml)	Cmax (ng/ml)	Tmax (hr)	Kel (hr^{-1})	$T_{1/2}$ (hr)	Fb (% bound)
Mean	Normal	1	317[a]	52[a]	5			
S.D.			57	14	2			
CV%			18	27	34			
Mean	Child-Pugh A&B	1	338[a]	50[a]	6			
S.D.			72	11	2			
CV%			21	22	36			
Mean	Normal	5	467[a]	68[a]	4	0.145	4.8[b]	99.92
S.D.			110	17	1	0.026		0.028
CV%			24	25	26	18		< 1
Mean	Child-Pugh A&B	5	590[a]	71[a]	4	0.097	7.1[b]	99.87
S.D.			184	20	2	0.025		0.082
CV%			31	28	43	26		< 1

[a]Geometric mean and standard deviation
[b]Calculated as ln 2/mean Kel

Source Data: Appendix IV, Tables 1 and 2; Appendix IV, Sub-Appendix 2

(5) Attachment 5

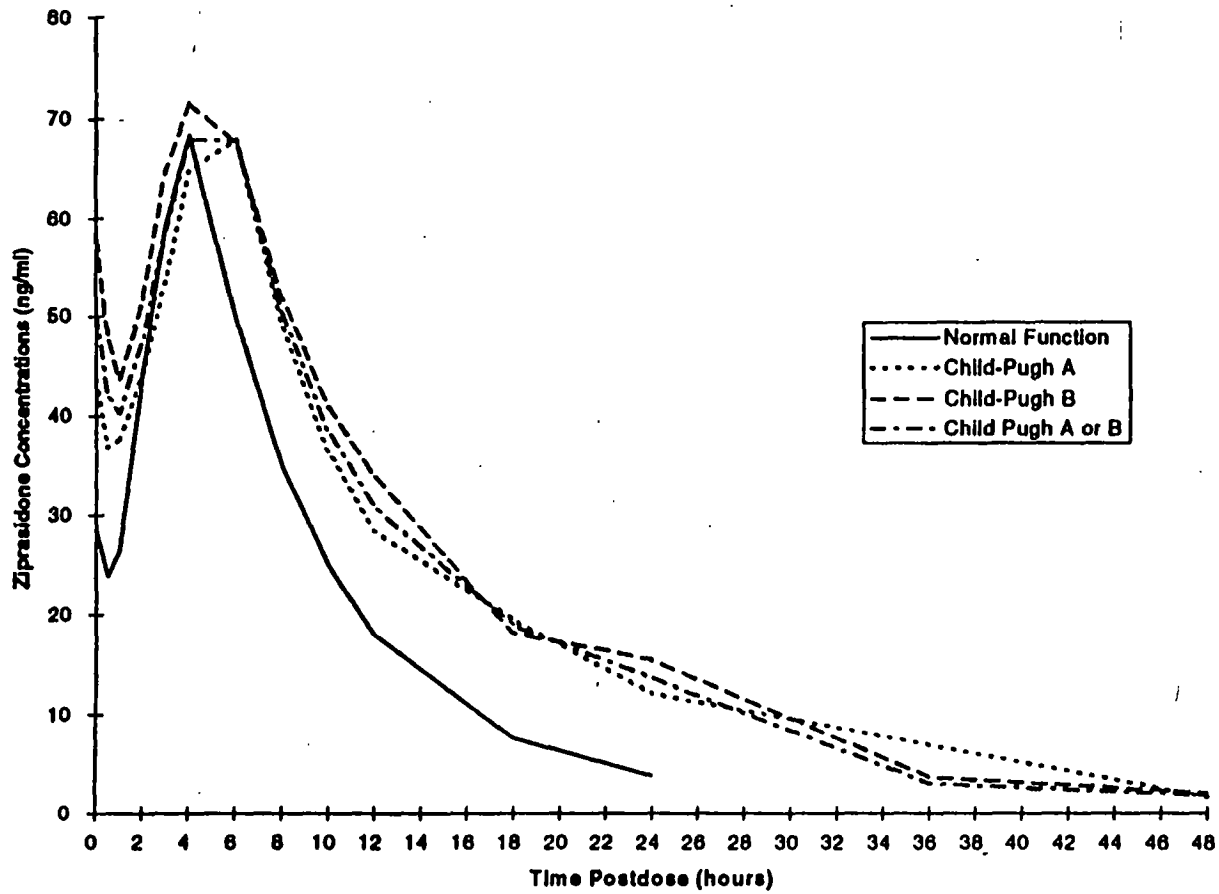
Figure 1.1 Mean Serum Ziprasidone Concentrations on Day 1 in Subjects with Normal Hepatic Function or Subjects with Impaired Hepatic Function
Ziprasidone 030



Source Data: Appendix IV, Table 1

(6) Attachment B

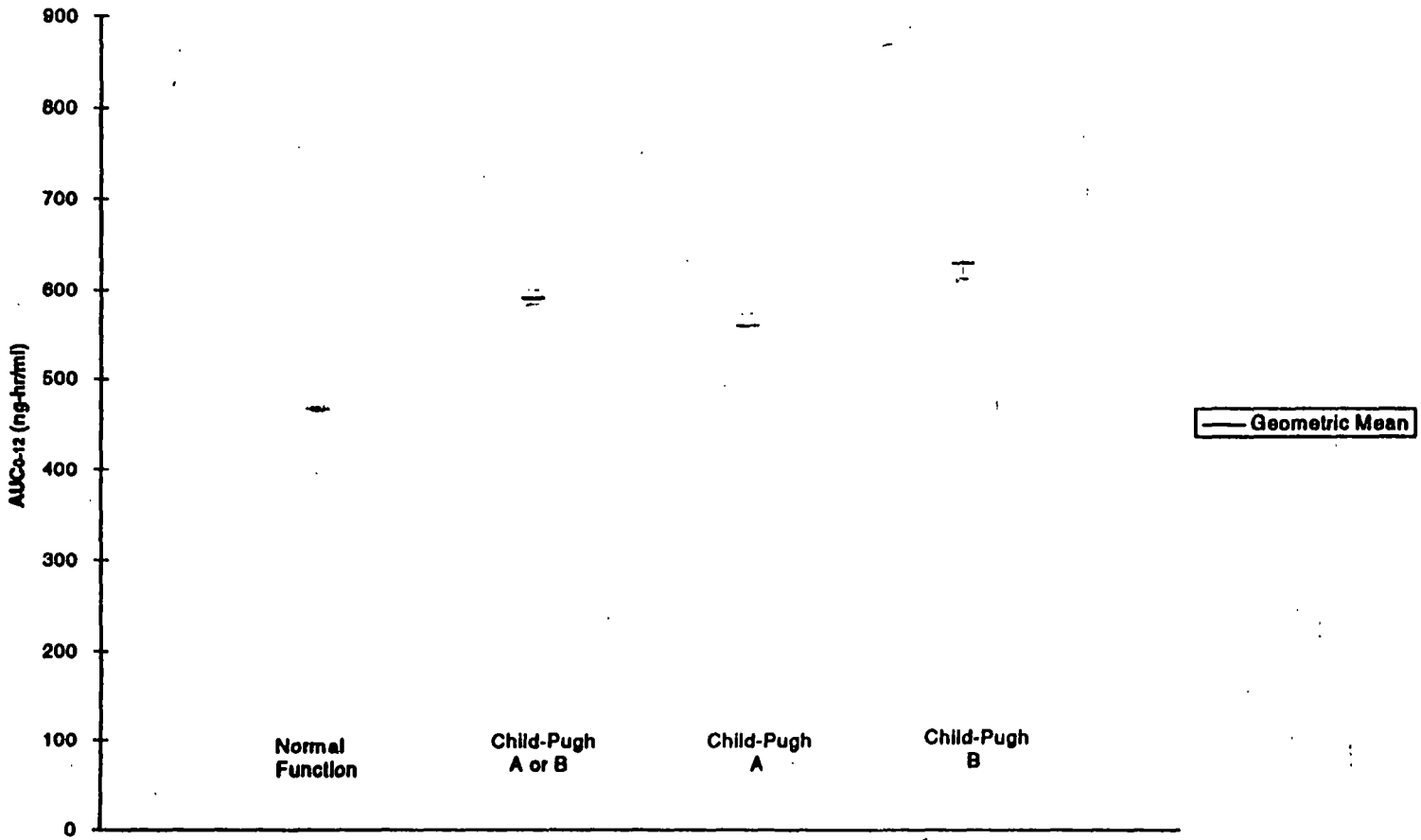
Figure 1.2 Mean Serum Ziprasidone Concentrations on Day 5 In Subjects with Normal Hepatic Function or Subjects with Impaired Hepatic Function
Ziprasidone 030



Source Data: Appendix IV, Table 2

(7) Attachment 8

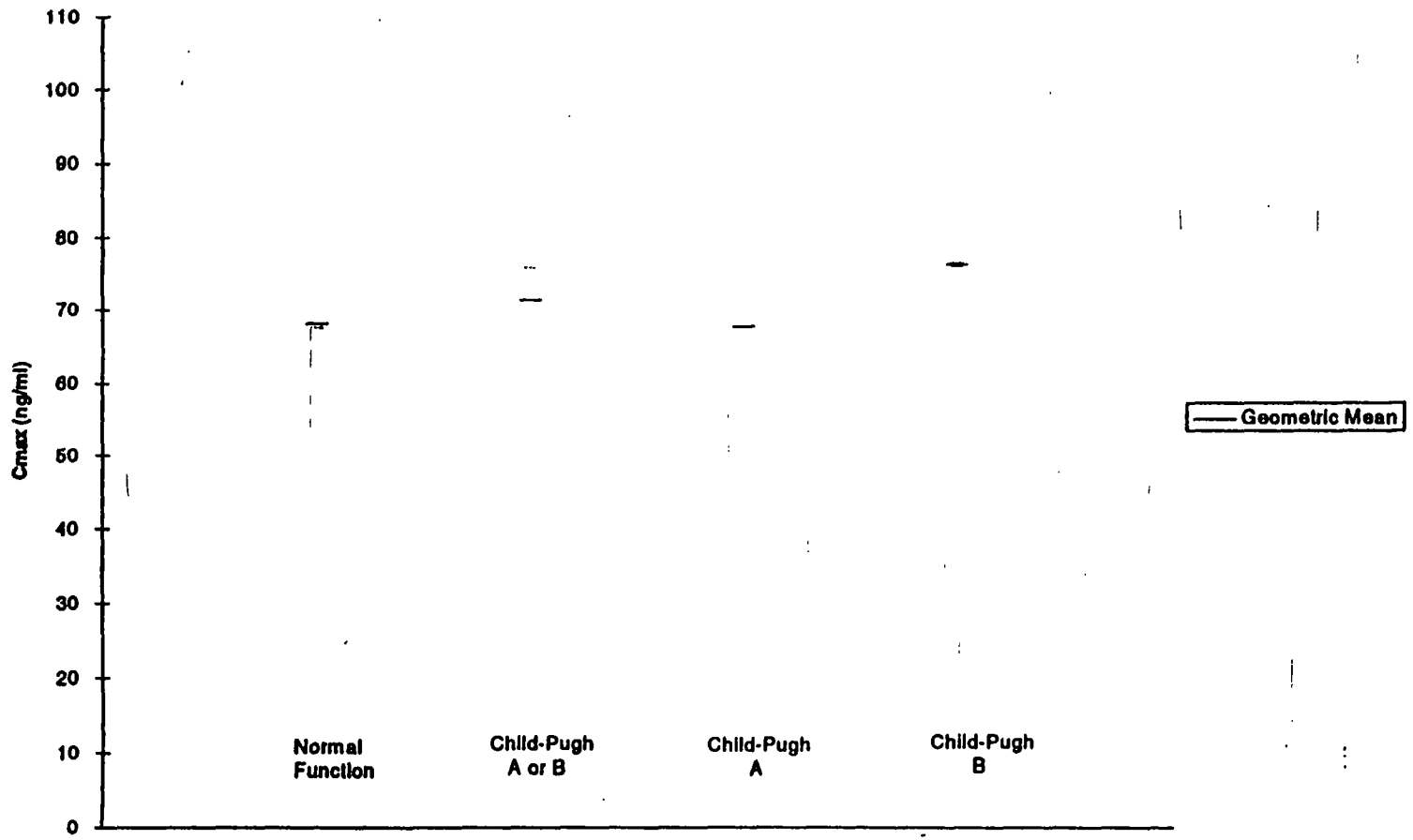
Figure 1.7 Comparison of Individual AUC_{0-12} Values on Day 5 by Hepatic Function
Ziprasidone 030



Source Data: Appendix IV, Table 2

(8) Attachment 8

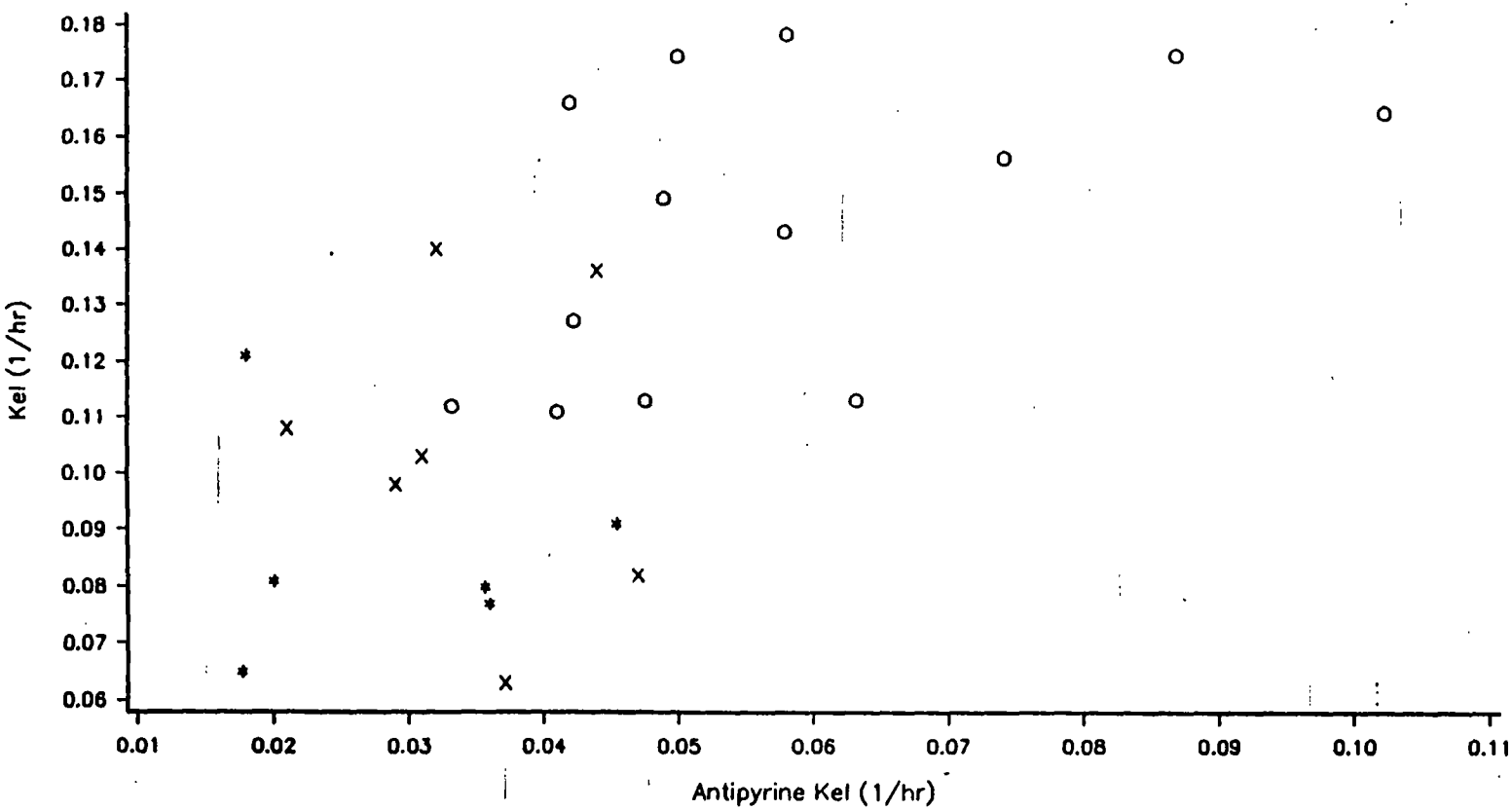
Figure 1.8 Comparison of Individual Cmax Values on Day 5 by Hepatic Function
Ziprasidone 030



Source Data: Appendix IV, Table 2

(6) Attachment 9

Figure 2
Kel (1/hr) vs Antipyrine Kel (1/hr)
Ziprasidone Protocol 030



Hepatic Function: ooo Normal xxx Child-Pugh A *** Child-Pugh B
R-square = 0.3946

Study 028: (Age and Gender):

Study Design and Summary:

(see attachments 1-4)

Results:

(See attachments 5-8)

1. In general, on day 1, there is no apparent gender or age difference in Cmaxs or AUCs (attachments 5-8).

2. In general, on day 8, the AUC was slightly higher in all groups as compared to day 1 (attachments 5-8).

3. In general, on day 8, the AUC was ~20% higher in elderly (560 ng.h/mL) than in young groups (465 ng.h/ml) and elderly females were being slightly higher (~23%) than elderly males (attachments 5 and 6).

4. The elderly groups appear to have a slightly longer half-life than the young groups (5.5 vs 3.5 hours). See attachment 6.

Conclusions:

1. Overall, the difference among the groups was less than 25%.
2. There is no need for a dosage adjustment in elderly subjects.

