3

(3)

Safety Results:

Number of Subjects With/Evaluated For:	20 mg Commercial Capsule, BID Titration	40 mg Proposed Commercial Capsule, BID	2 x 20 mg Commercial Capsules, BID
Adverse Events (All Causality)	17/26 (1)	19/24 (0)	18/25 (2)
Adverse Events (Treatment-emergent, treatment-related)	16/26 (0)	18/24 (0)	18/25 (2)
Clinically Significant Laboratory Test Abnormalities	N/A[a]	0/1[a](0)	N/A[a]

() subjects discontinued

[a]Laboratory tests were performed only at screening and prior to the first dose, unless follow-up was required. One subject had an additional urinalysis performed during the 1 x 40 mg BID treatment period.

Summary and Conclusions: Steady-state systemic exposures were attained by the fourth day of dosing. Mean T_{max} values ranged from 5 to 8 hours across the 1 x 40 mg capsule and 2 x 20 mg capsule treatments, with no statistically significant difference in T_{max} observed between treatments. Exposure was similar for both treatment groups. Mean relative bioavailability of the 40 mg capsule compared to 2 x 20 mg capsules was 92.5% based on AUC, and the 90% confidence intervals for both AUC_{0-12} and C_{max} were within the 80% to 125% acceptance limits for bioequivalence.

Three subjects discontinued from the study, two due to treatment-related anxiety, and one due to a non-treatment-related tooth abscess. No serious adverse events were reported. All adverse events were of mild to moderate severity, the majority of which were treatment-related. The most frequently reported adverse events following all treatments were nervous system effects. The incidence of adverse events following ziprasidone 1 x 40 mg capsule BID and 2 x 20 mg capsules BID was similar, the most frequent of which was mild treatment-related insomnia. Somnolence, anxiety, dizziness, euphoria, and nausea were other frequently reported treatment-related adverse events. One subject had a mild syncopal event following dosing with ziprasidone 1 x 20 mg capsule during the titration period.

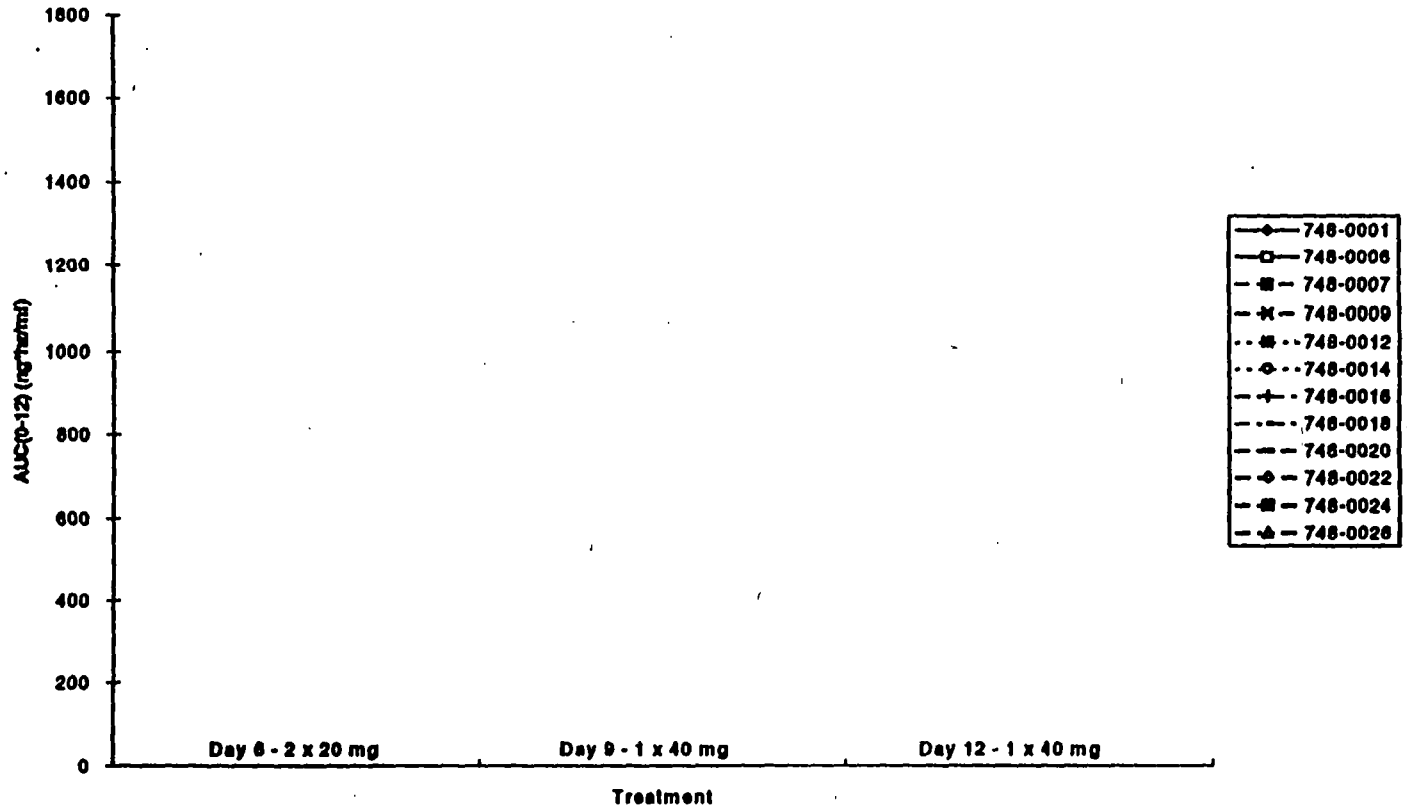
In conclusion, one 40 mg proposed commercial capsule of ziprasidone was bioequivalent to 2 x 20 mg commercial capsules in this study.

Table 5.2
Summary of Statistical Analyses of Pharmacokinetic Parameters (AUC(0-12), Cmax, and Tmax)
Ziprasidone Protocol 047

Pharmacokinetic Parameter	Comparison			90% Confidence Limits
		Adjusted Geometric Means	Ratio	
AUC(0-12) (ng.hr/ml)	1 x 40 mg vs. 2 x 20 mg	826.6 vs. 893.5	92.5%	(83.6%, 102.4%)
Cmax (ng/ml)	1 x 40 mg vs. 2 x 20 mg	111.5 vs. 121.7	91.7%	(80.8%, 103.9%)
		Adjusted Means	Difference	
Tmax (hr)	1 x 40 mg vs. 2 x 20 mg	5.6 vs. 6.0	-0.4	(-1.7, 0.9)

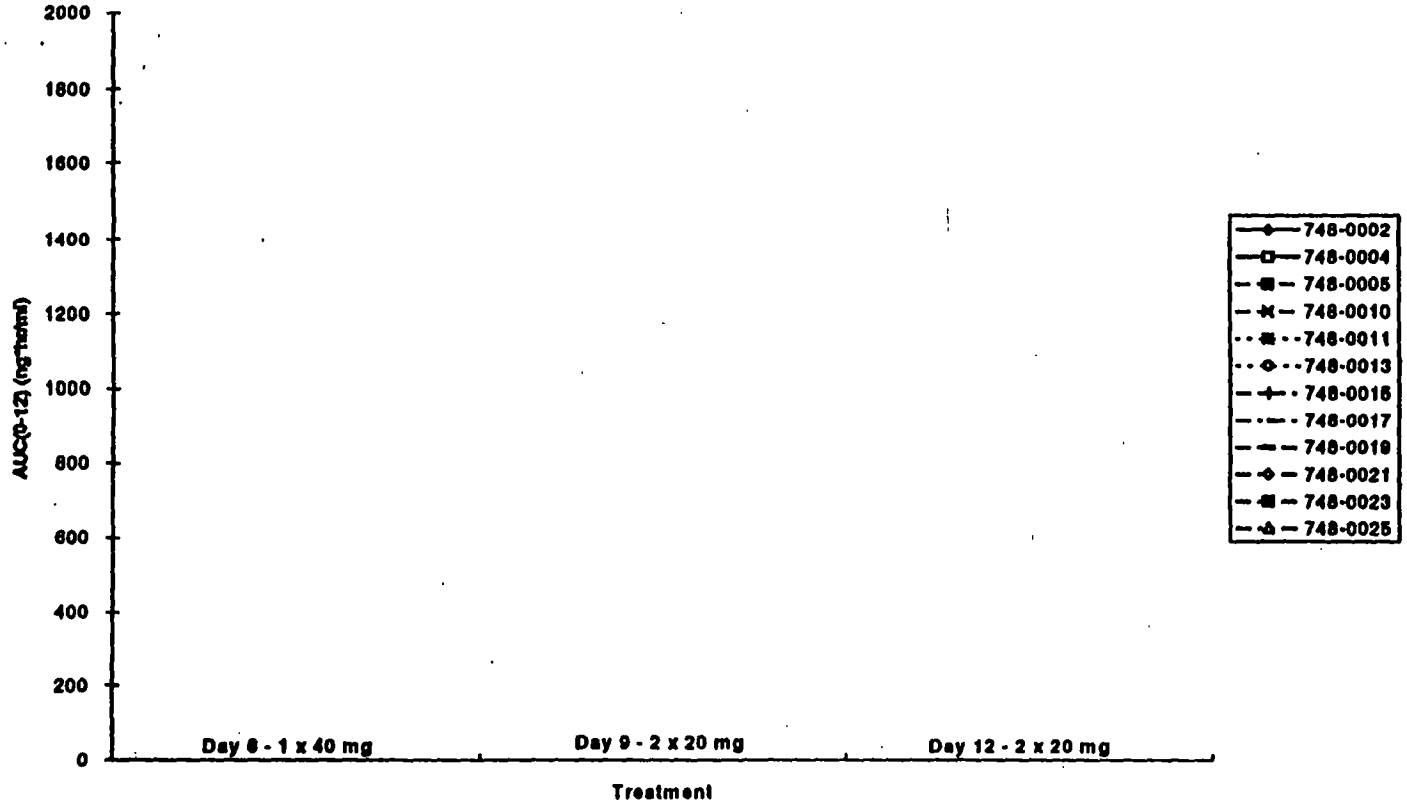
Source Data: Appendix III, Tables 1-3. Date of Data Extraction: 13SEP96 Date of Table Generation: 18OCT96

Figure 1.1 Ziprasidone AUC(0-12) Values in Subjects Receiving 40 mg Ziprasidone HCl BID Using 2 x 20 mg Capsules or 40 mg Capsules - Group 1
Ziprasidone Protocol 047