PROTOCOL 128-028: PHASE I MULTIPLE DOSE OPEN STUDY DESIGNED TO COMPARE THE PHARMACOKINETIC PARAMETERS OF ZIPRASIDONE BETWEEN HEALTHY ELDERLY AND YOUNG VOLUNTEERS

Principal Investigators: W. Colburn, Ph.D.

Study Publication: None

Study Dates: 28 November 1994 - 07 February 1995

Study Objective: To compare the disposition of oral ziprasidone at steady-state by age and gender.

Study Design: This was an open, multiple dose study of ziprasidone (20 mg BID) administered orally, twice daily, with food for 7 days (days 1-7) with a single morning dose on day 8. All doses are expressed as mg equivalents of ziprasidone free base.

Evaluation Groups:

	Young		Elderly	
	Male	Female	Male	Female
Entered Study	8	11	8	8
Completed Study	8	8	8	8
Evaluated for Pharmacokinetics	8	8	8	8
Assessed for Safety				
Adverse Events	8	11	8	8
Laboratory Tests	8	11	8	8

Subjects: Normal, healthy, young (18-42 years, inclusive) and elderly (65-76 years) subjects of either sex.

Drug Administration:

Dosage Form: 20 mg, CP-88,059-1 HCl capsules, FID #CS-90-031

Dosing: Subjects received ziprasidone 20 mg twice daily for 7 days (days 1-7) with a single 20 mg dose on day 8. For morning dosing, breakfast was to be consumed over a 20 minute period and study medication was to then be immediately administered with 50 ml of water. For evening dosing, dinner was to be consumed over a 20 minute period and study medication was to administered with 50 ml of water. The interval between morning and evening dosing was to be approximately 12 hours.

Pharmacokinetic and Safety Evaluations: On days 1 and 8, blood samples for determination of serum ziprasidone concentrations were to be collected prior to and up to 12 hours after the morning dose, and on day 8, up to 96 hours postdose. Serum samples were to be collected prior to ziprasidone morning dosing on days 2

through 7. On day 8, blood samples for protein binding determinations were to be collected in heparinized tubes from each subject just prior to the morning dose. Subjects were to be monitored for adverse events and changes in vital signs and laboratory data.

Analytical Methods:

Statistical Methods: Each pharmacokinetic parameter ($AUC_{(0-12)}$, C_{max}, T_{max}, and K_{el}) was analyzed as the dependent variable in a two-way analysis of variance model with age, sex and age*sex interaction as the classification variables. $AUC_{(0-12)}$ and C_{max} were also analyzed as the dependent variable in a two-way analysis of covariance model with age, sex, and age*sex interaction as the classification variable and with weight as the continuous covariant. For $AUC_{(0-12)}$ and C_{max}, the natural log transform was applied prior to the analysis.

Pharmacokinetic Results:

Mean ± Coefficients of Variation (%CV) of Pharmacokinetic Parameters

	Young					
	Male		Female		Male & Female	
	mean	CV%	mean	CV%	mean	CV%
	DAY 1					
$AUC_{(0-12)}$ (ng•hr/ml)[a]	359	30	330	19	344	24
C_{max}[a] (ng/ml)	60	21	53	30	56	26
T_{max} (hour)	4	29	4	33	4	30
	DAY 8					
$AUC_{(0-12)}$ (ng•hr/ml)[a]	451	32	479	17	465	25
C_{max} (ng/ml)[a]	67	23	72	18	69	20
T_{max} (hour)	4	40	3	27	4	38
K_{el} (1/hour)	0.225	26	0.169	17	0.197	27
$T_{1/2}$ (hour)[b]	3.1	-	4.1	-	3.5	-
Fb[c] (%)	99.9	0	99.8	0	99.85	0

[a]=Geometric means
b=Calculated as 0.693/mean K_{el}
c=Protein binding

Mean ± Coefficients of Variation (%CV) of Pharmacokinetic Parameters

	Elderly					
	Male		Female		Male & Female	
	mean	CV%	mean	CV%	mean	CV%
	DAY 1					
$AUC_{(0-12)}$ (ng•hr/ml)[a]	358	14	408	28	382	23
C_{max}[a] (ng/ml)	54	15	66	33	60	27
T_{max} (hour)	4	34	5	28	5	31
	DAY 8					
$AUC_{(0-12)}$ (ng•hr/ml)[a]	505	19	621	26	560	24
C_{max} (ng/ml)[a]	71	24	102	39	85	38
T_{max} (hour)	6	38	3	49	4	49
K_{el} (1/hour)	0.122	46	0.130	22	0.126	35
$T_{1/2}$ (hour)[b]	5.7	-	5.3	-	5.5	-
Fb[c] (%)	99.9	0	99.9	0	99.87	0

[a]=Geometric means
b=Calculated as 0.693/mean K_{el}

c=Protein binding

The 95% confidence intervals on difference for age group comparisons were: $AUC_{(0-12)}$ (101%, 143.6%), C_{max} (100.5%, 148.9%), K_{el} (-0.1042, -0.0379), and T_{max} (-0.4053, 1.9053). The 95% confidence intervals on difference for gender comparisons were: $AUC_{(0-12)}$ (95.8%, 136.2%), C_{max} (102%, 151%), K_{el} (-0.0576, 0.0087), and T_{max} (-2.7803, -0.4697). For the parameters $AUC_{(0-12)}$ and C_{max}, the differences between the geometric means are represented with the ratio between geometric means and the 95% confidence interval around the ratio.

Safety Results:

	Number of Subjects [With/Evaluated (Discontinued)]			
	Young		Elderly	
Findings	Male	Female	Male	Female
Adverse Events (All Causality)	7/8 (0)	11/11 (3)	8/8 (0)	7/8 (0)
Adverse Events (Treatment-emergent, Treatment-related)	7/8 (0)	11/11 (3)	6/8 (0)	6/8 (0)
Clinically Significant Laboratory Test Abnormalities	1/8 (0)	6/11 (0)	2/8 (0)	8/8 (0)

Summary and Conclusions:

Based upon $AUC_{(0-12)}$, C_{max}, T_{max} and K_{el} on day 8, there appears to be no difference between the pharmacokinetics of young male and female subjects. In addition, overall exposure, based upon $AUC_{(0-12)}$ and C_{max}, is very similar between the elderly male group and the young group.

Based upon $AUC_{(0-12)}$ and C_{max}, exposure in the elderly female group is slightly greater than in elderly male subjects (23% for AUC_{0-12} and 44% for C_{max}). Half-life ($T_{1/2}$) and accumulation ratio (R) are similar between all treatment groups. Normalized data for $AUC_{(0-12)}$ and C_{max} to a 70 kg person does not appear to account for the difference in exposure.

The elderly group appears to have a slightly longer $T_{1/2}$ than the young group (5.5 versus 3.5 hours). The elderly group appears to have a larger exposure than the young group as measured by $AUC_{(0-12)}$ and C_{max} primarily due to the greater exposure in the elderly female group.

There was no apparent difference in percent plasma protein binding among the four treatment groups.

Three subjects in the young female treatment group discontinued due to adverse events. The most common body system with treatment-emergent adverse events was the nervous system, with six out of eight subjects in the young male treatment group, 10 out of 11 subjects in the young female treatment group, 5 out of 8 subjects in the elderly male and female treatment groups having adverse events. Somnolence was the most common adverse event in this body system and was mild to moderate in severity. Asthenia was a commonly reported adverse event affecting the body as a whole experienced by 6 out of 8 subjects in the young male treatment group, 8 out of

11 subjects in the young female treatment group, 3 out of 8 subjects in the elderly male treatment group, and 2 out of 8 subjects in the elderly female treatment group. All adverse events were mild to moderate in intensity except for one subject in the young male treatment group with a severe respiratory infection. There were no serious adverse events in this study.

In conclusion, differences in overall exposure, based on AUC_{0-12} and C_{max}, were less than 50% among the treatment groups. Thus, there is no need for a dosage adjustment based upon pharmacokinetics. Adverse events were consistent with the pharmacological properties of this compound.

(5)

Attachment 1

5

Table 5.1.1. Summary of Pharmacokinetic Parameters for Ziprasidone Following a Single 20 mg Dose of Ziprasidone on Day 1 to Normal, Healthy Volunteers under Fed Conditions.

Ziprasidone Protocol 028.

	Gender	Age (yr)	WT (kg)	AUC(0-12) (ng•hr/ml)	70*AUC/WT (ng•hr/ml)	Tmax (hr)	Cmax (ng/ml)	70*Cmax/WT (ng/ml)
Mean	M	24	74.1	359	343	4	60	57
S.D.	M	7	11.4	107	142	1	13	19
% CV	M	29	15	30	42	29	21	32
Mean	F	29	70.1	330	332	4	53	53
S.D.	F	9	9.1	61	87	1	16	18
% CV	F	30	13	19	26	33	30	34
Mean	M&F	27	72.1	344	337	4	56	55
S.D.	M&F	8	10.1	84	113	1	14	18
% CV	M&F	30	14	24	34	30	26	32
Mean	M	70	78.9	358	319	4	54	48
S.D.	M	3	8.0	51	69	2	8	11
% CV	M	5	10	14	22	34	15	23
Mean	F	70	62.1	408	463	5	66	75
S.D.	F	4	8.7	115	158	1	22	27
% CV	F	5	14	28	34	28	33	36
Mean	M&F	70	70.5	382	384	5	60	60
S.D.	M&F	3	11.9	86	129	2	16	22
% CV	M&F	5	17	23	34	31	27	37

Source Data: Appendix IV, Tables 1-6.

(6) Attachment 2

Table 5.1.2. Summary of Pharmacokinetic Parameters for Ziprasidone on Day 8 Following Twice Daily Oral Administration of 20 mg of Ziprasidone for 7 Days to Normal, Healthy Volunteers under Fed Conditions.

Ziprasidone Protocol 028.

	Gender	Age (yr)	WT (kg)	AUC(0-12) (ng•hr/ml)	70*AUC/WT (ng•hr/ml)	AUC(0-∞) (ng•hr/ml)	Cmax (ng/ml)	70*Cmax/WT (ng/ml)	Tmax (hr)	Kel (1/hr)	T1/2 (hr)	Fb (%)
Mean	M	24	74.1	451	431	532	67	64	4	0.2251	3.1	99.87
S.D.	M	7	11.4	145	182	193	15	22	2	0.0588		0.03
% CV	M	29	15	32	42	36	23	34	40	26		0
Mean	F	29	70.1	479	481	589	72	72	3	0.1689	4.1	99.83
S.D.	F	9	9.1	83	133	134	13	19	1	0.0296		0.11
% CV	F	30	13	17	28	23	18	26	27	17		0
Mean	M&F	27	72.1	465	455	560	69	68	4	0.1970	3.5	99.85
S.D.	M&F	8	10.1	117	159	166	14	20	1	0.0535		0.08
% CV	M&F	30	14	25	35	30	20	30	38	27		0
Mean	M	70	78.9	505	450	706	71	63	6	0.1223	5.7	99.89
S.D.	M	3	8.0	98	92	133	17	15	2	0.0567		0.02
% CV	M	5	10	19	20	19	24	23	38	46		0
Mean	F	70	62.1	621	706	781	102	115	3	0.1296	5.3	99.86
S.D.	F	4	8.7	159	212	224	40	50	2	0.0284		0.06
% CV	F	5	14	26	30	29	39	44	49	22		0
Mean	M&F	70	70.5	560	563	742	85	85	4	0.1259	5.5	99.87
S.D.	M&F	3	11.9	137	192	178	31	39	2	0.0435		0.04
% CV	M&F	5	17	24	34	24	36	46	49	35		0

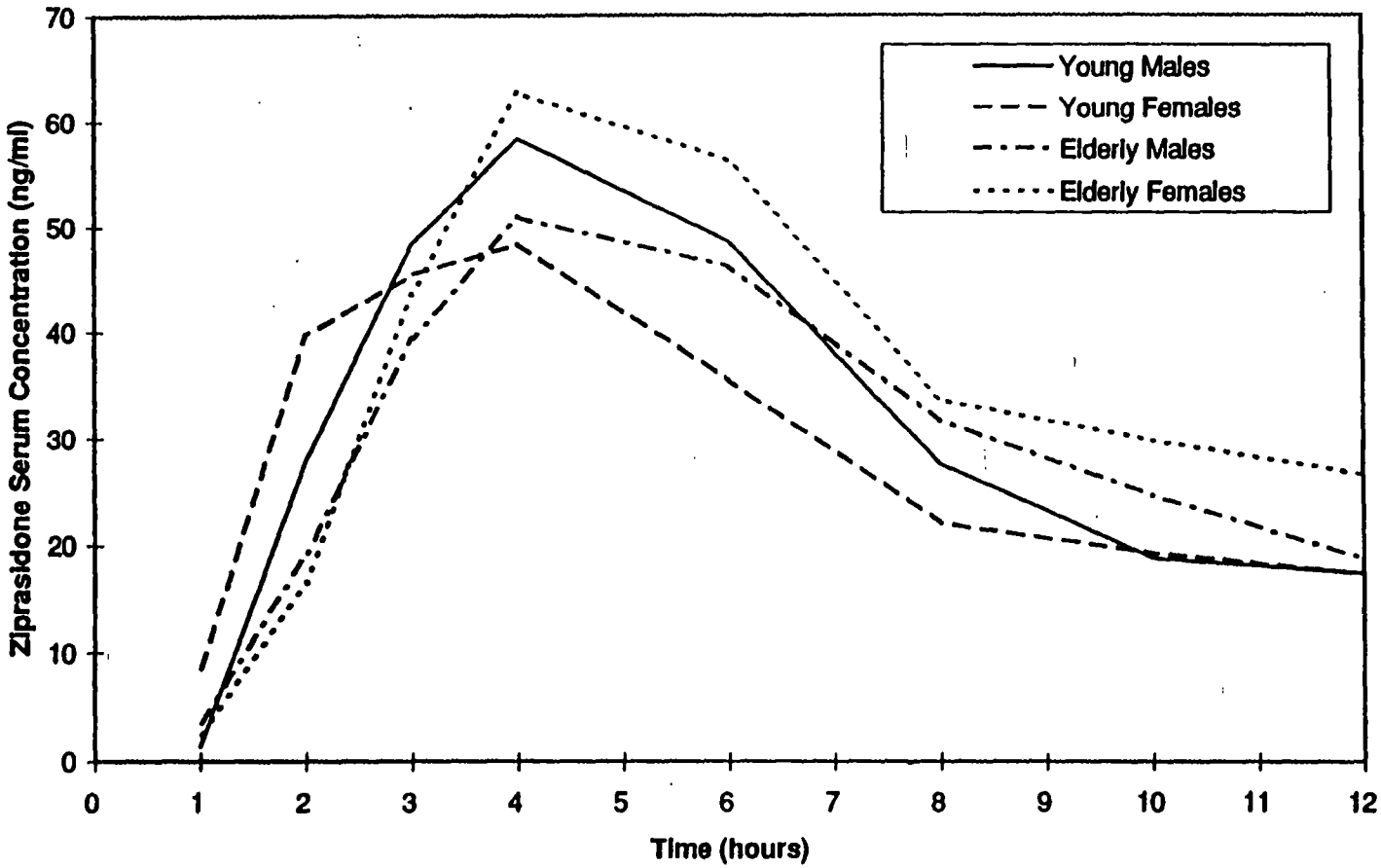
Source Data: Appendix IV, Tables 1-6.

Attachment 7

(7)

Figure 1.1. Mean Ziprasidone Serum Concentrations vs Time Following Oral Administration of a Single 20 mg Dose of Ziprasidone on Day 1 to Normal, Healthy Volunteers under Fed Conditions.

Ziprasidone Protocol 028.

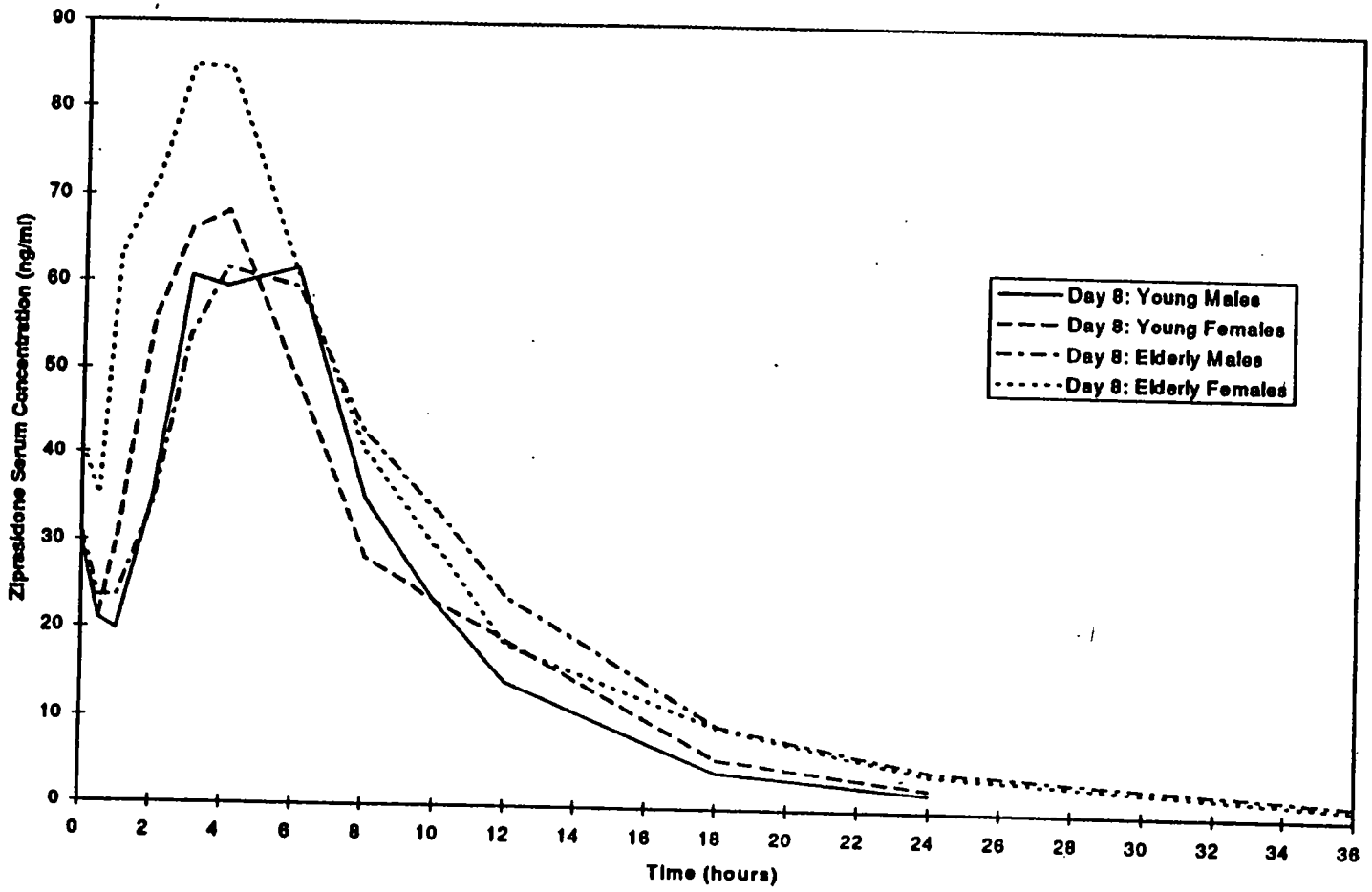


Source Data: Appendix IV, Tables 1 and 2.