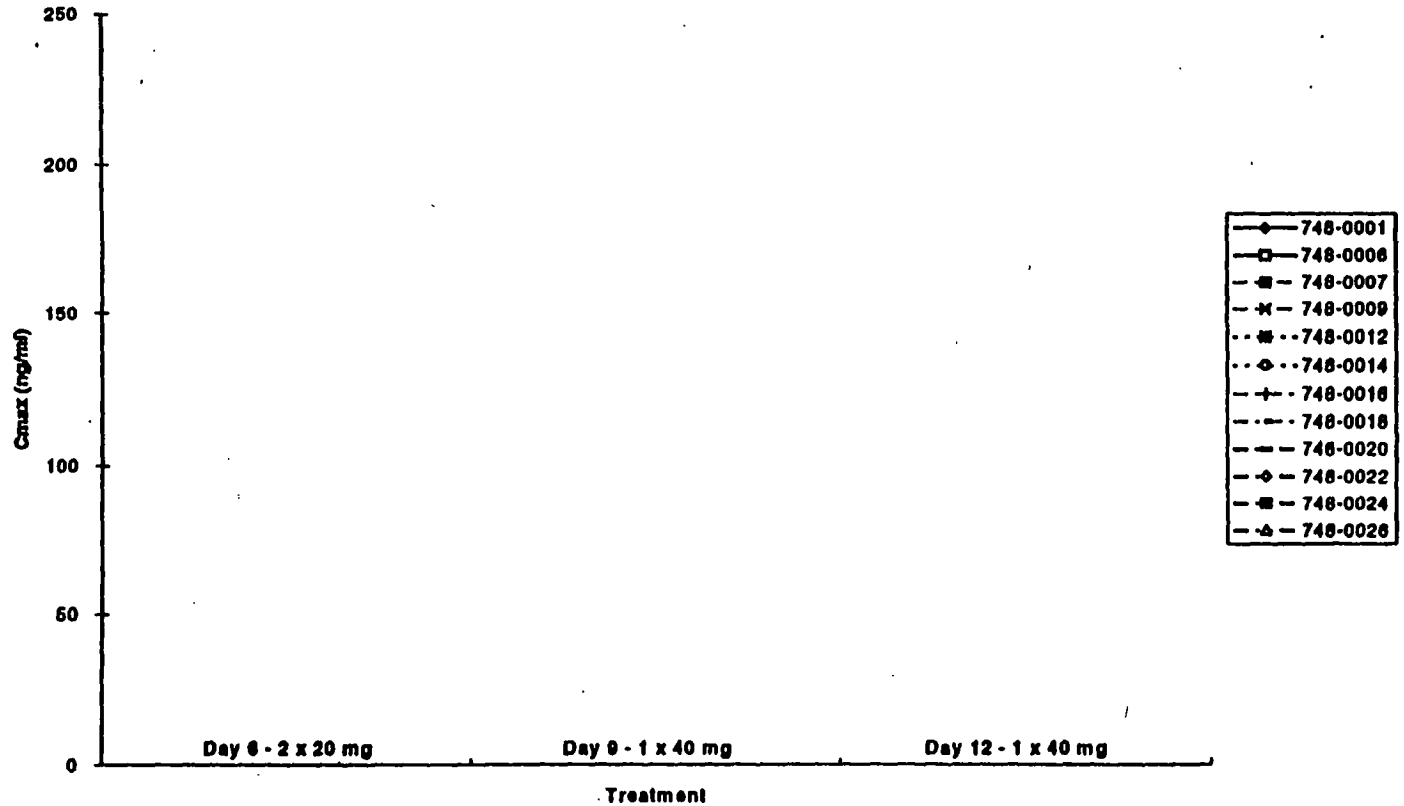
Source Data: Appendix IV, Tables 1 - 3

Figure 1.2 Ziprasidone AUC(0-12) Values in Subjects Receiving 40 mg Ziprasidone HCl BID Using 2 x 20 mg Capsules or 40 mg Capsules - Group 2
Ziprasidone Protocol 047



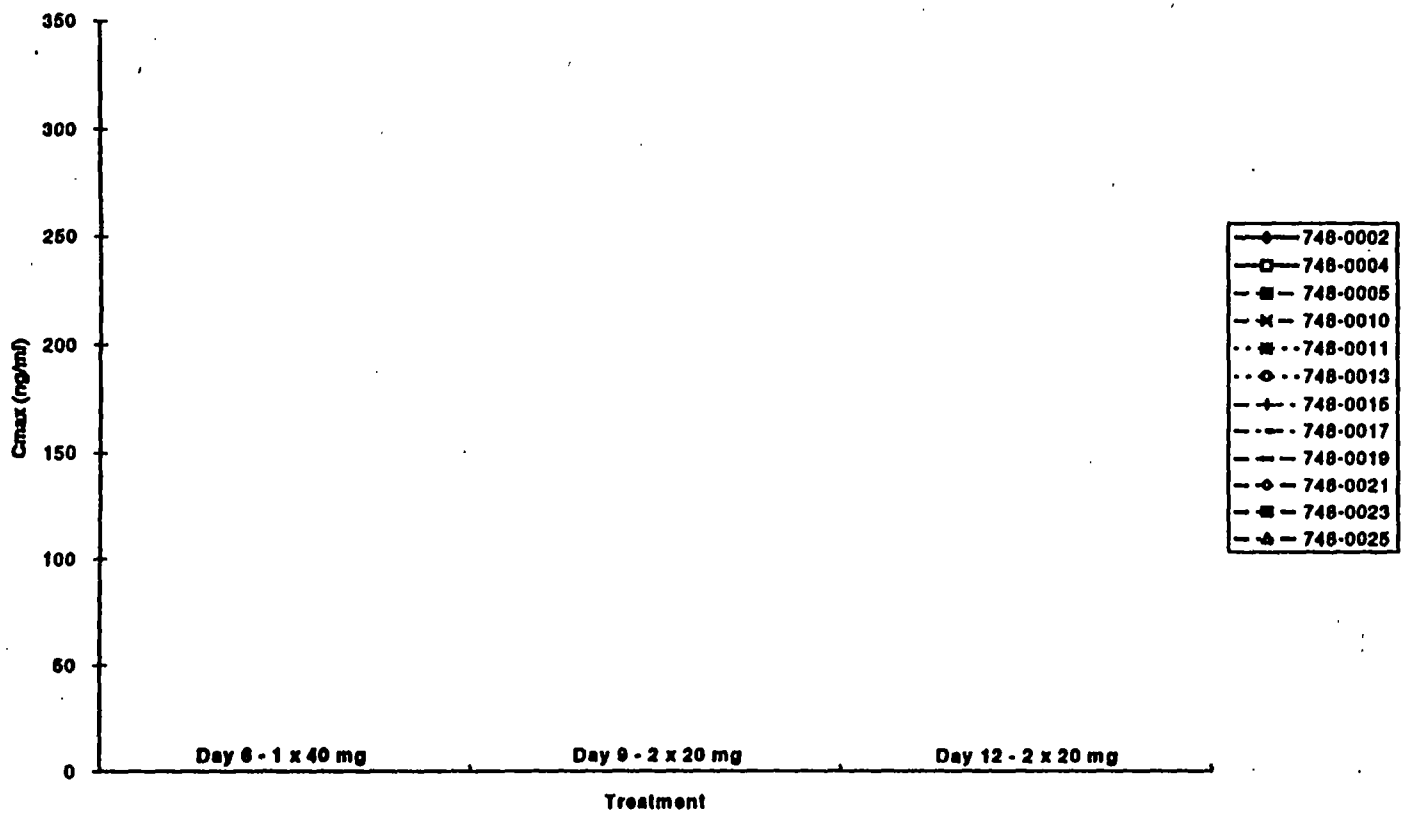
Source Data: Appendix IV, Tables 1 - 3

Figure 1.3 Ziprasidone Cmax Values in Subjects Receiving 40 mg Ziprasidone HCl BID Using 2 x 20 mg Capsules or 40 mg Capsules - Group 1
Ziprasidone Protocol 047



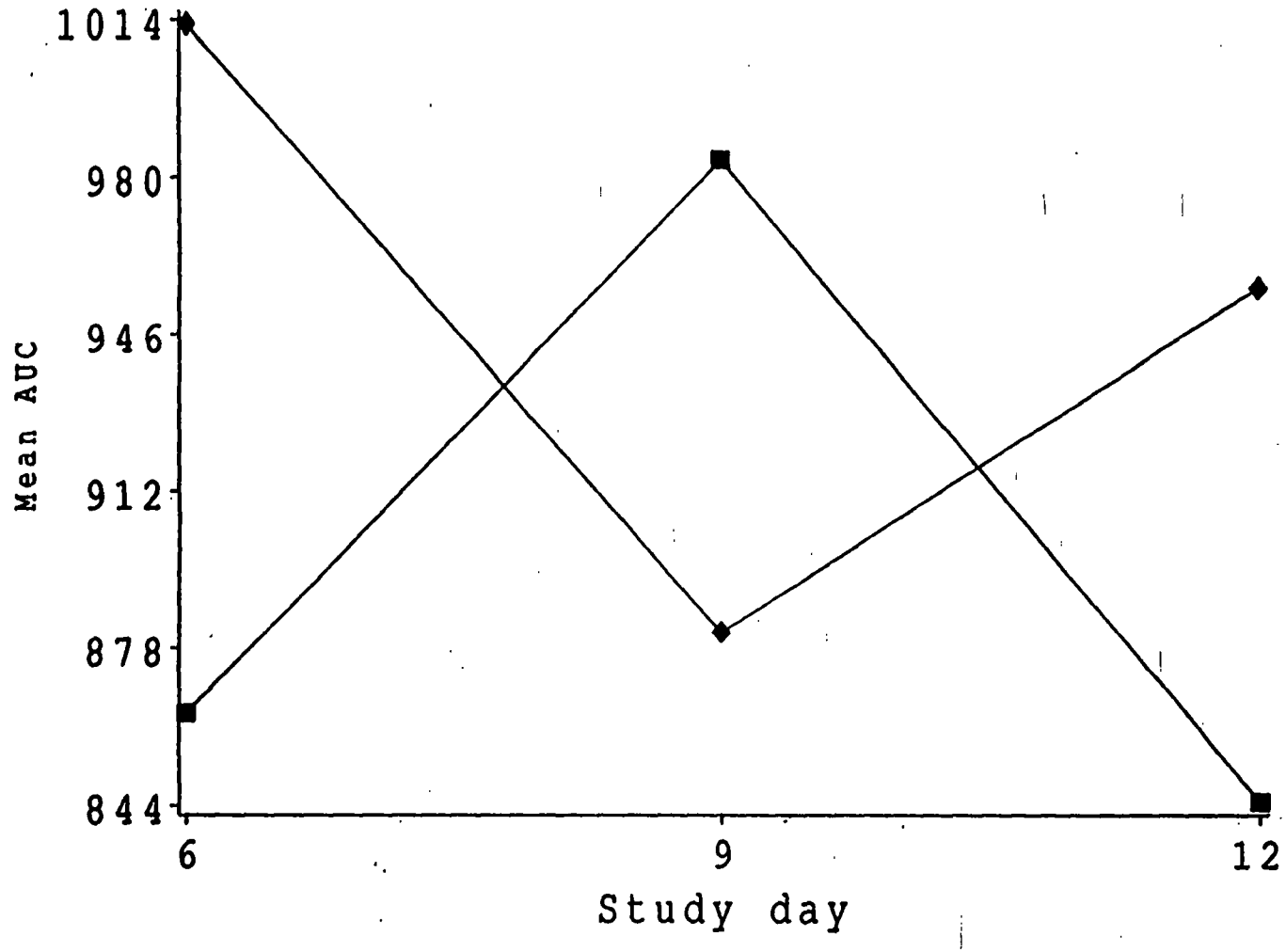
Source Data: Appendix IV, Tables 1 - 3

Figure 1.4 Ziprasidone Cmax Values in Subjects Receiving 40 mg Ziprasidone HCl BID Using 2 x 20 mg Capsules or 40 mg Capsules - Group 2
Ziprasidone Protocol 047