Attachment 8

Figure 1.2. Mean Ziprasidone Serum Concentrations vs Time on Day 8 Following Twice Daily Oral Administration of 20 mg of Ziprasidone for 7 Days to Normal, Healthy Volunteers under Fed Conditions.

Ziprasidone Protocol 028.



Source Data: Appendix IV, Tables 3 and 4.

Study 039: (Cimetidine and Antacid):

Study Design and Summary:

(see attachments 1-3)

Results:

(See attachments 4-9)

Reviewer's Comments:

1. Cimetidine should have been administered for at least one week prior to ziprasidone. However, in this study, cimetidine (800 mg) was administered once daily for only two days prior to ziprasidone administration and for one day post dosing. A longer duration for cimetidine treatment may be required for enzyme inhibition.

2. The coadministration of Maalox with ziprasidone is adequate since the interactions occur mainly physically at the absorption sites.

3. Overall, it does not seem there is any consistent differences in the data at the three arms of the studies (attachments 4-9). However, it appears that cimetidine slightly increased the AUC and Maalox slightly delayed the absorption (attachment 9), but examining the individual serum concentrations, there is no clear trend among the subjects.

Conclusions:

1. Based on this study, cimetidine and antacid do not affect the absorption of ziprasidone.

2. Cimetidine should have been given for longer duration of time (at least one week) prior to ziprasidone to see any significant effect.

PROTOCOL 128-039: PHASE I OPEN STUDY TO ASSESS THE POTENTIAL OF CIMETIDINE OR ANTACID TO ALTER THE PHARMACOKINETICS OF ZIPRASIDONE IN NORMAL HEALTHY SUBJECTS

Principal Investigators: P. Geoffroy, M.D.

Study Publication: None

Study Dates: 13 June 1996 - 19 July 1996

Study Objective: To determine whether multiple dose cimetidine or antacid administration alters the pharmacokinetics of ziprasidone.

Study Design: This was an open, randomized, three-way crossover study to evaluate ziprasidone pharmacokinetics in the same subjects. The study consisted of three one-day periods with at least seven days separating each period. The three treatment periods were as follows: (1) ziprasidone 40 mg alone; (2) ziprasidone 40 mg + 30 ml of the antacid Maalox®; and (3) ziprasidone 40 mg + 800 mg cimetidine.

Evaluation Groups:

	Ziprasidone	Ziprasidone and Maalox®	Ziprasidone and Cimetidine
Entered Treatment Leg	11	11	11
Completed Treatment Leg	10	11	10
Evaluated for Pharmacokinetics	10	10	10
Assessed for Safety			
Adverse Events	11	11	11
Laboratory Tests[a]	0	0	0

[a]Laboratory tests were performed only at screening and within 24 hours prior to the first dose, unless follow-up was required.

Subjects: Healthy male and female volunteers ranging in age from 21 to 44 years.

Drug Administration:

Dosage Form: ziprasidone 20 mg commercial capsule (FID #QC2327)

Maalox® suspension (aluminum hydroxide 450 mg and magnesium hydroxide 400 mg per 10 ml; manufactured by Rhone-Poulenc Rorer) and cimetidine 400 mg tablets (Tagamet®; manufactured by SK-Beecham) were supplied by the clinical research facility.

Dosing: Subjects were administered single oral doses (2 x 20 mg) of ziprasidone with 60 ml of water in an open fashion under fed

conditions at approximately 9 a.m. For the treatment leg in which Maalox® 30 ml was coadministered with ziprasidone, ziprasidone was administered immediately following administration of Maalox®. Maalox® 30 ml was also taken at bedtime the evening prior to ziprasidone dosing, and 20 minutes following consumption of lunch and dinner on the day of ziprasidone dosing. For the treatment leg in which cimetidine was coadministered with ziprasidone, cimetidine 2 x 400 mg tablets were administered once daily early in the morning commencing two days prior to ziprasidone administration and continuing until one day after dosing with ziprasidone.

Pharmacokinetic and Safety Evaluations: Blood samples for the determination of serum ziprasidone concentrations were collected immediately prior to and up to 36 hours after each dose of ziprasidone. Serum concentrations were used to estimate pharmacokinetic parameters ($AUC_{0-\infty}$, C_{max}, T_{max}, K_{el}, and $T_{1/2}$). Subjects were monitored for adverse events.

Analytical Methods:

Statistical Methods: Natural log-transformed $AUC_{0-\infty}$ and C_{max}, and untransformed T_{max} and K_{el} were analyzed using an ANOVA model. For $AUC_{0-\infty}$ and C_{max}, 95% confidence limits were calculated for the ratio of adjusted geometric means.

Pharmacokinetic Results:

Mean and Coefficients of Variation (%CV) of Pharmacokinetic Parameters (N=10)

Parameter	Ziprasidone	Ziprasidone + Maalox®	Ziprasidone + Cimetidine
$AUC_{0-\infty}$ (ng•hr/ml)[a]	939 (19)	952 (20)	998 (21)
C_{max} (ng/ml)[a]	91 (30)	96 (53)	92 (33)
T_{max} (hr)	8 (31)	11 (32)	9 (36)
K_{el} (hr^{-1})	0.182 (8)	0.181 (15)	0.176 (11)
$T_{1/2}$ (hr)[b]	3.81	3.82	3.93

[a]geometric means and standard deviations
[b]mean $T_{1/2}$ = ln 2/mean K_{el}

Safety Results:

Number of Subjects With/Evaluated For:	Ziprasidone	Ziprasidone + Maalox®	Ziprasidone + Cimetidine
Adverse Events (All Causality)	4/11 (1)	5/11 (0)	6/11 (0)
Adverse Events (Treatment-emergent, treatment-related)	3/11 (1)	2/11 (0)	2/11 (0)

() subjects discontinued

Summary and Conclusions: Although there was a statistically significant increase in the AUC in the ziprasidone + cimetidine group compared to the ziprasidone group, the

difference was only 6% and is not considered to be clinically meaningful. Additionally, there were no statistically significant changes in C_{max}, T_{max}, or K_{el} between the two groups. The administration of Maalox® with ziprasidone delayed the occurrence of C_{max} by 3 hours, but there were no statistically significant differences in $AUC_{0-\infty}$, C_{max}, T_{max}, or K_{el} between the ziprasidone + Maalox® group and the ziprasidone group.

Two subjects discontinued from the study, one due to treatment-related adverse events, and one due to personal reasons (family matters). No serious adverse events were reported. All adverse events were of mild severity, and the total number of adverse events was comparable among the treatment groups. Following administration of ziprasidone, treatment-related adverse events included asthenia, dizziness, headache, pain, anxiety, somnolence and tremor. Following administration of ziprasidone + Maalox®, treatment-related adverse events included asthenia, dizziness, and somnolence. Treatment-related adverse events following administration of ziprasidone + cimetidine included headache, nausea, dizziness, and somnolence.

In summary, concurrent administration of cimetidine or antacid does not affect the bioavailability of ziprasidone.

(5) (4)

Table 5.1.1 Summary of Pharmacokinetic Parameters; Mean (CV%)
Ziprasidone Protocol 039

	Ziprasidone (N=10)	Ziprasidone + Maalox® (N=10)	Ziprasidone + Cimetidine (N=10)
$AUC_{0-\infty}$ (ng•hr/ml)[a]	939 (19)	952 (20)	998 (21)
Cmax (ng/ml)[a]	91 (30)	96 (53)	92 (33)
Tmax (hr)	8 (31)	11 (32)	9 (36)
Kel (hr^{-1})	0.182 (8)	0.181 (15)	0.176 (11)
$T_{1/2\ (hr)}$[b]	3.81	3.82	3.93

[a]Geometric means and standard deviations
[b]Calculated as ln 2/mean Kel

Source Data: Appendix IV, Tables 1 - 3

(5) (5)

Table 5.1.2 Individual and Mean Ziprasidone Pharmacokinetic Parameters Following a Single 40 mg Dose of Ziprasidone Ziprasidone Protocol 039

Subject #	AUCo-t (ng•hr/ml)	AUCo-∞ (ng•hr/ml)	Cmax (ng/ml)	Tmax (hr)	Kel (hr^{-1})	T1/2 (hr)
746-0001						
746-0002						
746-0003						
746-0004						
746-0005						
746-0006						
746-0008						
746-0010						
746-0011						
746-0012						
Mean	930[a]	939[a]	91[a]	8	0.182	3.81[b]
S.D.	177	179	28	2	0.015	
CV%	19	19	30	31	8	

746-0007[c]

[a]Geometric means and standard deviations
[b]Calculated as ln 2/mean Kel
[c]Subject who did not complete the study and whose data were excluded from summary statistics
[d]Not sufficient data to estimate AUCo-∞, Kel and T1/2

Source Data: Appendix IV, Table 1

(6) (6)

Table 5.1.3 Individual and Mean Ziprasidone Pharmacokinetic Parameters Following 40 mg Dose of Ziprasidone + 30 ml of Maalox® Ziprasidone Protocol 039

Subject #	AUCo-t (ng•hr/ml)	AUCo-∞ (ng•hr/ml)	Cmax (ng/ml)	Tmax (hr)	Kel (hr^{-1})	T1/2 (hr)
746-0001						
746-0002						
746-0003						
746-0004						
746-0005						
746-0006						
746-0008						
746-0010						
746-0011						
746-0012						
Mean	940[a]	952[a]	96[a]	11	0.181	3.82[b]
S.D.	190	192	51	3	0.028	
CV%	20	20	53	32	15	

746-0009[c]

[a]Geometric means and standard deviations
[b]Calculated as ln 2/mean Kel
[c]Subject who did not complete the study and whose data were excluded from summary statistics

Source Data: Appendix IV, Table 2

Table 5.1.4 Individual and Mean Ziprasidone Pharmacokinetic Parameters Following 40 mg Dose of Ziprasidone + 800 mg of Cimetidine Ziprasidone Protocol 039

Subject #	AUCo-t (ng•hr/ml)	AUCo-∞ (ng•hr/ml)	Cmax (ng/ml)	Tmax (hr)	Kel (hr^{-1})	T1/2 (hr)
746-0001						
746-0002						
746-0003						
746-0004						
746-0005						
746-0006						
746-0008						
746-0010						
746-0011						
746-0012						
Mean	987[a]	998[a]	92[a]	9	0.176	3.93[b]
S.D.	203	205	30	3	0.019	
CV%	21	21	33	36	11	
746-0009[c]						

[a]Geometric means and standard deviations
[b]Calculated as ln 2/mean Kel
[c]Subject who did not complete the study and whose data were excluded from summary statistics

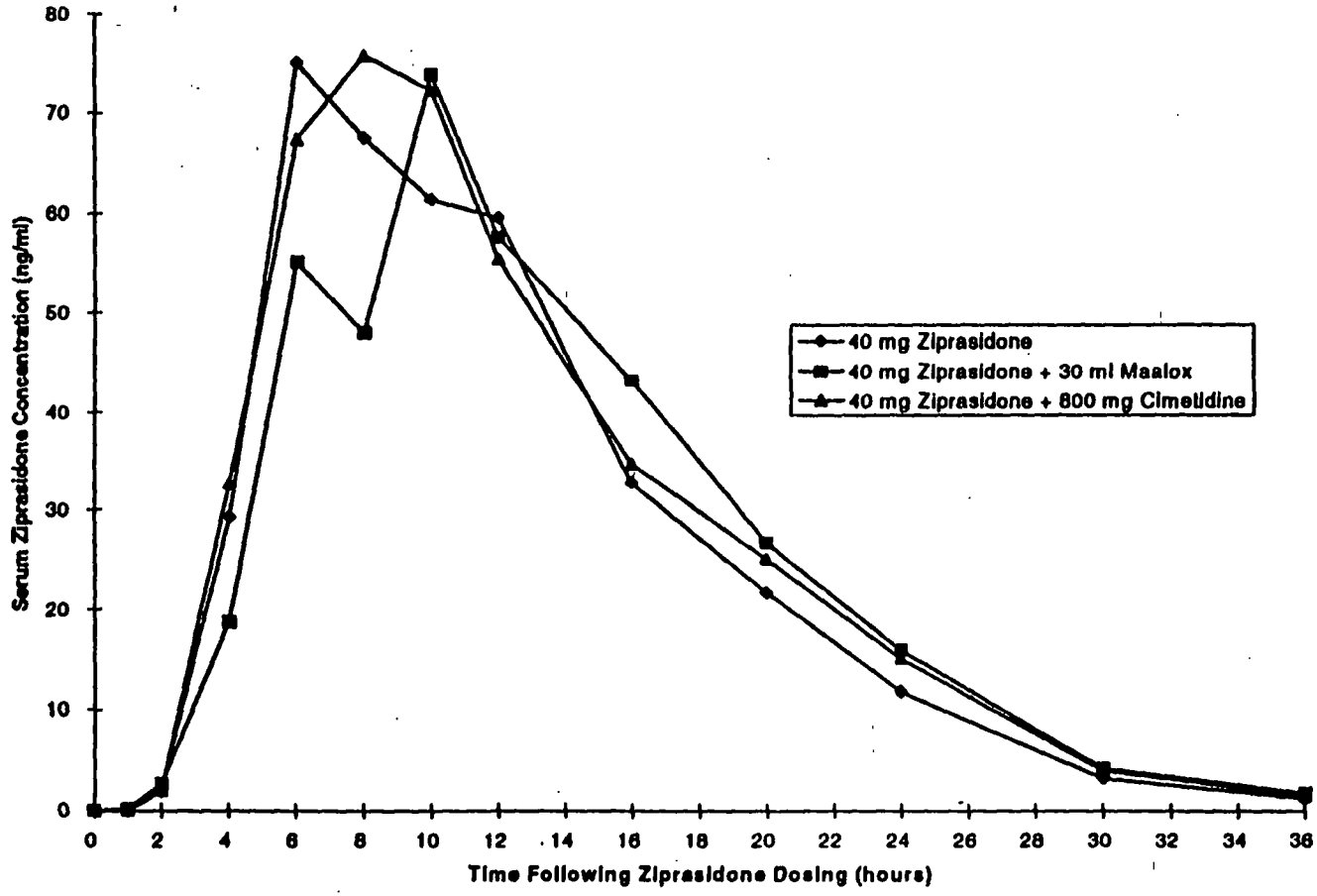
Source Data: Appendix IV, Table 3

Table 5.2
Summary of Statistical Analysis of Pharmacokinetic Parameters
(AUC, Cmax, Tmax, and Kel)
Ziprasidone Protocol 039

Pharmacokinetic Parameter	Comparison			95% Confidence Limits
		Adjusted Geometric Means	Ratio	
AUC(0 inf) (ng.hr/ml)	40mg + MLX vs. 40mg	942.49 vs. 929.68	101.4%	(95.6%, 107.5%)
	40mg + CMT vs. 40mg	993.45 vs. 929.68	106.9%	(100.6%, 113.5%)
Cmax (ng/ml)	40mg + MLX vs. 40mg	92.82 vs. 88.14	105.3%	(82.8%, 134.0%)
	40mg + CMT vs. 40mg	90.03 vs. 88.14	102.1%	(80.0%, 130.4%)
		Adjusted Means	Difference	
Tmax (hr)	40mg + MLX vs. 40mg	10.88 vs. 8.28	2.60	(0.11, 5.09)
	40mg + CMT vs. 40mg	9.33 vs. 8.28	1.05	(-1.48, 3.58)
Kel (1/hr)	40mg + MLX vs. 40mg	0.1809 vs. 0.1814	-0.0005	(-0.0153, 0.0143)
	40mg + CMT vs. 40mg	0.1781 vs. 0.1814	-0.0033	(-0.0183, 0.0118)

40mg, MLX and CMT represent 40mg Ziprasidone, 30ml Maalox and 800mg Cimetidine respectively.
Source Data: Appendix III Tables 1-4 Date of Data Extraction: 24SEP96. Date of Table Generation: 24OCT96.