Source Data: Appendix IV, Tables 1 - 3

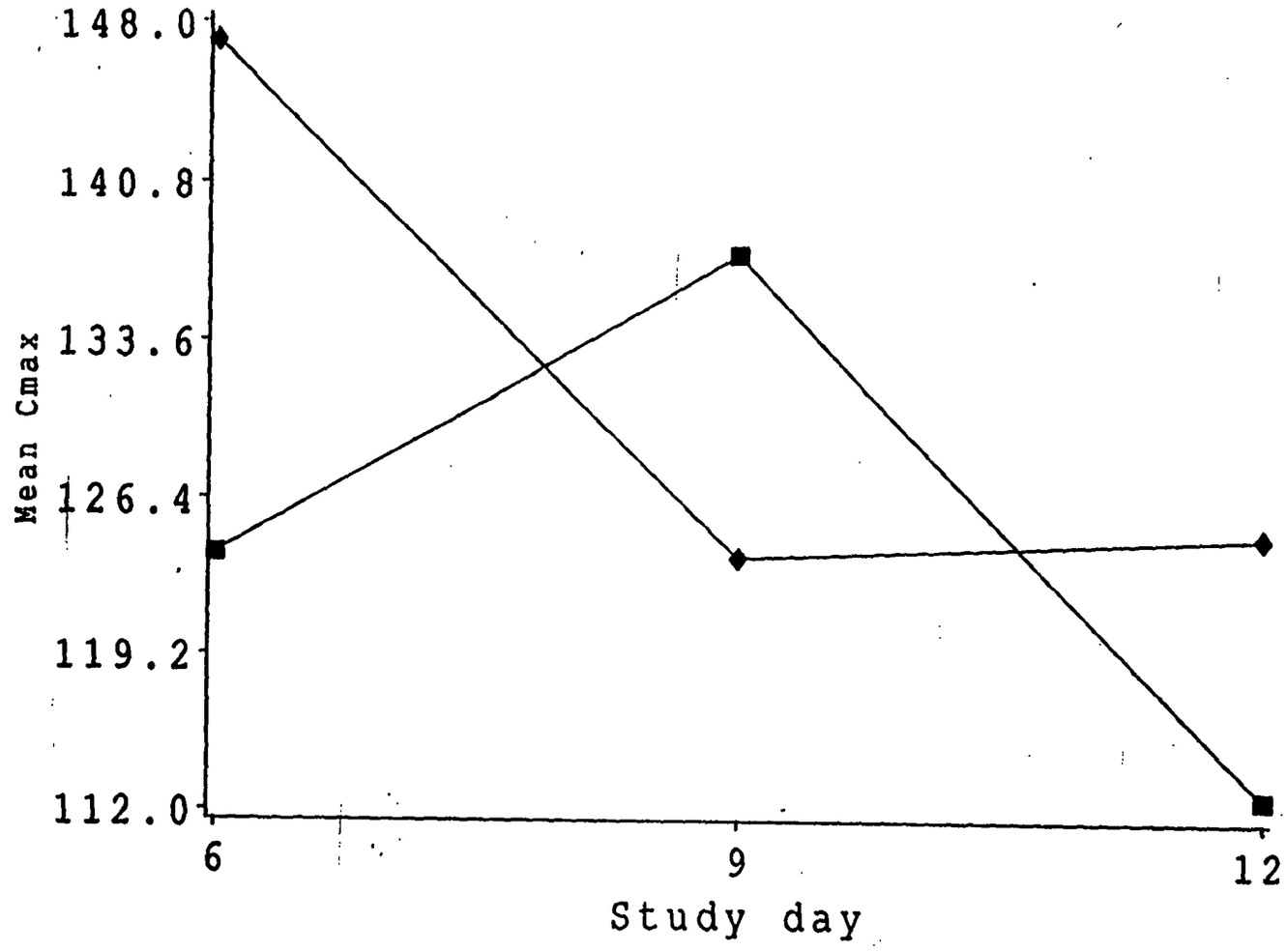
FIGURE 2.1
Mean AUC(0–12) (ng*hr/ml) by Day
Ziprasidone Protocol 047



■ Sequence ABB: 1 x 40 mg > 2 x 20 mg > 2 x 20 mg ◆ Sequence BAA: 2 x 20 mg > 1 x 40 mg > 1 x 40 mg

Source Data : Appendix IV Table 1-3 Date of Data Extraction : 13SEP96 Date of Figure Generation: 18OCT96

FIGURE 2.2
Mean Cmax (ng/ml) by Day
Ziprasidone Protocol 047

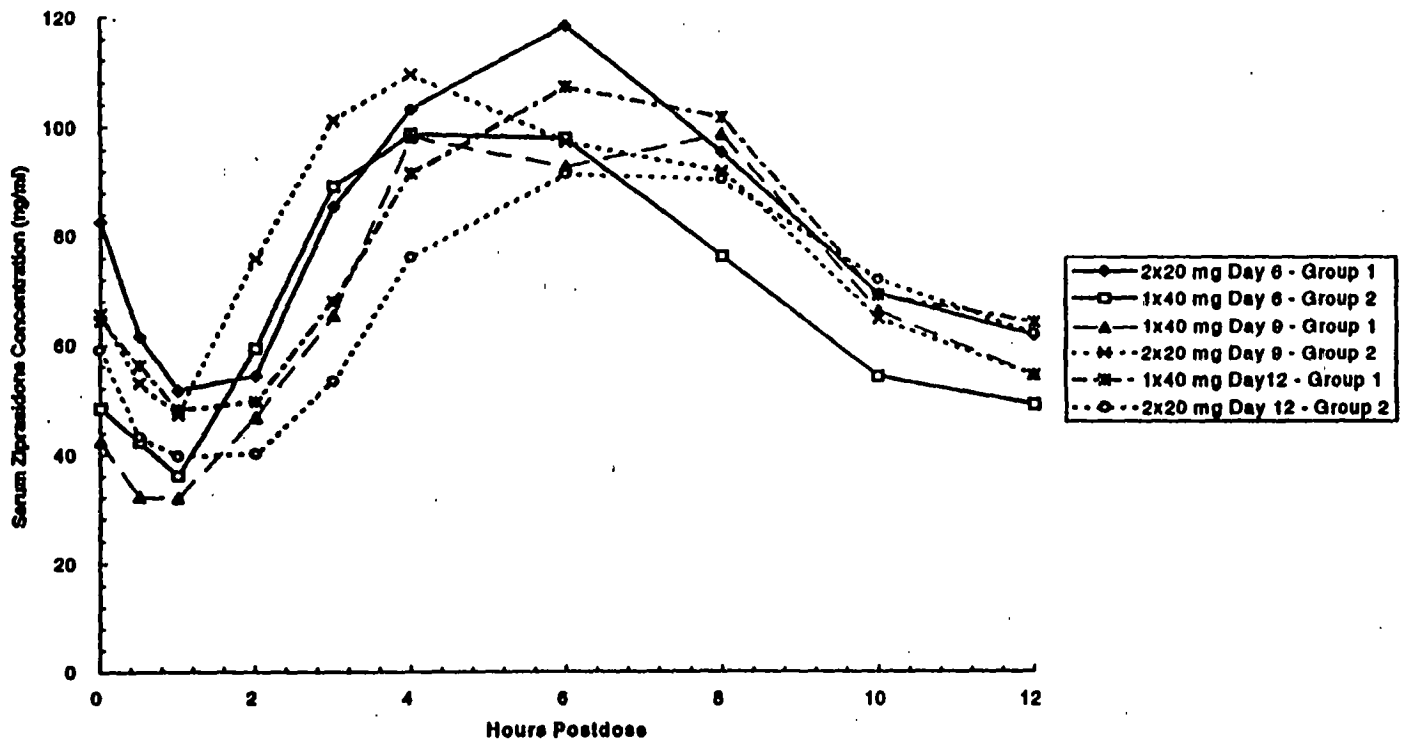


■ Sequence ABB: 1 x 40 mg > 2 x 20 mg > 2 x 20 mg

◆ Sequence BAA: 2 x 20 mg > 1 x 40 mg > 1 x 40 mg

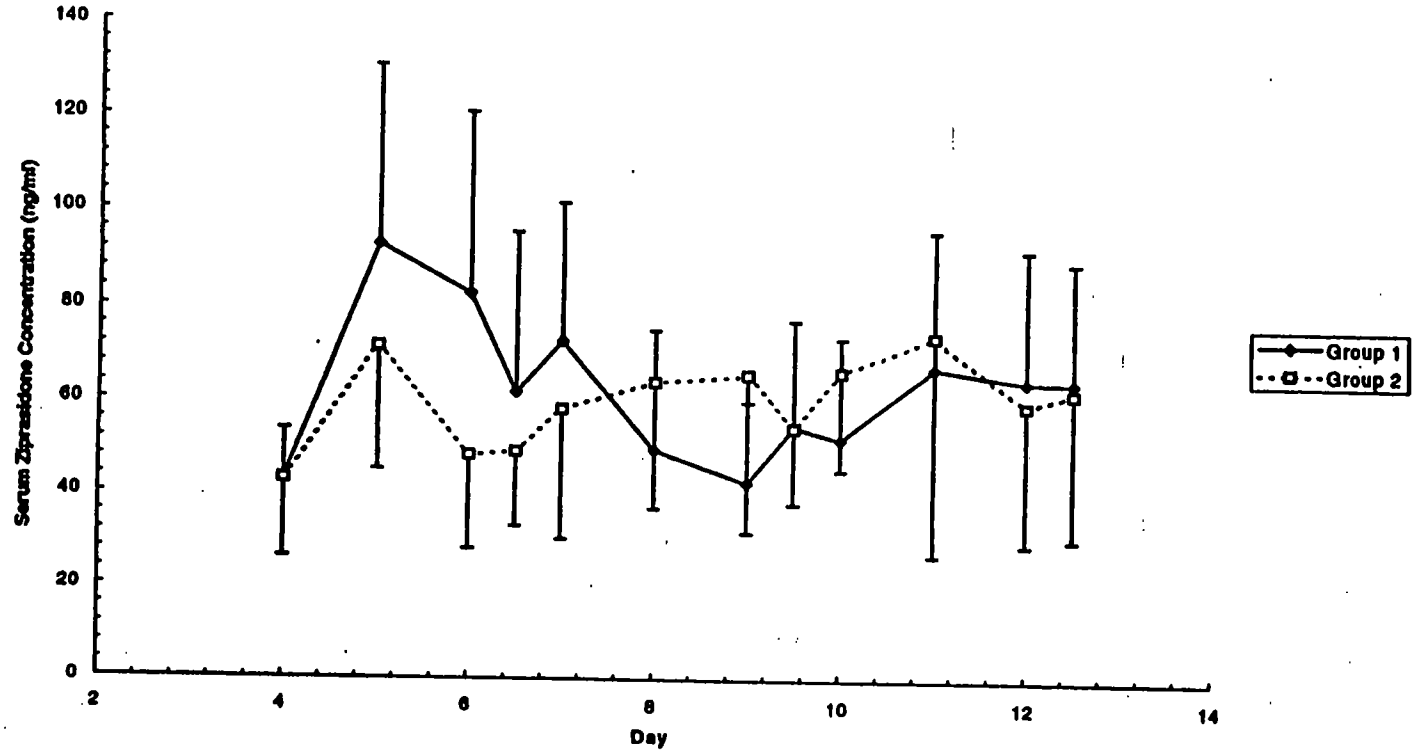
Source Data : Appendix IV Table 1-3 Date of Data Extraction : 13SEP96 Date of Figure Generation: 18OCT96

Figure 4.1 Mean Serum Ziprasidone Concentrations on Days 6, 9 and 12 in Subjects Receiving 40 mg Ziprasidone HCl BID Using 2 x 20 mg Capsules or 40 mg Capsules
Ziprasidone Protocol 047



Source Data: Appendix IV, Tables 1 - 3

Figure 4.2 Mean Trough Serum Ziprasidone Concentrations on Days 4 Through 12 in Subjects Receiving 40 mg Ziprasidone HCl BID Using 2 x 20 mg Capsules or 40 mg Capsules - Groups 1 and 2[a]
Ziprasidone Protocol 047



[a] = Group 1 Dosing Sequence: 20 mg capsule bid on days 1 to 3 → 2 x 20 mg capsules bid on days 4 to 6 → 1 x 40 mg capsule bid on days 7 to 9 → 1 x 40 mg capsule bid on days 10 to 12 (AM dose only on day 12)
Group 2 Dosing Sequence: 20 mg capsule bid on days 1 to 3 → 1 x 40 mg capsule bid on days 4 to 6 → 2 x 20 mg capsules bid on days 7 to 9 → 2 x 20 mg capsules bid on days 10 to 12 (AM dose only on day 12)

Source Data: Appendix IV, Table 4

Study 018: (BE of 1 X 60 mg vs 3 X 20 mg, single dose)

Study Design and Summary:

(see attachments 1 and 3)

Results:

(See attachments 4-5)

Reviewer's Comments:

1. This was a pilot study to compare the BE of ziprasidone at a single dose of 1 X 60 mg capsule vs 3 X 20 mg capsules.

2. Overall, the AUCs for the two formulations met the BE criteria in which the 90% CI ranged from 84% to 92%. However, the 90% CI for the Cmaxs ranged from 94% to 128% (attachment 4). Thus, the BE criteria were not met.