Figure 1. Mean Serum Ziprasidone Concentrations vs Time Following 40 mg Dose of Ziprasidone, 40 mg Ziprasidone + 30 ml of Maalox®, and 40 mg Ziprasidone + 800 mg of Cimetidine
Ziprasidone Protocol 039



Source Data: Appendix IV, Tables 1 - 3

Study 049: (Carbamazepine):

Study Design and Summary:

(see attachments 1-3)

Results:

(See attachments 4 and 5)

Reviewer's Comments:

1. This was an excellent study design (parallel, placebo control, steady-state, escalating carbamazepine dose for 21 days)

2. Compared to placebo, the data clearly shows that the carbamazepine decreases the ziprasidone AUC and Cmax by about 40%. The half life was slightly shorten (by about 17%) and Tmax was not affected (attachments 4 and 5).

3. The effect of ziprasidone on carbamazepine PK was not studied.

Conclusions:

1. Based on this study, carbamazepine at a dose of 200 mg BID for 21 days markedly reduced the ziprasidone serum level. It should be noted that the effect could be even higher at the commonly recommended carbamazepine maintenance doses (800 to 1200 mg daily).

2. In the label, carbamazepine dose should read "100 to 200 mg) and not "<200 mg".

3. Dose adjustment may be necessary in patients receiving carbamazepine.

PROTOCOL 128-049: PHASE I OPEN, MULTIPLE DOSE ORAL STUDY TO ASSESS THE EFFECTS OF CARBAMAZEPINE (TEGRETOL) ON THE STEADY-STATE PHARMACOKINETICS OF ZIPRASIDONE IN NORMAL, HEALTHY SUBJECTS

Principal Investigators: A. Laurent, M.D.

Study Publication: None

Study Dates: 26 August 1996 - 25 November 1996

Study Objective: To assess the effect of sub-chronic carbamazepine administration on the steady-state pharmacokinetics of ziprasidone.

Study Design: This was an open, parallel study to evaluate the effect of carbamazepine on the steady-state pharmacokinetics of ziprasidone in healthy subjects. Two treatment groups were enrolled in the study and were to complete three treatment periods. All subjects were administered ziprasidone 20 mg BID on days 1 and 2 and a single 20 mg dose on the morning of day 3 to establish baseline steady-state ziprasidone pharmacokinetics. Subjects were subsequently randomized to receive either carbamazepine or placebo BID for 21 days (days 5-25) followed by the coadministration of ziprasidone and carbamazepine or placebo BID on days 26-28 with a single dose of ziprasidone administered on the morning of day 28 and a single dose of carbamazepine or placebo administered on the morning of day 29.

Evaluation Groups:

	Group 1 Ziprasidone	Group 1 Carbamazepine	Group 1 Ziprasidone + Carbamazepine	Group 2 Ziprasidone	Group 2 Placebo	Group 2 Ziprasidone + Placebo
Entered Study	13	11	9	12	12	10
Completed Study	11	9	9	12	10	10
Evaluated for Pharmacokinetics (Day 3 + Day 28)	9	0	9	10	0	10
Assessed for Safety						
Adverse Events	13	11	9	12	12	10
Laboratory Tests*	0	10	1	0	11	1

* Laboratory tests were not done during the first treatment period (ziprasidone, days 1-3) and were done only for follow-up in treatment period 3 (ziprasidone + carbamazepine or placebo, Days 26-29).

Subjects: Healthy male or female subjects, between the ages of 23 and 45, inclusive.

Drug Administration:

Dosage Form

Drug	Lot Number	FID Number	Potency	Formulation
Ziprasidone HCl	N5056	QC2327	20 mg	commercial capsules
Carbamazepine	100 mg: 1B175597 200 mg: 1B176920	Tegretol XR/Ciba-Geneva	100 mg, 200 mg	tablets
Placebo	ED-G-181-694	G00524AA	———	capsules

Dosing: All subjects received oral ziprasidone 20 mg BID on days 1-2 and days 26-27. On days 3 and 28, only the morning dose of ziprasidone was administered. On days 5-29, subjects received either carbamazepine (Group 1), or placebo (Group 2). Subjects in Group 1 were administered a starting dose of cabamazepine (100 mg QD) on days 5-6, then the dose was escalated to 100 mg BID on days 7-8. Subjects then received 200 mg carbamazepine BID on

days 9-25 (the remainder of treatment period 2) and on days 26-28, with a single dose administered on the morning of day 29 (treatment period 3). If plasma trough concentrations of carbamazepine did not fall within the protocol specified therapeutic range of 4 to 12 µg/ml, the dose was adjusted accordingly. Subjects in Group 2 were administered the same dose regimen of placebo. All study medication was administered in the fed state.

Pharmacokinetic and Safety Evaluations: Blood samples for determination of serum ziprasidone concentrations were collected prior to the morning dose on day 1, and prior to and up to 36 hours after morning dosing on days 3 and 28. Blood samples for the determination of plasma carbamazepine concentrations were collected at regular intervals prior to morning carbamazepine dosing on days 5 through 28.

Analytical Methods:

Statistical Methods: Pharmacokinetic and safety results were summarized using descriptive statistics and graphical presentations. Statistical analyses of the pharmacokinetic data were performed using a two-sample t-test comparing the carbamazepine and placebo treatment groups. The mean differences between treatment groups were examined with 95% confidence intervals.

Pharmacokinetic Results:

Mean ± Coefficients of Variation (%CV) of Pharmacokinetic Parameters

		Group 1 - Carbamazepine	
$AUC_{(0-12)}$	Day 3	Day 28	Ratio Day 28/Day 3
	445 ± 35[a]	285 ± 28[a]	0.64 ± 31[a]
C_{max} (ng/ml)	65 ± 38[a]	48 ± 28[a]	0.73 ± 28[a]
T_{max} (hr)	5 ± 59	6 ± 24	
K_{el} (hr^{-1})	0.160 ± 15	0.211 ± 20	
$T_{1/2}$ (hr) Day 3	4.3[b]	3.3[b]	0.77 ± 17
		Group 2 - Placebo	
$AUC_{(0-12)}$	532 ± 27[a]	495 ± 26[a]	0.93 ± 12[a]
C_{max} (ng/ml)	76 ± 4[a]	79 ±24[a]	1.04 ± 24[a]
T_{max} (hr)	6 ± 33	6 ± 28	
K_{el} (hr^{-1})	0.171 ± 15	0.175 ± 27	
$T_{1/2}$ (hr) Day 3	4.1[b]	4.0[b]	1.06 ± 41

[a] (geometric mean)
[b] (harmonic mean)

APPEARS THIS WAY
ON ORIGINAL

Safety Results:

Number of Subjects [With/Evaluated (Discontinued)]

Findings	Group 1 Ziprasidone	Group 1 Carbamazepine	Group 1 Ziprasidone + Carbamazepine	Group 2 Ziprasidone	Group 2 Placebo	Group 2 Ziprasidone + Placebo
Adverse Events (All Causality)	8/13(1)	7/11(1)	3/9(0)	6/12(0)	9/12(1)	7/10(0)
Adverse Events (Treatment-emergent, Treatment-related)	6/13(1)	6/11(1)	1/9(0)	4/12(0)	8/12(1)	5/10(0)
Clinically Significant Laboratory Test Abnormalities*	0/0 (0)	0/10 (0)	0/1(0)	0/0(0)	2/11(0)	0/1(0)

* Laboratory tests were not performed during treatment period 1 (ziprasidone - days 1-3), and only for follow-up in treatment period 3 (ziprasidone + carbamazepine or placebo, Days 26-29).

Summary and Conclusions:

No statistical differences were observed in mean ziprasidone pharmacokinetic parameters between the carbamazepine and placebo treatment groups on day 3. In contrast to day 3, statistically significant differences in mean AUC_{0-12} and C_{max} values were observed between the treatment groups on day 28. There were also significant differences between the two treatment groups in the mean difference between day 28 and day 3 values for AUC_{0-12}, C_{max}, and K_{el}. The significant difference on day 28 is related to decreases in ziprasidone exposure coupled with faster terminal elimination rates for the carbamazepine treatment group. Compared to day 3, day 28 mean C_{max} values for the carbamazepine group (Group 1) decreased by 27% and mean AUC_{0-12} decreased by 36%. Mean K_{el} increased by 32% which corresponded to a decrease in mean half-life of 1 hour. In contrast, mean pharmacokinetic changes from day 3 to day 28 for the placebo group were less than 10%. Mean plasma carbamazepine trough concentrations between days 5 and 28 were within the desired therapeutic range.

The most frequently reported adverse events during the ziprasidone treatment periods were insomnia, headache and pharyngitis, and during the carbamazepine and placebo treatment periods were insomnia and pharyngitis. All adverse events were of mild to moderate severity. No serious adverse events were reported. Two subjects in Group 1 and one subject in Group 2 were discontinued from the study due to adverse events that were judged by the investigator to be related to treatment with the study drug (swelling of the tongue, urticaria and extrapyramidal reaction, respectively).

In summary, the decrease in steady-state ziprasidone exposure (AUC) coupled with the reduction in terminal phase half life following carbamazepine treatment and relative to placebo are attributable to carbamazepine's induction on P450 CYP3A4 leading to enhanced ziprasidone metabolism.

Table 5.1.1 Individual and Mean Ziprasidone Pharmacokinetic Parameters On Days 3 and 28 Following BID Administration of 20 mg Ziprasidone Ziprasidone Protocol 049 - Carbamazepine Treatment Group

Subject	Gender	Day 3 AUC(0-12) (ng•hr/ml)	Day 28 AUC(0-12) (ng•hr/ml)	AUC(0-12) Ratio Day 28/ Day 3	Day 3 Cmax (ng/ml)	Day 28 Cmax (ng/ml)	Cmax Ratio Day 28/ Day 3	Day 3 Tmax (hr)	Day 28 Tmax (hr)	Day 3 Kel (hr^{-1})	Day 28 Kel (hr^{-1})	Day 3 T1/2 (hr)	Day 28 T1/2 (hr)	T1/2 Ratio Day 28/ Day 3
748-0002	F													
748-0004	M													
748-0006	M													
748-0008	M													
748-0009	M													
748-0014	M													
748-0019	M													
748-0023	M													
748-0026	M													
MEAN		445[a]	285[a]	0.64[a]	65[a]	48[a]	0.73[a]	5	6	0.160	0.211	4.3[b]	3.3[b]	0.77
SD		155	79	0.20	25	13	0.20	3	1	0.024	0.042	--	--	0.13
CV%		35	28	30.95	38	28	28	59	24	15	20	--	--	17
748-0011[c]	M													
748-0017[c]	M													
748-0021[c]	M													

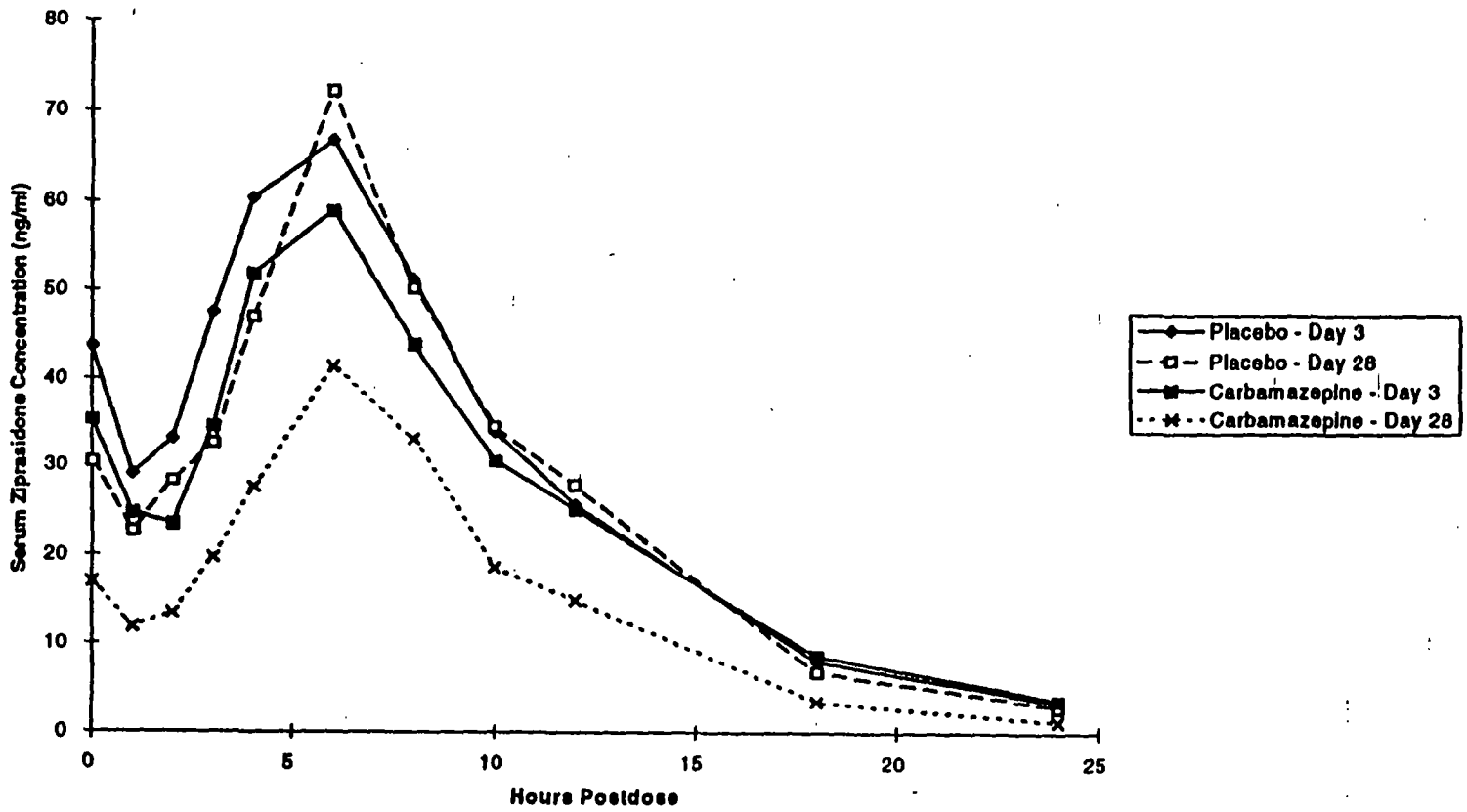
[a] = Geometric mean.

[b] = Harmonic mean.

[c] = Subject did not complete the study; excluded from summary statistics.

Source Data: Appendix IV, Tables 1 and 2

Figure 1. Mean Steady-State Serum Ziprasidone Concentrations on Days 3 and 28 in Subjects Receiving 20 mg Ziprasidone BID Prior to and Following Administration of Placebo or Carbamazepine for 21 Days
Ziprasidone Protocol 049



Source Data: Appendix IV, Tables 1 and 2

Study 025: (Effect of ziprasidone on Lithium Clr and Css):

Study Design and Summary:

(see attachments 1-3)

Results:

(See attachments 4-7)

Reviewer's Comments:

1. In this study, the steady-state serum and urine lithium concentrations were determined up to 12 hours on days 8 and 15 (i.e., prior to and after ziprazidone administration, respectively).

2. There was no difference in the lithium steady-state renal clearance between ziprasidone and placebo treated groups (attachment 5).

3. There was an excellent correlation between the lithium Css on day 8 (pre-ziprasidone) and day 15 (post-ziprasidone) and similarly between lithium Clr on day 8 and day 15 (attachments 6 and 7).

Conclusions:

1. Based on this study, ziprasidone did not show any significant effect on lithium Css or Clr.

2. The dose of ziprasidone used in this interaction study (40 mg BID) should be indicated in the label.

PROTOCOL 128-025: PHASE I OPEN STUDY TO ASSESS THE POTENTIAL OF ZIPRASIDONE TO ALTER THE RENAL CLEARANCE OF LITHIUM AND STEADY-STATE SERUM LITHIUM LEVELS IN NORMAL, HEALTHY MALE VOLUNTEERS

Principal Investigator: N. Gerber, M.B.

Study Publication: None

Study Dates: 15 July 1994 - 06 September 1994

Study Objective: To determine the effects of ziprasidone on the renal clearance of lithium and on the steady-state serum levels in healthy volunteers.

Study Design: This was an open, randomized, parallel study of the potential of ziprasidone to alter the renal clearance of lithium and steady state serum lithium levels in twenty-four healthy male subjects. Steady-state lithium levels were achieved by oral administration (450 mg, bid) for a 7-day period after which subjects were continued on lithium and started on ziprasidone (40 mg, bid titrated from 20 mg, bid) or placebo (bid) for an additional 7 days (days 9-15).

Evaluation Groups:

	Lithium Monotherapy	Lithium with Ziprasidone	Lithium with Placebo
Entered Study	34	12	13
Completed Study	25	12	13
Evaluated for Pharmacokinetics	25	12	13
Assessed for Safety			
Adverse Events	34	12	13
Laboratory Tests	34	12	13

Subjects: Healthy male volunteers ranging in age from 19 to 45 years.

Drug Administration:

Dosage Form

Drug	Lot Number	FID Number	Potency	Formulation	Total Daily Dosing
Lithium carbonate	3883J10	Smith Kline Beecham	450 mg	Tablets	Days 1-14 900 mg Day 15 450 mg
Ziprasidone	ED-G-124-593	CS-90-031	20 mg	Capsules	Days 9-11 40 mg Days 12-14 80 mg Day 15 40 mg
Placebo	ED-G-319-Z91	BK-87-007	—	Capsules	Days 9-11 2 Capsules Days 12-14 4 Capsules Day15 2 Capsules

Dosing: Subjects were fasted overnight and administered lithium carbonate (450 mg) orally twice daily on days 1-14 and once in the morning on day 15. Lithium was administered with 120 ml of water 2 hours following the completion of a standard breakfast and dinner. Once steady-state lithium levels had been achieved for 7 days,

each subject was administered ziprasidone or placebo with 50 ml of water on days 9-15 immediately following breakfast and dinner.