3. In general, the mean Cmax was higher after the 1X 60 mg capsules and the Tmax was about 1.7 h shorter than after the 3 X 20 mg capsules (attachment 5).

Conclusions:

1. In this pilot study, the BE criteria were not met since the 90% CI for the Cmax was 94% to 128% which is outside the currently required limits (80% to 125%).

2. The mean Cmax was slightly higher after the 1 X 60 mg than the 3 X 20 mg (~197 vs 180 ng/mL).

PROTOCOL 128-018: PHASE I OPEN PILOT STUDY TO COMPARE THE PHARMACOKINETICS OF A SINGLE 60 MG ORAL DOSE OF CP-88,059-1 ADMINISTERED AS THREE 20 MG CAPSULES AND ONE 60 MG CAPSULE TO NORMAL, HEALTHY MALE VOLUNTEERS

Principal Investigator: P. Leese, M.D.

Study Publication: None

Study Dates: 29 November 1993 - 22 December 1993

Study Objective: To compare the pharmacokinetics of a single oral 60 mg dose of ziprasidone HCl (CP-88,059-1) administered as 3 x 20 mg capsules (FID #CS-090-031) and as one 60 mg capsule (FID #G00355AA), both under fed conditions.

Study Design: This was an open, randomized, two-way crossover pilot study comparing the pharmacokinetics of ziprasidone administered as 3 x 20 mg capsules and one 60 mg capsule, both under fed conditions. Subjects completing the study received both formulations as single doses separated by at least seven days.

Evaluation Groups:

Entered Study	12
Completed Study	7
Evaluated for Pharmacokinetics	7
Assessed for Safety	
Adverse Events	12
Laboratory Tests	0[a]

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

Subjects: Healthy male volunteers ranging in age from 20 to 36 years.

Drug Administration:

Dosage Form	3 x 20 mg capsules (FID #CS-090-031) 60 mg capsule (FID #G00355AA)
Dosing	Subjects were administered single 60 mg doses of ziprasidone as either 3 x 20 mg capsules or one 60 mg capsule on the first treatment day immediately following a standard breakfast. After a washout period of at least seven days, subjects received the alternate treatment. All doses were administered with 50 ml of water.

Pharmacokinetic and Safety Evaluations: Blood samples for the determination of serum ziprasidone concentrations were collected prior to and up to 48 hours after

each dose of study drug. Serum concentrations were used to estimate pharmacokinetic parameters (AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, K_{el}, and $T_{1/2}$). Subjects were monitored for adverse events and changes in vital signs.

Analytical Methods:

Statistical Methods: Natural log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}, and untransformed T_{max} and K_{el} were analyzed using an ANOVA model. For AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}, the 90% confidence limits were calculated for the ratio of geometric means. Relative bioavailability expressed in percent was calculated from the ratio of adjusted mean $AUC_{0-\infty}$ values comparing the 1 x 60 mg capsule to 3 x 20 mg capsules. Data for the 3 x 20 mg capsules served as the reference.

Pharmacokinetic Results:

Mean and Coefficients of Variation (%CV) of Pharmacokinetic Parameters (n = 7)

	Ziprasidone			
	1 x 60 mg capsule		3 x 20 mg capsules	
Parameter	Mean	CV%	Mean	CV%
AUC_{0-t}(ng•hr/ml)[a]	1354.6	23	1484.9	26
$AUC_{0-\infty}$(ng•hr/ml)[a]	1332.2	24	1495.4	26
C_{max} (ng/ml)[a]	200.7	26	186.0	36
T_{max} (hours)	5.6	10	7.3	28
K_{el} (hr^{-1})	0.158	42	0.152	39
$T_{1/2}$ (hours)[b]	4.4	--	4.6	--

[a] geometric mean
[b] mean $T_{1/2}$ = 0.693/mean K_{el}

Safety Results:

	Ziprasidone	
	1 x 60 mg capsule	3 x 20 mg capsules
Adverse Events (All Causality)[a]	10/10 (3)	9/9 (1)

( ) subjects discontinued due to adverse events
[a] All subjects in the study experienced adverse events, and all except two adverse events (sinusitis following each treatment in the same subject) were treatment-related.

Summary and Conclusions: After administration of a single dose of ziprasidone, the extent of absorption was less for 1 x 60 mg capsule than for 3 x 20 mg capsules. Mean $AUC_{0-\infty}$ values for the 1 x 60 mg and 3 x 20 mg capsules were 1332.2 and 1495.4 ng•hr/ml, respectively. The mean C_{max} values comparing the 1 x 60 mg capsule to 3 x 20 mg capsules were 200.7 and 186.0 ng/ml, respectively. The 90% confidence interval was within acceptable limits for $AUC_{0-\infty}$ (83.6%, 91.9%) and outside acceptable limits for C_{max} (93.5%, 127.8%). Mean T_{max} was shorter by 1.7 hours following the 1 x 60 mg capsule. Terminal phase half-lives were similar,

with mean values of 4.4 and 4.6 hours following the 1 x 60 mg capsule and 3 x 20 mg capsules, respectively.

Four subjects discontinued from the study due to adverse events which were considered related to treatment. Three subjects withdrew from the study after receiving the 1 x 60 mg capsule: one subject due to dizziness and asthenia, another subject due to anxiety, nausea, and somnolence, and the third subject due to somnolence. One subject withdrew from the study following administration of 3 x 20 mg capsules due to dyspnea, nausea, asthenia, and vasodilatation.