Pharmacokinetic and Safety Evaluations: Blood samples for the determination of serum lithium levels were collected prior to morning lithium dosing on days 5-7 and 9-14, and up to 12 hours after morning lithium dosing on days 8 and 15. Serum samples collected on days 8 and 15 were used to determine pharmacokinetic parameter AUC_{0-12}. Blood samples for the determination of serum ziprasidone levels were collected prior to morning ziprasidone dosing on days 9 and 15. Urine samples were collected from each subject on day 1 prior to morning lithium dosing. On days 8 and 15, a 12 hour urine collection following the morning lithium dosing was done for the determination of creatinine and lithium concentrations. Subjects were monitored for adverse events, laboratory test abnormalities, and changes in vital signs.

Analytical Methods:

Statistical Methods: Changes between day 8 and day 15 were examined for lithium renal clearance (L/hr) and steady-state concentration (mEq/L). Each parameter was analyzed using a two-sample t-test comparing the ziprasidone and placebo groups for day 8, day 15 and day 15 - day 8 (within subject change). Mean differences between treatment groups were examined with 95% confidence intervals.

Pharmacokinetic Results:

Parameter	Visit	Ziprasidone Mean	Placebo Mean	95% C.I.* on Difference	p-value
Lithium Clearance (L/hr)	Day 8	1.6895	1.5625		
	Day 15	1.6008	1.4217		
	Day 15-Day 8	-0.0887	-0.1408	(-0.185,0.2892)	0.6537
Lithium Concentration (pre-dose) (mEq/L)	Day 8	0.4942	0.5508		
	Day 15	0.5600	0.6085		
	Day 15-Day 8	0.0658	0.0577	(-0.0536,0.0699)	0.7875

* Confidence Interval

Predose Serum Ziprasidone Concentration (ng/ml) on Days 15 Following Twice Daily Oral Administration of Ziprasidone:
Mean Ziprasidone Concentration (pre-dose): 54 ± 24 ng/ml
%CV = 44

Safety Results:

	Lithium Monotherapy	Lithium with Ziprasidone	Lithium with Placebo
# of Subjects with Adverse Events (All Causality)	19/34 (2)	12/12 (0)	6/13 (0)
# of Subjects with Adverse Events (Treatment-emergent, treatment-related)	0/34 (0)	11/12 (0)	0/13 (0)
# Subjects with Clinically Significant Laboratory Test Abnormalities	4/34 (0)	0/12 (0)	1/13 (0)

( ) subjects discontinued

Adverse events related to lithium monotherapy are not considered treatment related, as lithium is categorized as a background study drug.

Summary and Conclusions: All subjects in the lithium with ziprasidone and lithium with placebo treatment groups completed the study. Nine of 34 subjects receiving lithium monotherapy discontinued the study; two due to adverse events (1 skin rash, 1 viral syndrome), six because they did not meet randomization criteria and one due to a personal reason.

Ziprasidone administered concomitantly with lithium for 7 days was associated with a 0.066 mEq/L (13%) increase in steady-state lithium levels compared with an increase of 0.058 mEq/L (10%) in subjects who received placebo. Renal clearance of lithium decreased by 0.089 L/h (5%) in the ziprasidone group and decreased by 0.141 L/h (9%) in the placebo group. These differences between the two groups were neither statistically or clinically significant.

Nineteen of 34 subjects receiving lithium monotherapy had a total of 37 adverse events. Severe headache was reported in 3 subjects, and severe anorexia, nausea, vomiting, and rash were reported in 1 subject each. All other adverse events were of mild to moderate severity. Treatment related adverse events were considered those related to ziprasidone or placebo only; all adverse events occurring in subjects receiving lithium monotherapy were recorded as non treatment related.

Twelve of 12 subjects receiving lithium with ziprasidone had a total of 87 mild to severe adverse events. Severe adverse events included insomnia (8 subjects: most subjects receiving lithium with ziprasidone who experienced severe insomnia did so following completion of the treatment period), headache and dizziness (3 subjects each), nausea and somnolence (2 subjects each) and abdominal pain, asthenia, palpitation, syncope, anorexia, constipation, agitation, confusion, hyperkinesia, and urinary frequency (1 subject each). Other adverse events were of mild to moderate severity. Seventy of the 87 adverse events were considered treatment related, primarily somnolence (10 subjects), insomnia (9 subjects), dizziness (6 subjects), and asthenia and headache (5 subjects each).

Six of thirteen subjects receiving lithium with placebo had a total of 11 adverse events including one case of severe insomnia. All other adverse events were of mild to moderate severity and none were considered treatment related.

(5)

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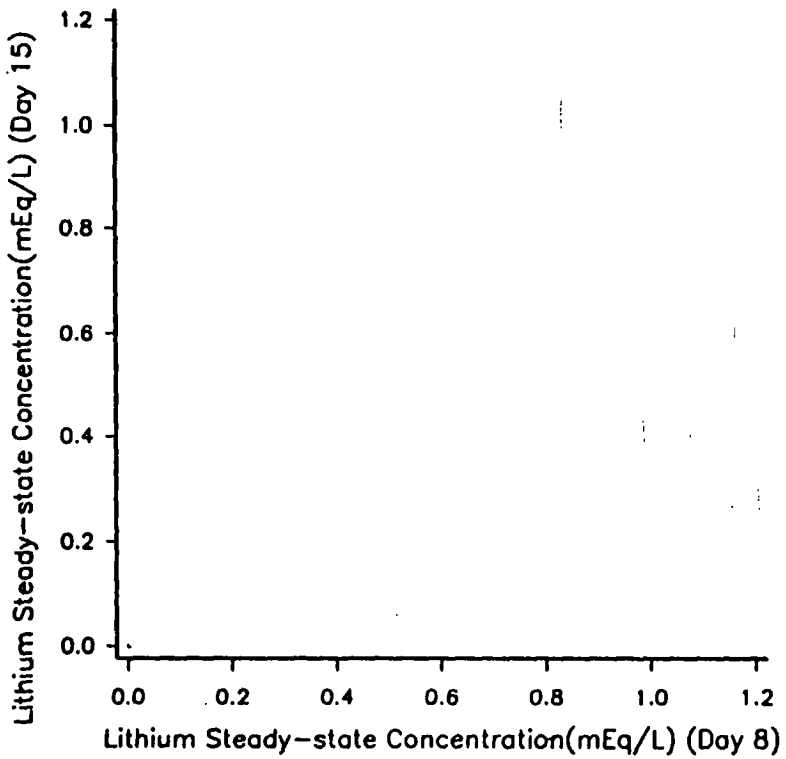
Table 5.2
Analysis of Lithium Pharmacokinetic Parameters
Ziprasidone Protocol 025

Parameter	Visit	Ziprasidone Mean	Placebo Mean	Difference Between Means	SE	95% Confidence Interval on Difference	P-value
Li Clearance (L/hr)	Day 8	1.6895	1.5625	0.1271	0.1539	(-0.1913,0.4454)	0.4175
	Day 15	1.6008	1.4217	0.1792	0.1107	(-0.0498,0.4081)	0.1191
	Day 15 - Day 8	-.0887	-.1408	0.0521	0.1146	(-0.185,0.2892)	0.6537
Li Steady State (mEq/L)	Day 8	0.4942	0.5508	-.0566	0.0423	(-0.1441,0.0309)	0.1941
	Day 15	0.5600	0.6085	-.0485	0.0472	(-0.146,0.0491)	0.3148
	Day 15 - Day 8	0.0658	0.0577	0.0081	0.0299	(-0.0536,0.0699)	0.7875

Means are Least Squares Means, the P-Values test the Null Hypothesis that the means are equal.
Lithium Steady State is the hour 0 Lithium concentration at day 8 and 15.
Lithium is abbreviated Li.
Source Data : Appendix III Table 1 Date of Data Extraction : 06DEC95 Date of Table Generation : 15JAN96

Figure 1
Day 8 vs Day 15 Lithium Steady-state Concentration(mEq/L)
Ziprasidone Protocol 025

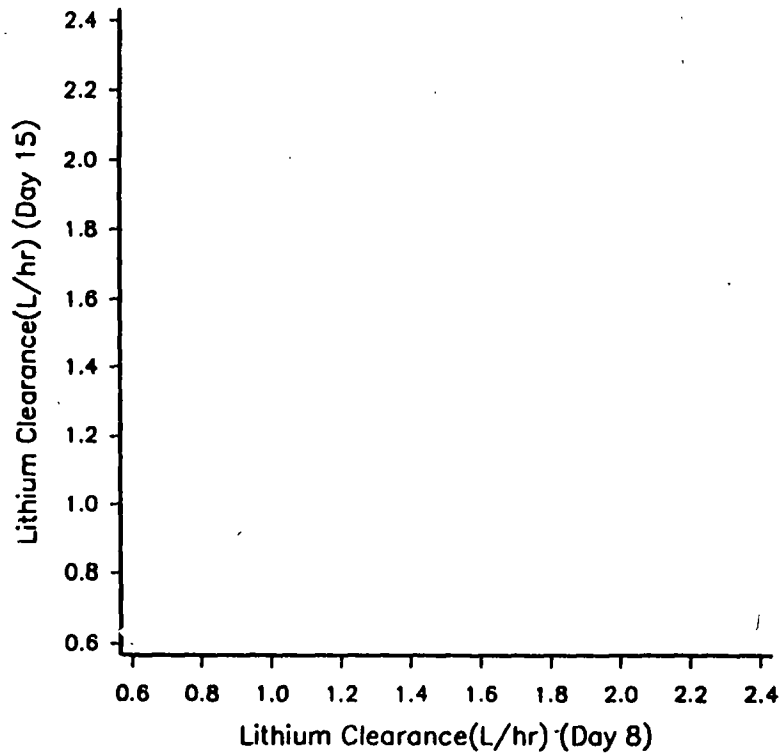


Treatment +++ Li + Zip ooo Li + PBO — Reference Line

Source Data : Appendix III Table 1 Date of Data Extraction : 08DEC95 Date of Figure Generation : 21MAY96

(2)

Figure 2
Day 8 vs Day 15 Lithium Clearance(L/hr)
Ziprasidone Protocol 025



Treatment +++ Li + Zip ooo Li + PBO — Reference Line

Source Data : Appendix III Table 1 Date of Data Extraction : 06DEC95 Date of Figure Generation : 21MAY96

Study 203: (Effect of Ziprasidone On Oral Contraceptives and Prolactin)

Study Design and Summary:

(see attachments 1 and 2)

Results:

(See attachments 3-8)

Reviewer's Comments:

1. In general, there were no PK differences of clinical significance for the tested oral contraceptives (Ethinyloestradiol and Levonorgestrel), when ziprasidone was administered.

2. It is clear that ziprasidone increased prolactin levels compared to the placebo (attachments 7 and 8). On day 15, prolactin level was about 3 folds higher compared to the placebo (~23 ng/mL vs 9 ng/mL). In addition, in the ziprasidone arm, there was a wide variation in prolactin serum levels, particularly at pre-dose, compared to the placebo (attachment 8). The sponsor did not provide any explanations on the variability nor on the mechanism (s) of the marked increase in prolactin levels.

Conclusions:

1. Based on this study, ziprasidone does not appear to affect the PK of the oral contraceptives.

2. It is clear that ziprasidone caused marked variation and increased the prolactin serum levels by about 3 folds as compared to the placebo.

PROTOCOL 128-203: A double-blind, placebo controlled, two-way cross-over study to investigate the effect of multiple oral administration of ziprasidone on the steady state plasma concentrations of an oral contraceptive in healthy female volunteers

Principal Investigators: Drs. S Oliver and PR Holt, UK.

Study Publication: None

Study Dates: 1 November 1994 - 1 April 1995

Study Objectives: To observe (1) the effect of multiple doses of ziprasidone on the pharmacokinetics of the component steroids, ethinyloestradiol (EE) and levonorgestrel (LNG), of an oral contraceptive, (2) the safety and toleration of multiple doses of ziprasidone when co-administered with an oral contraceptive, (3) in the event of a significant lowering of plasma concentrations of LNG and EE, i.e. a ≥30% decrease in AUC_{0-24} and/or C_{max}, whether ziprasidone prevents the suppression of luteinising hormone (LH), follicle stimulating hormone (FSH) and progesterone associated with the inhibition of ovulation by oral contraceptives, and (4) the effect of multiple doses of ziprasidone on plasma concentrations of prolactin.

Study Design: A double-blind, placebo-controlled, two-way cross-over study in which 19 female subjects taking an oral contraceptive received 20 mg BID oral ziprasidone or matching placebo, as determined by randomisation, for 8 days in one of two 21 day study periods separated by a 7 day washout. The 21 day study periods and the 7 day washout were to coincide with the normal cycle of oral contraceptive administration.

Evaluation Groups:

	Number of subjects		
	OC[1]	OC with 20 mg BID ziprasidone	OC with placebo
Randomised to treatment 19			
Completed Study Period	19	18	19
Evaluated for Pharmacokinetics	-	18	18
Assessed for Safety	19	19	19

[1]Subjects were assessed for safety in the 7 days preceding treatment with ziprasidone or placebo when they were taking oral contraceptive (OC) alone.

Subjects: Healthy female volunteers aged 22-39 years who had been using the oral contraceptives, Microgynon or Ovranette for a minimum of three menstrual cycles,.

Drug Administration:

Dosage Form: Oral contraceptive tablets, Microgynon and Ovranette, containing 0.03 mg EE and 0.15 mg LNG, produced by Schering and Wyeth, respectively. Oral capsules containing 20 mg ziprasidone HCl (CP-88,059-1, FID No. G00513AB, formulation Lot No ED-B-195-694 and local Lot No. 3713-059) and matching placebo (FID No. G00524AA, formulation Lot No ED-G-110-494 and local Lot No. 3713-060).

Dosing: Oral contraceptive tablet daily after breakfast throughout the two study periods and the washout. Oral ziprasidone or matching placebo capsules were administered BID on Days 8-15 of each study period after breakfast and an evening meal.

Pharmacokinetic and Safety Evaluations: On Day 15 of each study period the pharmacokinetics of EE and LNG were estimated from plasma collected 0-24 hours post-dose. Prolactin was measured in plasma collected 0 and 4 hours post-dose on Day 15 of each study period. Plasma was collected prior to dosing on Days 8, 19, 20 and 21 of each study period for measurement of FSH, LH and progesterone. Throughout the

study safety was evaluated from adverse event reports, blood pressure measurements, 12-lead ECGs and clinical laboratory tests on blood and urine.

Analytical Methods:

Statistical Methods: The effect of ziprasidone treatment on the pharmacokinetics of EE and LNG was compared with placebo in an ANOVA model containing period, sequence and treatment effects. $AUC_{0\text{-}24}$ and C_{max} were $\log_e$ transformed for the analysis. Mean plasma prolactin concentrations pre-dose and at 4 hours post-dose were calculated. Safety data were reviewed and summarised by the appropriate descriptive statistics.

Pharmacokinetic Results:

		OC with 20 mg BID ziprasidone	OC with placebo	p-values	90% CIs lower, upper
Plasma EE mean ± SD (CV%):	C_{max} (pg/ml)	72.4 ± 22.9[a] (32)	77.1 ± 25.6[a] (33)	0.1694	87, 101
	T_{max} (hr)	2.9 ± 1.3 (44)	2.3 ± 1.2 (53)	0.1401	-0.1, 1.2
	$AUC_{0\text{-}24}$ (pg.hr/ml)	964 ± 204[ab] (21)	971 ± 225[ab] (23)	0.8077	95, 104
Plasma LNG mean ± SD (CV%):	C_{max} (ng/ml)	5.95 ± 1.86[a] (31)	6.42 ± 2.00[a] (31)	0.1042	86, 100
	T_{max} (hr)	2.3 ± 1.1 (49)	1.7 ± 1.0 (62)	0.0317	0.2, 1.2
	$AUC_{0\text{-}24}$ (ng.hr/ml)	85.7 ± 25.3[a] (30)	87.7 ± 23.7[a] (27)	0.3736	94, 102
Mean ± SD plasma prolactin (ng/ml):	Pre-dose	22.57 ± 14.33	8.80 ± 4.79		
	4 hours post-dose	18.96 ± 8.65	3.09 ± 1.47		

[a] = geometric mean and standard deviation, [b] = excluding subjects 2 and 31, CIs = confidence intervals on adjusted means. CV% = coefficient of variation.

Safety Results

	No. subjects: with/evaluated (discontinued)		
	OC	OC with 20 mg BID ziprasidone	OC with placebo
Treatment-emergent, all causality adverse events	5/19(0)	18/19(1)	11/19(0)
Treatment-emergent, treatment-related adverse events	1/19(0)	18/19(1)	7/19(0)
Serious adverse events	0/19	0/19	0/19
Clinically significant lab test abnormalities	NA	4/19(0)	0/19(0)

Summary and Conclusions: In a placebo-controlled, double-blind, two-way crossover study with 19 healthy female subjects taking oral contraceptive steroids, the pharmacokinetics of the component steroids, EE and LNG in plasma, were not statistically significantly altered after 8 days treatment with ziprasidone or placebo. The exception was T_{max} for LNG, which was statistically significantly greater after ziprasidone treatment compared to placebo. However, this finding was not considered clinically relevant. Plasma concentrations of prolactin were higher after ziprasidone treatment compared to placebo. Treatment-emergent adverse events (all causality) were reported for 18 and 11 subjects during treatment with ziprasidone and placebo respectively, and for 5 subjects while taking oral contraceptive alone. Of these, 18, 7 and 1, had events considered treatment-related by the investigator. The most common adverse events attributed to ziprasidone were asthenia which was reported in 13 subjects and somnolence which was reported in 6 subjects. The majority of treatment-related adverse events were of mild to moderate severity, of relatively short duration, with one discontinuation from ziprasidone treatment for asthenia, dizziness, nausea and vomiting. Four subjects demonstrated laboratory test abnormalities considered by the sponsor to be clinically significant, but which did not indicate any particular trend with treatment. A review of the vital signs and 12-lead ECG recordings did not reveal any clinically relevant changes after treatment.

In conclusion, no clinically significant effects were observed when multiple doses of ziprasidone were taken concomitantly with oral contraceptive steroids.

Table 5.2.1
Summary of Statistical Analyses of Ethinyl Estradiol Pharmacokinetic Parameters
Ziprasidone Protocol 203

Pharmacokinetic Parameter	OC with Ziprasidone	OC with Placebo		90% Confidence Limits
	Adjusted Geometric Means		Ratio	
AUC (0-24) (pg.hr/ml)	954	960	99.3%	(94.8%, 104.1%)
Cmax (pg/ml)	72	77	93.9%	(87.0%, 101.3%)
	Adjusted Means		Difference	
Tmax (hr)	2.9	2.3	0.6	(-0.1, 1.2)

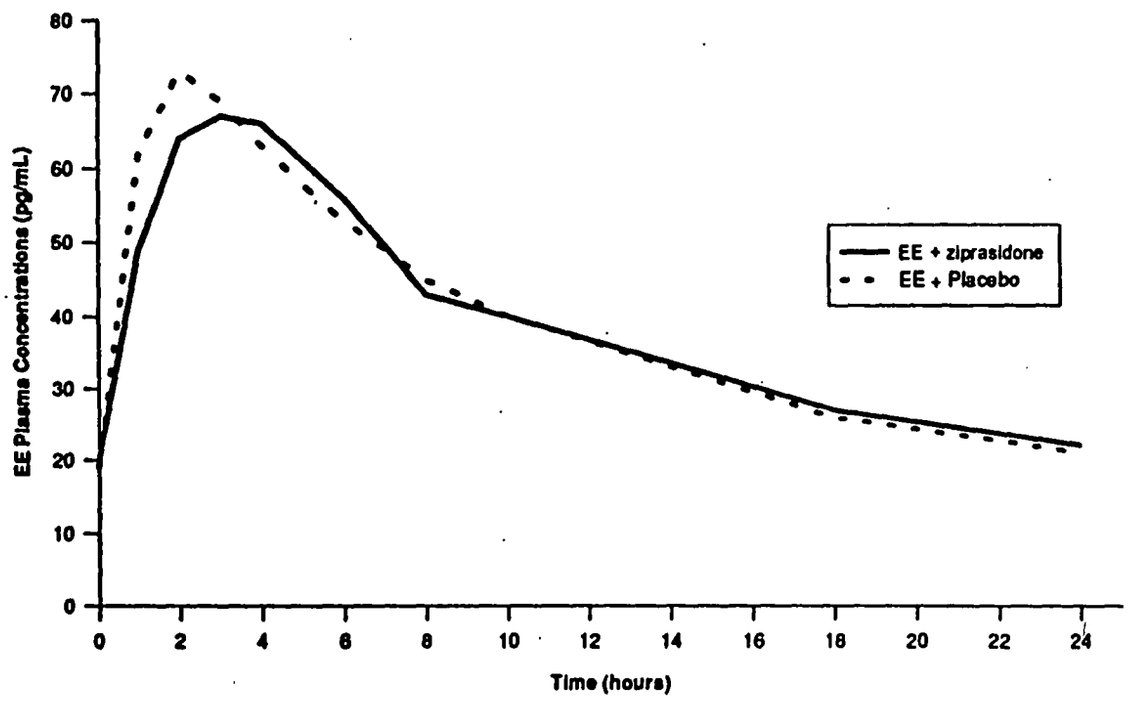
Source Data: Appendix III Tables 1.1, 2.1, and 3.1
Date of Data Extraction: 11OCT95. Date of Table Generation: 03MAY96.

Table 5.2.2
Summary of Statistical Analyses of Levonorgestrel Pharmacokinetic Parameters
Ziprasidone Protocol 203

Pharmacokinetic Parameter	OC with Ziprasidone	OC with Placebo		90% Confidence Limits
	Adjusted Geometric Means		Ratio	
AUC (0-24) (ng.hr/ml)	86	88	97.8%	(93.6%, 102.1%)
Cmax (ng/ml)	6	6	92.7%	(85.9%, 100.1%)
	Adjusted Means		Difference	
Tmax (hr)	2.3	1.7	0.7	(0.2, 1.2)

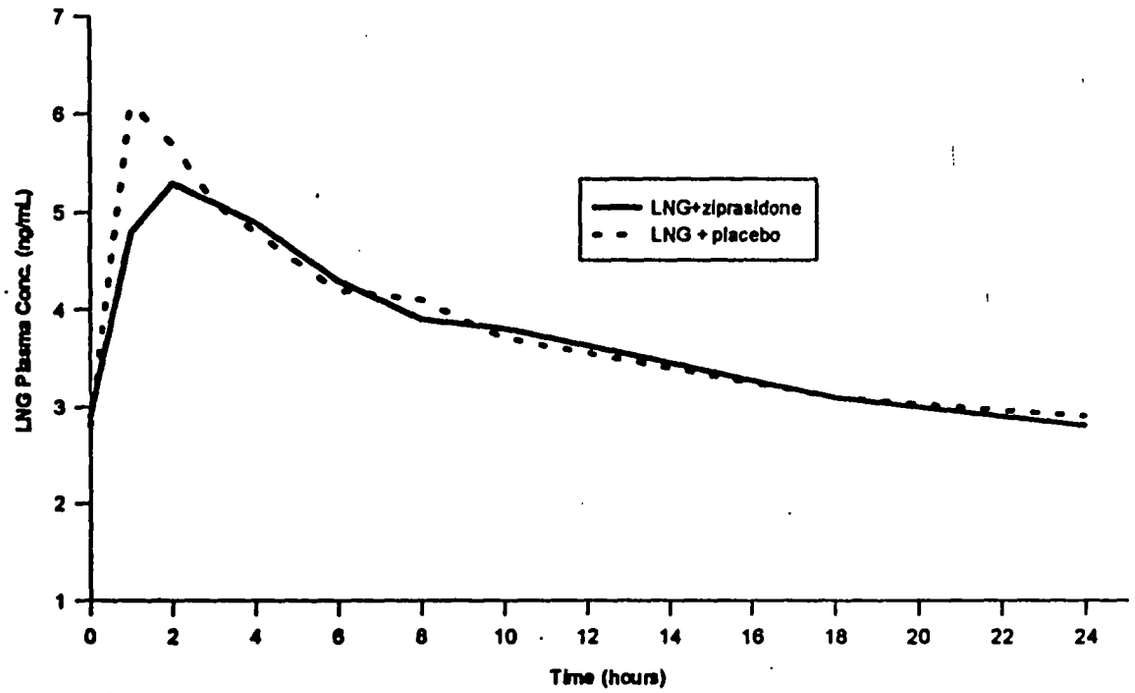
Source Data: Appendix III Tables 1.2, 2.2, and 3.2
Date of Data Extraction: 19SEP95. Date of Table Generation: 03OAY96.

FIGURE 1.1. MEAN PLASMA ETHINYLOESTRADIOL (EE) CONCENTRATIONS VS TIME FOLLOWING COADMINISTRATION OF AN ORAL CONTRACEPTIVE (MICROGYNON, OVRANETTE) WITH 20mg BID ZIPRASIDONE OR PLACEBO FOR 8 DAYS



Source data: Appendix IV, Tables 1 and 2

FIGURE 1.2. MEAN PLASMA LEVONORGESTREL (LNG) CONCENTRATIONS VS TIME FOLLOWING COADMINISTRATION OF AN ORAL CONTRACEPTIVE (MICROGYNON, OVRANETTE) WITH 20mg BID ZIPRASIDONE OR PLACEBO FOR 8 DAYS



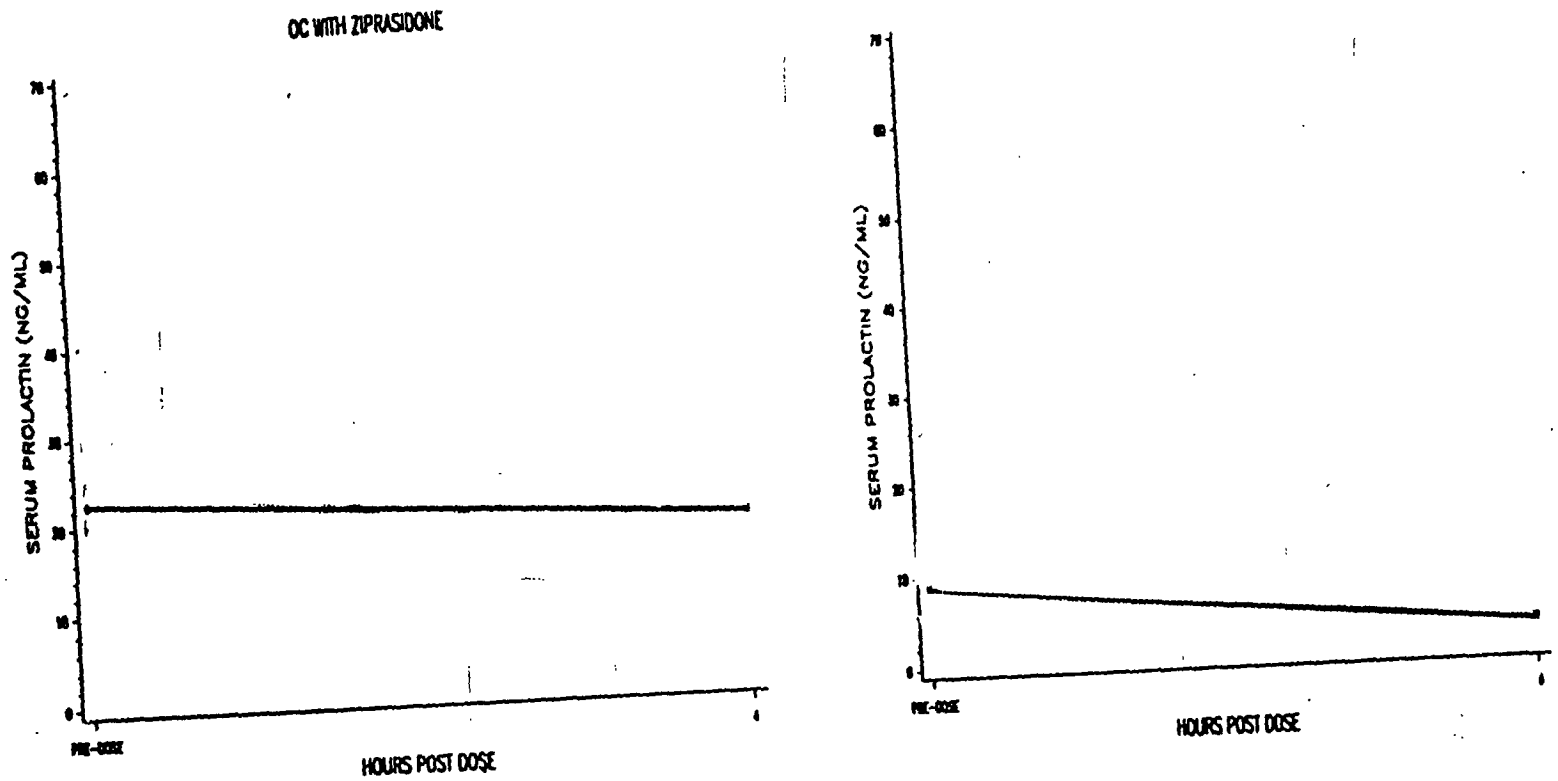
Source data: Appendix IV, Tables 3 and 4

TABLE 5.3. MEAN PLASMA PROLACTIN CONCENTRATIONS ON DAY 15 OF ORAL CONTRACEPTION THERAPY (OC) WITH CONCOMITANT MULTIPLE DOSES OF 20mg B.D. ZIPRASIDONE OR PLACEBO FOR 8 DAYS
ZIPRASIDONE PROTOCOL 203

	OC with 20 mg b.d. ziprasidone			OC with placebo		
Hours post dose	N	Mean (ng/ml)	SD	N	Mean (ng/ml)	SD
0	18	22.57	14.33	10	8.80	4.79
4	18	18.96	8.65	10	3.09	1.47

1.50 ng/ml was substituted for prolactin values that were BLQ
Source Data: Appendix III, Table 5

FIGURE 4.1
PLASMA PROLACTIN (ng/ml) BY HOUR POST DOSE ON DAY 15 OF EACH TREATMENT LEG
ZIPRASIDONE PROTOCOL 203



SOLID LINES REPRESENT MEAN SERUM PROLACTIN CONCENTRATION
DASHED LINES REPRESENT INDIVIDUAL SERUM PROLACTIN CONCENTRATIONS

Source Data : Appendix III, Tables 4 and 5 Date of Data Extraction : 09NOV95 Date of Figure Generation : 18NOV95

Study 048: (Ziprasidone Potential for 2D6 Inhibition-Dextromethorphan):

Study Design and Summary:

(see attachments 1-3)

Results:

(See attachments 4 and 5)

Reviewer's Comments:

1. The sponsor did not indicate as to why this study was conducted at the fasting state whereas all other studies on this drug were conducted at nonfasting state. The drug is also labeled to be administered with food.

2. The AUC was calculated up 10 hours only. Blood was collected up to 10 hours only for measurement of ziprasidone and paroxetine serum concentrations, however, urine was collected up to 8 hours for the determination of dextromethorphan/dextrophan ratio.

4. It should be noted that the mean AUC0-10 of ziprasidone in this study was 310 ng.h/mL (attachment 4) which is markedly lower than the mean AUC0-12 (~1550 ng.h/mL) after the same dose (80 mg dose) in the fed subjects (study #043). This major discrepancy are not clear, but could be due to the food effect.

5. The data clearly shows that paroxetine (a positive control), but not ziprasidone, significantly (P = 0.0001) increased the dextromethorphan/dextrophan ratio (attachment 5).

Conclusions:

Based on this study, ziprasidone does not appear to inhibit drugs metabolized by CYP 2D6.

PROTOCOL 128-048: PHASE I OPEN STUDY TO ASSESS THE POTENTIAL OF A CYP 2D6 INTERACTION OF ZIPRASIDONE USING DEXTROMETHORPHAN IN NORMAL, HEALTHY SUBJECTS

Principal Investigators: N. Gerber, M.B., B.S.

Study Publication: None

Study Dates: 14 August 1996 - 08 September 1996

Study Objective: To determine whether ziprasidone alters the CYP 2D6 metabolizing activity of normal volunteers who are extensive metabolizers of dextromethorphan, using paroxetine as a positive control.

Study Design: This was an open, randomized, parallel study to evaluate whether ziprasidone has the potential to inhibit the activity of cytochrome P450 (CYP) 2D6, using dextromethorphan as a model CYP2D6 substrate. During the screening period subjects received dextromethorphan on three separate occasions (separated by at least one day) to determine their dextromethorphan/dextrorphan urinary ratio. Subjects meeting the entrance criteria were randomized to receive ziprasidone 80 mg, paroxetine 20 mg, or placebo. On day 1, each subject received a single oral dose of study medication (ziprasidone, paroxetine or placebo) two hours prior to dextromethorphan administration. Study medication was administered under fasting conditions.

Evaluation Groups:

	Ziprasidone 80 mg	Paroxetine 20 mg	Placebo
Entered Study	8	8	8
Completed Study	8	8	8
Evaluated for Pharmacokinetics	8	8	8
Assessed for Safety			
Adverse Events	8	8	8
Laboratory Tests[a]	0	0	0

[a] Laboratory tests were performed only at screening and prior to dosing unless follow-up was required.

Subjects: Healthy male or female volunteers ranging in age from 20-39 years who were extensive metabolizers of dextromethorphan (dextromethorphan/dextrorphan ratio ≤ 0.03).

Drug Administration:

Dosage Form

Drug	Lot Number	FID Number	Potency	Formulation
Ziprasidone	N5115	QC2214	40 mg	Commercial Capsules
Paroxetine	227 6B11-G1	SmithKline Beecham	20 mg	Paxil® Tablets
Placebo	ED-G-181-694		...	Capsules

Dosing: During the screening period subjects received dextromethorphan on three separate occasions separated by at least one day to identify extensive metabolizers of dextromethorphan. Subjects meeting the entry criteria received a single dose of study drug (ziprasidone 80 mg, paroxetine 20 mg or placebo) on day 1 two hours prior to dextromethorphan administration. The study medication dose was administered in the early morning following an overnight fast of at least 8 hours.

Pharmacokinetic and Safety Evaluations: Subjects randomized to ziprasidone had blood samples collected for the determination of serum ziprasidone concentrations prior to and up to 10 hours following ziprasidone dosing. Serum concentrations were used to determine pharmacokinetic parameters ($AUC_{0\text{-}10}$, C_{max}, T_{max}). Subjects randomized to paroxetine had blood samples collected for the determination of plasma paroxetine concentrations prior to and up to 10 hours following paroxetine dosing. Plasma concentrations were used to determine pharmacokinetic parameters ($AUC_{0\text{-}10}$, C_{max}, T_{max}). Urine was collected over the 8 hour period following dextromethorphan dosing to determine the urinary dextromethorphan/dextrorphan ratio.

Analytical Methods:

Statistical Methods: Pharmacokinetic and safety results were summarized using descriptive statistics and graphical presentations. A t-test was performed on the change in the dextromethorphan/dextrorphan ratio from baseline (defined as the average of the three screening dm/dp ratios) for ziprasidone treated subjects compared to paroxetine and placebo treated subjects using PROC GLM in SAS.

Pharmacokinetic Results:

Mean ± Coefficients of Variation (%CV) of Pharmacokinetic Parameters

Parameter	Ziprasidone	Paroxetine [b]
$AUC_{0\text{-}10}$ [a]	311 ± 51	32.9 ± 52
C_{max} [a]	55 ± 63	6 ± 61
T_{max}	4 ± 40	6 ± 27

[a] geometric means

[b] Does not include one subject who received paroxetine but did not have detectable concentrations during the postdose sampling period.

Summary of Dextromethorphan/Dextrorphan Ratios

	Mean Baseline Ratio	Mean Change from Baseline
Ziprasidone	0.009	-0.002
Paroxetine	0.007	0.065
Placebo	0.005	-0.001

Safety Results:

Findings	Number of Subjects [With/Evaluated (Discontinued)] Ziprasidone	Paroxetine	Placebo
Adverse Events*	7/8(0)	5/8(0)	0/8(0)
Adverse Events (Treatment-Related)	7/8(0)	5/8(0)	0/8(0)

* All adverse events were treatment-emergent.

Summary and Conclusions: The mean ziprasidone C_{max} observed in this study (80 mg under fasting conditions) was similar to that observed for a 20 mg dose of ziprasidone administered under fed conditions in another protocol (128-031). The paroxetine C_{max} and T_{max} values were similar to those previously reported in other studies. No statistically significant changes in the urinary dextromethorphan/dextrorphan ratio was seen between the ziprasidone and placebo treatment groups (with mean reductions of 0.002 and 0.001, respectively). There was a 10-fold increase in the urinary dextromethorphan/dextrorphan ratio for the paroxetine group (0.065) which differed significantly from the ziprasidone and placebo groups (p=0.0001).

The most frequently reported adverse events among subjects receiving ziprasidone were asthenia and somnolence including one severe case of each. The most frequently reported adverse events among subjects receiving paroxetine were nausea and diarrhea, including one case of severe nausea. No adverse events were reported by subjects in the placebo group. No serious adverse events were reported.

In conclusion, the change from screening dextromethorphan/dextrorphan urinary ratio for ziprasidone treated subjects did not differ significantly from that of placebo treated subjects. These results suggest that ziprasidone does not inhibit drugs metabolized by CYP 2D6. .

Table 5.1 Individual and Mean Ziprasidone and Paroxetine Pharmacokinetic Parameters
Ziprasidone Protocol 048

Subject #	AUC 0-10	Cmax	Tmax
	Ziprasidone 80 mg		
769-0001			
769-0006			
769-0009			
769-0011			
769-0013			
769-0017			
769-0020			
769-0023			
Mean[a]	311	55	4
S.D.	157	35	1.4
CV%	51	63	40
	Paroxetine 20 mg		
769-0003	[b]	[b]	[b]
769-0004			
769-0007			
769-0010			
769-0015			
769-0018			
769-0019			
769-0024			
Mean[a]	32.9	6	6
S.D.	17.1	4	1.6
CV%	52	61	27

[a]Geometric means and standard deviations are reported for AUC0-10 and Cmax
[b]Subject who received paroxetine but did not have detectable concentrations during the 10-hour postdose sampling period. Data are excluded from summary statistics.

Source Data: Appendix IV, Tables 1 and 2

(5)

(5)

Table 5.2
Summary of Dextromethorphan/Dextrorphan (DM/DP) Urinary Ratios
Ziprasidone Protocol 048

Treatment	Mean Baseline* Ratio	Mean Day 1 Ratio	Change from Baseline Mean	S.D.	P-value vs Placebo	P-value vs Paroxetine
Ziprasidone	0.009	0.007	-0.002	0.004	0.9231	0.0001
Paroxetine	0.007	0.072	0.065	0.043	0.0001	.
Placebo	0.005	0.004	-0.001	0.001	.	.

* Baseline was defined as the mean of the three screening Dextromethorphan ratios.
Source Data: Appendix III Table 1 and Appendix V Table II Date of Data Extraction: 06NOV96 Date of Table Generation: 19DEC96

Study 050: (Ketoconazole In Healthy Subjects-Inerim Report Submitted January 23, 1998)

Study Design and Summary:

(see attachments 1-3)

Results:

(See attachments 4 and 6)

Reviewer's Comments:

1. The doses and the duration of treatments for both ziprasidone and ketoconazole were adequate.

2. Based on the available data, ketoconazole causes about 30% increase in both AUC and Cmax of ziprasidone, relative to the placebo (attachments 4 to 6). This suggests that ketoconazole inhibits CYP3A4.

Conclusions:

Based on this interim report, it can be concluded that ketoconazole increase ziprasidone systemic exposure by about 30%. This could be due to a competitive inhibition of CYP3A4 by ketoconazole.

PROTOCOL 128-050: PHASE I OPEN, MULTIPLE DOSE ORAL STUDY TO ASSESS THE EFFECTS OF KETOCONAZOLE ON THE PHARMACOKINETICS OF ZIPRASIDONE IN NORMAL, HEALTHY SUBJECTS

Principal Investigator: A. Laurent, M.D.

Study Publication: None

Study Dates: 13 January 1997 - 27 February 1997

Study Objective: To assess the effect of multidose ketoconazole administration on the pharmacokinetics of ziprasidone.

Study Design: This was an open, randomized, crossover study to examine the effect of multiple dose ketoconazole administration on the single dose pharmacokinetics of ziprasidone in the same subjects. One-half of the subjects received ketoconazole once daily in the fed state on days 1 through 6 [200 mg tablet on day 1, 400 mg (2 x 200 mg tablets) on days 2 through 6]. Ziprasidone HCl (40 mg, orally) was administered with food on day 5 and blood samples were taken for pharmacokinetic analysis. After a two-day washout period, subjects received placebo in the fed state on days 9 through 14 (1 capsule on day 10, 2 capsules on days 11 through 14); the pharmacokinetics of ziprasidone were determined following a single 40 mg oral dose on day 13. The second group of subjects was treated identically except that the order of the ketoconazole-placebo treatments was reversed.

Evaluation Groups:

	Ziprasidone with Ketoconazole	Ziprasidone with Placebo	Ketoconazole	Placebo
Entered Study	14	13	14	14
Completed Study	14	13	14	13
Evaluated for Pharmacokinetics	13	13	0	0
Assessed for Safety				
Adverse events	14	13	14	14
Laboratory tests[a]	0	0	14	13

[a]Laboratory tests were performed only at screening, baseline (study day 0) and within 24 hours of each ziprasidone dosing day, unless follow-up was required. Evaluable laboratory data corresponded to study days 4 and 12 during the ketoconazole and placebo treatment legs.

Subjects: Fourteen healthy male and female subjects ranging in age from 18 to 44 years entered the study. Thirteen subjects completed both treatment legs.

Drug Administration:

Dosage Form

Ziprasidone 20 mg capsules (FID# QC2327)

Ketoconazole 200 mg tablets (Nizoral®/Jannsen Pharmaceuticals)

Placebo capsules (FID# G00275AC)

Dosing

Subjects were randomized to one of two treatment sequences. One-half of the subjects (Group 1) received a 200 mg dose of ketoconazole on day 1 and 400 mg (2 x 200 mg) on days 2 through 6. On days 1 through 4 and on day 6, ketoconazole was administered immediately after a light breakfast with 50 ml of water. On day 5, ketoconazole was coadministered with ziprasidone (2 x 20 mg

capsules) with 100 ml of water immediately after a high fat breakfast. After a two-day washout, subjects received a single placebo capsule on day 9 and two capsules on days 10 through 14. On days 9 through 12 and on day 14, placebo was administered with 50 ml of water immediately after a light breakfast. On day 13, placebo was coadministered with a 40 mg dose of ziprasidone immediately after a high fat breakfast with 100 ml of water. Dosing for the second group of subjects (Group 2) was identical except that the order of ketoconazole and placebo treatments was reversed.

Pharmacokinetic and Safety Evaluations: Blood samples for determining serum ziprasidone concentrations were collected on days 5 and 13 immediately prior to and for up to 36 hours after each dose of ziprasidone. Serum concentrations were used to estimate pharmacokinetic parameters ($AUC_{0-\infty}$, C_{max}, T_{max}, K_{el}, and $T_{1/2}$). Blood was also collected prior to dosing on days 1, 4, 5, 6, 12, 13, and 14 for determining trough plasma concentrations of ketoconazole. Subjects were continuously monitored for adverse events.

Analytical Methods:

Statistical Methods: Natural log-transformed $AUC_{0-\infty}$ and C_{max} and untransformed T_{max} and K_{el} were analyzed using an ANOVA model containing sequence, subject-within-sequence, period, and treatment effects. For $AUC_{0-\infty}$ and C_{max}, 95% confidence intervals were constructed for the ratio between the ketoconazole and placebo adjusted geometric means.

Pharmacokinetic Results:

Means And Coefficients Of Variation (%CV) On Days 5 / 13 For Ziprasidone With Ketoconazole And Ziprasidone With Placebo (n=13)

Pharmacokinetic Parameter	Ziprasidone + Ketoconazole/Ziprasidone + Placebo (n = 6)	Ziprasidone + Placebo/ Ziprasidone + Ketoconazole (n = 7)
	Day 5 (%CV) / Day 13 (%CV)	Day 5 (%CV) / Day 13 (%CV)
$AUC_{0-\infty}$ (ng·hr/ml)[a]	1107 (21) / 917 (18)	882 (38) / 1299 (27)
C_{max} (ng/ml)[a]	117 (31) / 101 (28)	79 (39) / 121 (47)
T_{max} (hr)[b]	8.3 (35) / 7.0 (40)	10.0 (26) /10.0 (26)
K_{el} (hr^{-1})[b]	0.198 (34) / 0.177 (28)	0.151 (19) / 0.169 (30)
$T_{1/2}$ (hr)[c]	3.5 / 3.9	4.6 / 4.1

[a]Geometric Mean [b]Arithmetic Mean [c] Harmonic mean calculated as 0.693/mean K_{el}

Summary of Statistical Analyses of Pharmacokinetic Parameters (n = 13)

Pharmacokinetic Parameter	Ziprasidone + Ketoconazole	Ziprasidone + Placebo		95% Confidence Interval
	Adjusted Geometric Means		Ratio	
$AUC_{0-\infty}$ (ng·hr/ml)	1199	899	133.3%	(112.4%, 158.1%)
C_{max} (ng/ml)	119	89	133.5%	(106.9%, 166.7%)
	Adjusted Means		Difference	
T_{max} (hr)	9.2	8.5	0.7	(-1.7, 3.0)
K_{el} (hr^{-1})	0.183	0.164	0.019	(-0.012, 0.051)

Safety Results:

	Number of Subjects Evaluated (With Event) [Disc'd Due to Event]			
	Ziprasidone with Ketoconazole	Ziprasidone with Placebo	Ketoconazole	Placebo
Adverse events (all causality)	14(10)[0]	13(4)[0]	14(4)[0]	14(2)[0]
Treatment emergent, treatment-related adverse events	14(10)[0]	13(4)[0]	14(4)[0]	14(2)[0]
Clinically significant laboratory test abnormalities[a]	NA	NA	14(0)[0]	13(0)[0]

[a]Laboratory tests were performed only at screening, baseline (study day 0) and within 24 hours of each ziprasidone dosing day, unless follow-up was required. Evaluable laboratory data corresponded to study days 4 and 12 during the ketoconazole and placebo treatment legs.

Summary and Conclusions: Coadministration of ziprasidone with ketoconazole increased systemic exposure to ziprasidone based on a 33% increase in $AUC_{0-\infty}$ and a 34% increase in C_{max} relative to placebo. K_{el}, T_{max}, and $T_{1/2}$ were not affected. There were no apparent differences in pharmacokinetics based on gender. Mean trough concentrations of ketoconazole determined 24 hours after administration of ziprasidone were, on average, two-fold higher than the corresponding predose measurements.

One subject discontinued from the study after receiving placebo for four days in his second treatment leg to take a job. All adverse events in this study were treatment-emergent and all but two (experienced while the subjects were taking ziprasidone with ketoconazole) were classified as treatment-related by the investigator. Two adverse events (headache, dizziness) were judged to be moderate in severity. All other adverse events were considered mild. Subjects taking ziprasidone with ketoconazole had the highest incidence of treatment-related adverse events. The most common treatment-related adverse events experienced after coadministration of ziprasidone and ketoconazole were dizziness, asthenia and somnolence; individual cases of headache, chills, pain, back pain, nausea, paresthesia and tremor were also reported by subjects receiving this treatment. Subjects experienced asthenia, syncope, dizziness and somnolence while taking ziprasidone with placebo; headache, somnolence and dizziness while taking ketoconazole alone; and headache and nausea while taking placebo alone. No serious adverse events were reported.

In summary, coadministration of ziprasidone and ketoconazole increased systemic exposure to ziprasidone. The increase in ziprasidone exposure probably reflected competitive inhibition by ketoconazole of CYP3A4, the primary P450 isoenzyme involved in ziprasidone metabolism. An elevation in mean trough plasma ketoconazole concentrations was observed 24 hours after ziprasidone treatment. This elevation probably reflected an increase in ketoconazole bioavailability due to consumption of a high fat breakfast.

Table 5.1.1 Individual and Mean Ziprasidone Pharmacokinetic Parameters for Group 1 Following 40 mg Ziprasidone On Day 5 During Ketoconazole (KETO) Administration and Day 13 During Placebo Administration (PBO)
Ziprasidone Protocol 050

Subject #	Day 5 KETO AUC(0-∞) (ng•hr/ml)	Day13 PBO AUC(0-∞) (ng•hr/ml)	AUC Ratio KETO/ PBO	Day 5 KETO Cmax (ng/ml)	Day13 PBO Cmax (ng/ml)	Cmax Ratio KETO/ PBO	Day 5 KETO Kel (1/hr)	Day13 PBO Kel (1/hr)	Day 5 KETO T1/2 (hr)	Day13 PBO T1/2 (hr)
748-0002										
748-0004										
748-0005										
748-0008										
748-0010										
748-0014										
MEAN	1107[a]	917[a]	1.21[a]	117[a]	101[a]	1.16[a]	0.198	0.177	3.5[b]	3.9[b]
SD	232	165	0.1	36	28	0.42	0.067	0.050	--	--
CV%	21	18	8	31	28	36	34	28	--	--
748-0001[c]										

[a] = Geometric mean.

[b] = Harmonic mean.

[c] = Subject did not complete the study; excluded from summary statistics.

Source Data: Appendix IV, Table 1

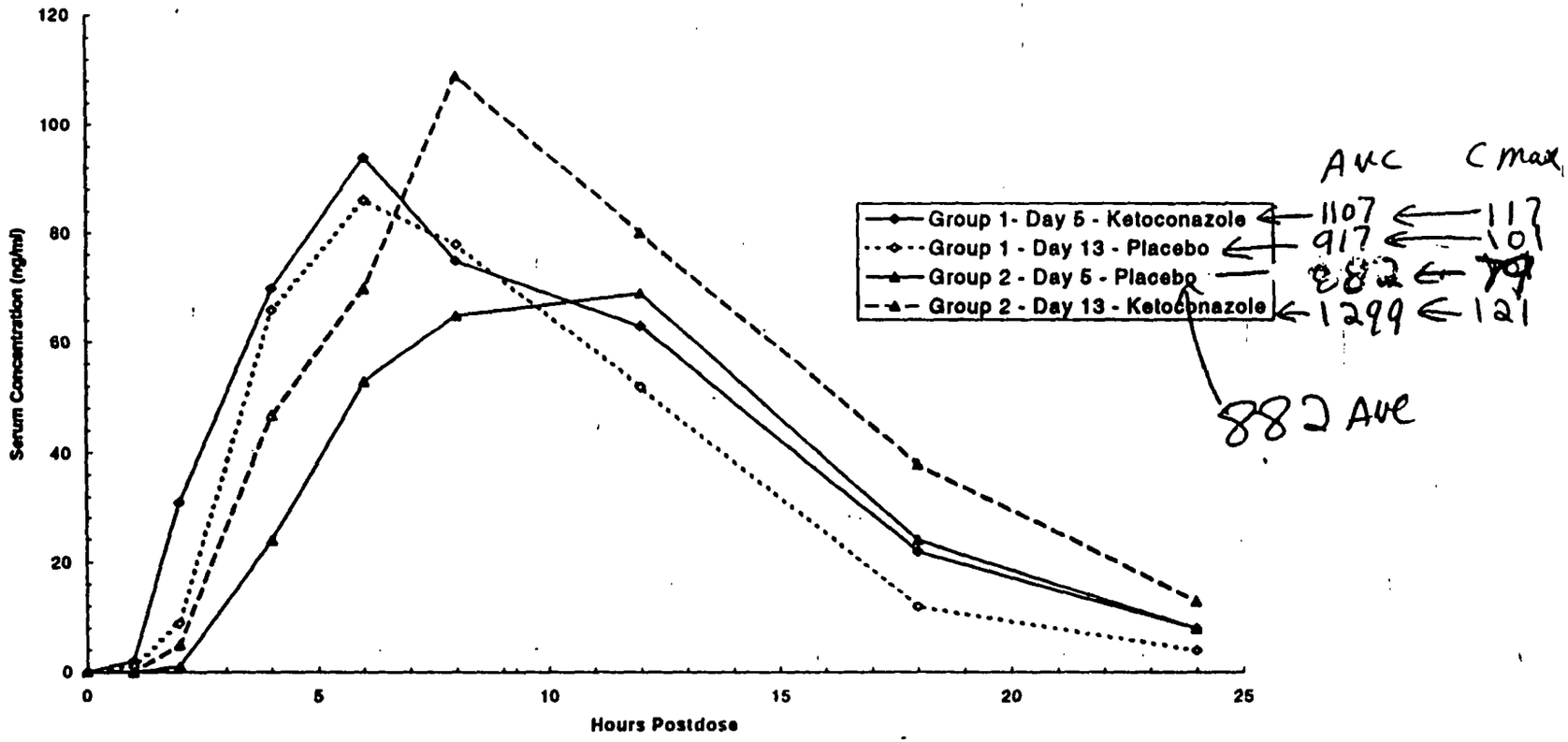
Table 5.1.2 Individual and Mean Ziprasidone Pharmacokinetic Parameters for Group 2 Following 40 mg Ziprasidone On Day 5 During Placebo (PBO) Administration and Day 13 During Ketoconazole Administration (KETO)
Ziprasidone Protocol 050

Subject #	Day 5 PBO AUC(0-∞) (ng•hr/ml)	Day 13 KETO AUC(0-∞) (ng•hr/ml)	AUC Ratio KETO/ PBO	Day 5 PBO Cmax (ng/ml)	Day 13 KETO Cmax (ng/ml)	Cmax Ratio KETO/ PBO	Day 5 PBO Kel (1/hr)	Day 13 KETO Kel (1/hr)	Day 5 PBO T1/2 (hr)	Day 13 KETO T1/2 (hr)
748-0001										
748-0003										
748-0006										
748-0007										
748-0009										
748-0012										
748-0013										
MEAN	882[a]	1299[a]	1.47[a]	79[a]	121[a]	1.54[a]	0.151	0.169	4.6[b]	4.1[b]
SD	335	351	0.54	31	57	0.55	0.029	0.051	--	--
CV%	38	27	37	39	47	36	19	30	--	--

[a] = Geometric mean.
[b] = Harmonic mean.

Source Data: Appendix IV, Table 2

Figure 1. Mean Serum Ziprasidone Concentrations on Days 5 and 13 in Subjects Receiving 40 mg Ziprasidone in the Presence of Placebo and Ketoconazole
Ziprasidone Protocol 050



Source Data: Appendix IV, Tables 1 and 2

Study DM-95-128-31: (*In Vitro* Plasma Protein Binding)

Study Design and Summary:

(see attachment 1)

Results:

(See attachment 2)

Reviewer's Comments:

1. This protein binding study was performed at only one concentration of ziprasidone (400 ng/ml). The study should have been performed over a wide range of drug concentration for the following reasons:

    a. To determine the relationship between the plasma protein binding and the drug concentration. However, since the drug is highly bound, the binding may not be concentration dependent.

    b. The Cmax after the maximum recommended oral dose is approximately 200 ng/ml.

2. It appears that the binding was performed in plasma not serum since all drug analyses were done in the serum. However, this may not be of any major significance.

3. The mean percent binding in human plasma was 99.91% (attachment 2).

Conclusions:

Based on this *in vitro* study, the fraction bound in humans was 99.91% at ziprasidone plasma concentration of approximately 400 ng/ml.

(1)

Binding of CP-88,059 in Monkey and Human Plasma

(DM95-128-31)

Objectives:

To determine the degree of plasma protein binding of CP-88,059 in *cebus* monkey, *cynomolgus* monkey, and human blood.

Methods:

The plasma protein binding of CP-88,059 was determined by
at °C, employing a
The 1 ml plasma chamber and the 1 ml buffer (0.067 M phosphate; pH 7.5) chamber were separated by a cellulose membrane (molecular weight cutoff of 12000 to 14000 daltons). The *cebus* monkey plasma samples were obtained from
The *cebus* monkey plasma samples from six animals were combined to generate one pool. The *cynomolgus* monkey plasma was obtained from and the human serum were obtained from in-house donors. Plasma was spiked at 400 ng/ml of CP-88,059. Five sets of cells were dialyzed for the monkey pooled plasma samples and two sets for the individual human plasma samples. Mixing times to allow for equilibrium to occur were typically 19 hours. At that time, samples were removed from both chambers and their volumes recorded. Samples were stored at °C until the day of analysis.

Aliquots µl) of the plasma samples were extracted with 5 ml of m-t-butyl ether. Samples were assayed by nm. The lower limit of quantitation of drug was ng/ml. Aliquots µl) of the buffer samples were extracted, in silylated glass tubes, with 5 ml m-t-butyl ether. Samples were assayed by The lower limit of quantitation was pg/ml. Due to an inability to accurately quantitate drug on the plasma side of the *cebus* monkey cells the protein binding was determined for only one set of the five dialysis cells that were prepared.

The percent drug bound to plasma proteins was calculated using the following equation (Boudinot and Jusko, 1984):

$$Fb = (Cpe-Cbe)(Vpe/Vpi)/\{[(Cpe-Cbe)(Vpe/Vpi)] + Cbe\} * 100$$

Fb= Percent of bound drug

Cpe = Concentration of drug in plasma

Cbe = Concentration of drug in buffer

PE = Volume of plasma at equilibrium

Vpi = Volume of plasma before dialysis

Table 1
Summary of CP-88,059 Protein Binding Calculations

Species	Initial Plasma Conc. (ng/ml)	Cpe (ng/ml)	Cbe (ng/ml)	Recovery (%)	Vpi (ml)	Vpe (ml)	Fb (%)
Monkey							
cebus	354.747	136.021	0.648	**38.34**	1	1.486	**99.68**
Monkey							
cynomolgus	406.79	240.022	0.575	59.00	1	1.313	99.82
		261.072	0.7	64.18	1	1.423	99.81
		271.227	0.77	66.67	1	1.36	99.79
		263.151	0.717	64.69	1	1.348	99.8
		294.006	0.697	72.27	1	1.442	99.84
			Mean	**65.64**		**Mean**	**99.83**
			S.D.	**4.79**		**S.D.**	**0.02**
Human							
#1	n.d.*	278.47	0.296	n.d.	1	1.575	99.93
		230.1	0.361	n.d.	1	1.606	99.9
						Mean	**99.92**
						S.D.	**0.02**
#2	436.421	260.15	0.492	59.61	1	1.394	99.88
		290.06	0.339	66.46	1	1.434	99.92
			Mean	**63.04**		**Mean**	**99.90**
			S.D.	**4.84**		**S.D.**	**0.03**
						Mean	**99.91**
	*n.d. = not determined					**S.D.**	**0.005**

Fb= (Cpe-Cbe)(Vpe/Vpi)/[[(Cpe-Cbe)(Vpe/Vpi)] + Cbe]*100
Fb = Percent of bound drug to serum proteins
Cpe = Concentration of drug in plasma
Cbe = Concentration of drug in buffer
Vpe = Volume of plasma at equilibrium
Vpi = Volume of plasma before dialysis

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Study DM-96-128-36: (*In Vitro* Plasma Protein Binding-Interaction of Ziprasidone With Warfarin and Propranolol)

Study Design and Summary:

(see attachment 1-4)

Results:

(See attachment 5-9)

Reviewer's Conclusion:

Based on this *in vitro* study, ziprasidone did not affect the binding of warfarin or propranolol. In addition, neither warfarin or propranolol affected the binding of ziprasidone (attachments 5-9).

(1)

Protein Binding of CP-88,059 to Human Albumin and α_1-Acid Gycoprotein and the Interaction of CP-88,059 with Warfarin and Propranolol

(DM-96-128-36)

Objectives:

To determine ~~the~~ if warfarin or propranolol alters the plasma protein binding of CP-88,059 and if CP-88,059 alters the plasma protein binding of warfarin and propranolol.

To determine the extent of binding of CP-88,059 to human α_1-acid glycoprotein (AAG) and albumin.

Methods:

The protein binding of CP-88,059 was determined by employing a
The 1 ml serum chamber and the 1 ml buffer (0.067 M phosphate; pH 7.5) chamber were separated by a cellulose membrane (molecular weight cutoff of 12000 to 14000 daltons). Dialysis cells were placed, rotating, in a water bath at °C; mixing times to allow for equilibrium to occur were typically 19 hours. At that time, samples were removed from both chambers and their volumes recorded.

To determine if CP-88,059 altered the plasma protein binding of warfarin or propranolol, CP-88,059 at concentrations of 0, 200 and 400 ng/ml (Lot #20480-71-2MS), was incubated with [^{14}C]-warfarin) at a concentration of 7.4 µg/ml or [^{3}H]-propranolol ( ) at a concentration of 50 ng/ml. To determine if warfarin or propranolol altered the plasma protein binding of CP-88,059, warfarin at a concentration of 0, 7.4, and 74 µg/ml and propranolol at a concentration of 0, 50 and 500 ng/ml was incubated with CP-88,059 at a concentration of 400 ng/ml. Human plasma from three sources was obtained and was performed as described above in duplicate for each human at each concentration. The radioactivity, representing the amounts of warfarin or propranolol, present in each fraction was monitored by counting. In order to determine the concentrations of CP-88,059 present in the plasma and buffer samples each sample was extracted using m-t-butyl-ether. The extracted plasma samples were then assayed by nm and the extracted buffer samples were then assayed by . The low concentrations of CP-88,059 present in the buffer samples necessitated use of the for detection of the unbound fraction of CP-88,059.

To determine the degree of protein binding of CP-88,059 to human AAG and albumin, solutions of AAG (16 µM) and albumin (600 µM) were spiked at 400 ng/ml using CP-88,059-01 (Lot #20480-71-2MS). , for each matrix (samples), was performed as described above. One AAG plasma sample could not be assayed due to insufficient sample volume recovered, thus only three AAG samples are included in the data. Plasma and buffer samples were assayed by at nm (plasma samples) or (buffer samples).

The percent drug bound to proteins was calculated using the following equation:

$$Fb = [(DTe-DF)*(Vpe/Vpi)/[((DTe-DF)*(Vpe/Vpi))+DF] * 100$$
$$Fb = [(Cpe-Cb)*(Vpe/Vpi)/[((Cpe-Cb)*(Vpe/Vpi)) +Cb] * 100$$

Fb - Fraction drug bound
DTe - Total radioactivity of free and bound drug in serum
Cpe - Concentration of drug in serum
DF - Radioactivity of free drug in plasma and/or buffer
Cb - Concentration of drug in buffer
Vpe - Final volume of plasma
Vpi - Initial volume of plasma

(Boudinot and Jusko, 1984).

Results:

The calculations to determine if warfarin or propranolol altered the plasma protein binding of CP-88,059 are presented in Table 1. The mean protein binding (%) of CP-88,059 incubated at a concentration of 400 ng/ml in the presence of warfarin at concentrations of 0, 7.4 and 74 µg/ml or propranolol at concentrations of 0, 50 and 500 ng/ml are listed below:

Warfarin Conc. (µg/ml)	CP-88,059 Mean Fb ± S.D.	Propranolol Conc. (ng/ml)	CP-88,059 Mean Fb ± S.D.
0	99.91 ± 0.02	0	99.93 ± 0.02
7.4	99.91 ± 0.01	50	99.95 ± 0.00
74	99.90 ± 0.01	500	99.91 ± 0.01

The mean binding of CP-88,059 to plasma proteins ranged from 99.90% to 99.95% at various concentrations of warfarin or propranolol.

The calculations to determine the if CP-88,059 altered the plasma protein binding of warfarin or propranolol are presented in Table 2. The mean protein binding (%) of warfarin and propranolol incubated at concentrations of 7.4 µg/ml and 50 ng/ml, respectively, to plasma proteins in the presence of 0, 200 and 400 ng/ml CP-88,059 are listed below:

CP-88,059 Conc. (ng/ml)	Warfarin Mean Fb ± S.D.	Propranolol Mean Fb ± S.D.
0	99.47 ± 0.06	89.96 ± 3.03
200	99.38 ± 0.33	92.22 ± 0.79
400	99.51 ± 0.01	91.37 ± 2.14

The mean binding of warfarin and propranolol in the absence of CP-88,059 was 99.47% and 89.96%, respectively. The binding of warfarin and propranolol to plasma proteins was not altered in the presence of 200 or 400 ng/ml concentrations of CP-88,059.

The calculations to determine the protein binding of CP-88,059 to human AAG and albumin are presented in Table 3. The mean protein binding (%) of CP-88,059 to human AAG and albumin are listed below:

Matrix	Mean Fb ± S.D.
AAG	98.21 ± 1.41
Albumin	97.96 ± 0.39

The mean percent binding of CP-88,059 to α_1-acid glycoprotien and albumin was 98.2% and 98.0%, respectively.

Interpretation:

The changes in plasma protein binding of CP-88,059 that may occur as a result of combination therapy with another drug was assessed using warfarin, a compound that binds mainly to serum albumin and using propranolol, a compound that binds mainly to serum AAG. The mean (±SD) percent binding of CP-88,059 at plasma concentrations 400 ng/ml to human plasma was 99.91% (±0.02) and when co-dialysed (at the same concentration) with warfarin at concentrations of 7.4 and 74 µg/ml the mean (±SD) percent binding of CP-88,059 was 99.91% (±0.01) and 99.90% (±0.01), respectively. In a second experiment, the mean (±SD) percent binding of CP-88,059 at plasma concentrations of 400 ng/ml to human plasma was 99.93% (±0.02) and when co-dialysed (at the same concentration) with propranolol at concentrations of 50 and 500 ng/ml the mean (±SD) percent binding of CP-88,059 was 99.95% (±0.00) and 99.91% (±0.01), respectively. Thus, the plasma protein binding of CP-88,059 in human plasma was not altered significantly by the presence of either warfarin or propranolol.

The changes in plasma protein binding of warfarin or propranolol that may occur as a result of combination therapy with CP-88,059 was also assessed. The CP-88,059 concentrations studied (200 and 400 ng/ml) were similar and 2-fold higher than the Cmax values observed after multiple doses of 80 mg BID (study #128-109). Both warfarin and propranolol were incubated at the maximum plasma concentration associated with the suggested efficacious dose for each drug. The mean (±SD) percent binding of warfarin at a plasma concentration of 7.4 µg/ml to human plasma was 99.47% (±0.06) and when co-dialysed (at the same

concentration) with CP-88,059 at concentrations of 200 and 400 ng/ml the mean (±SD) percent binding of warfarin was 99.38% (±0.33) and 99.51% (±0.01), respectively. The mean (±SD) percent binding of propranolol at a plasma concentration of 50 ng/ml to human plasma was 89.96% (±3.03) and when co-dialysed (at the same concentration) with CP-88,059 at concentrations of 200 and 400 ng/ml the mean (±SD) percent binding of propranolol was 92.22% (±0.79) and 91.37% (±2.14), respectively. Thus, the plasma protein-binding of warfarin or propranolol in human plasma was not altered significantly by the presence of CP-88,059.

The mean (±SD) percent binding of CP-88,059 to the two major plasma proteins, human α_1-acid glycoprotein (AAG) and human serum albumin was 98.21% (±1.41) and 97.96% (±0.39), respectively. Thus binding to these two proteins was high and therefore changes to concentrations of one of these plasma proteins caused by a particular disease should not influence the low free fraction of CP-88,059.

In summary, CP-88,059 is a highly bound drug to human plasma proteins with a free fraction of ≤0.35%. The binding of CP-88,059 to the two major plasma proteins, AAG and serum albumin was also high with a free fraction of <2%. At an 80 mg BID dose, the plasma concentrations of CP-88,059 (~200 ng/ml, 0.5 µM) compared to the concentrations of the plasma proteins (16 µM for AAG and 600 µM for albumin) is estimated to be relatively low and thus changes in protein concentrations caused by a disease state should not significantly change the free fraction of CP-88,059. This is also the likely explaination for the lack of an interaction of CP-88,059 on the binding of warfarin or propranolol or for the lack of interaction of warfarin or propranolol on the binding of CP-88,059.

Reference:

F. D. Boudinot and W. J. Jusko, Fluid Shifts and Other Factors Affecting Plasma Protein Binding of Prednisolone by Equilibrium Dialysis. J. Pharm. Sci. 6: 774-780 (1984).

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Table 1
Summary of CP-88,059 Protein Binding Calculations

Effect of Warfarin on CP-88,059 Plasma Protein Binding

	Cpe (ng/ml)	Cbe (ng/ml)	Vpe (ml)	Vpi (ml)	Fb (Zip) (%)
Warfarin Concentration: 0 µg/ml; CP-88,059 Concentration: 400 ng/ml					
Human #1	280	0.353	1.52	1.00	99.92
	341	0.369	1.48	1.00	99.93
Average	310	0.361	1.50	1.00	99.93
Human #2	273	0.385	1.53	1.00	99.91
	280	0.366	1.48	1.00	99.91
Average	277	0.376	1.51	1.00	99.91
Human #3	287	0.389	1.39	1.00	99.90
	284	0.483	1.47	1.00	99.88
Average	285	0.436	1.43	1.00	99.89
	2	0.066	0.05	0.00	0.01
Warfarin Concentration: 7.4 µg/ml; CP-88,059 Concentration: 400 ng/ml					
Human #1	290	0.381	1.41	1.00	99.91
	272	0.392	1.42	1.00	99.9
Average	281	0.387	1.42	1.00	99.91
Human #2	271	0.334	1.50	1.00	99.92
	262	0.363	1.51	1.00	99.91
Average	267	0.349	1.51	1.00	99.92
Human #3	294	0.411	1.39	1.00	99.90
	286	n.s.	1.42	1.00	
Warfarin Concentration: 74 µg/ml; CP-88,059 Concentration: 400 ng/ml					
Human #1	272	0.394	1.33	1.00	99.89
	285	0.411	1.40	1.00	99.90
Average	279	0.403	1.36	1.00	99.90
Human #2	279	0.352	1.46	1.00	99.91
	272	0.523	1.45	1.00	99.87
Average	276	0.438	1.45	1.00	99.89
Human #3	283	0.329	1.43	1.00	99.92
	284	0.383	1.38	1.00	99.9
Average	283	0.356	1.40	1.00	99.91