One subject withdrew following administration of three 20 mg capsules for personal reasons unrelated to treatment.

All subjects in the study experienced at least one adverse event. All treatment-emergent adverse events were treatment-related except for two unrelated adverse events, both severe sinusitis, that were experienced by the same subject following each treatment.

Treatment-emergent, treatment-related adverse events of greatest frequency following the 1 x 60 mg capsule were somnolence of moderate to severe severity. Asthenia of mild to severe severity were the most common adverse events following the 3 x 20 mg capsules. Dizziness of moderate severity and asthenia of moderate to severe severity occurred with the next greatest frequency in subjects receiving the 1 x 60 mg capsule, whereas somnolence of moderate to severe severity occurred with the next greatest frequency in subjects receiving 3 x 20 mg capsules. Mild to moderate anorexia occurred with similar incidence following both treatments. One moderate and one severe case of anxiety occurred after treatment with 1 x 60 mg capsule. Other adverse events following both treatments were of mild to moderate severity, including instances of pallor, chest pain, vasodilation, nausea, paresthesia, abnormal thinking, dyspnea, and sweating. No serious adverse events were reported.

In this pilot study with a small number of subjects comparing treatment with 1 x 60 mg capsule to 3 x 20 mg capsules bioequivalence criteria was not met. Ziprasidone 60 mg was associated with somnolence, asthenia, and dizziness. The adverse events reported following a single 60 mg dose of ziprasidone, administered either as a single capsule or as 3 x 20 mg capsules, were consistent with the pharmacologic properties of the drug.

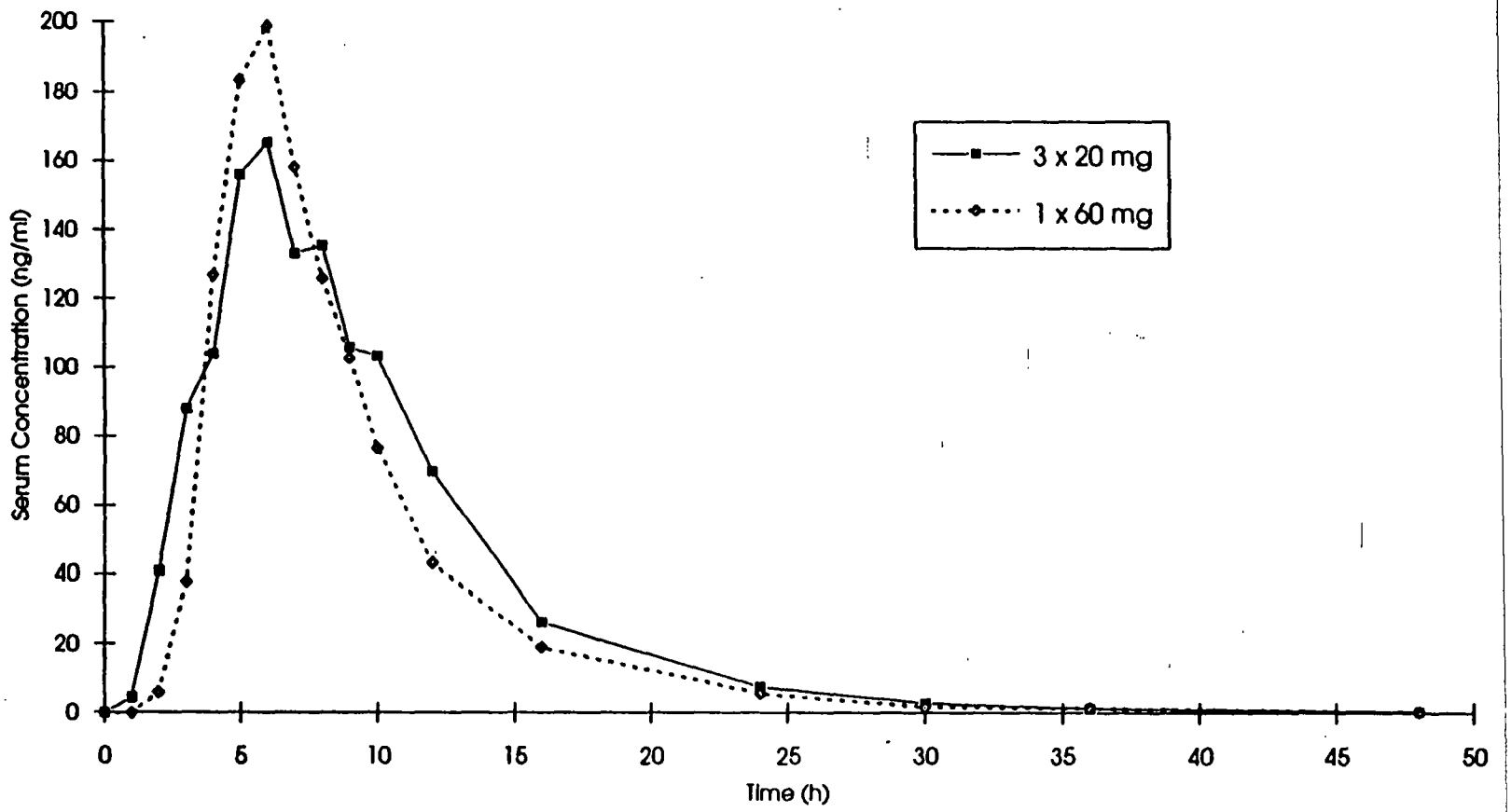
Table 5.2
Summary of Statistical Analyses of Pharmacokinetic Parameters (AUC, Cmax, Tmax, Kel, and T1/2)
Ziprasidone Protocol 018

Pharmacokinetic Parameter	Comparison			90% Confidence Limits
		Adjusted Geometric Means	Ratio	
AUC(0-t) (ng.hr/ml)	1 x 60 mg vs. 3 x 20 mg	1304.9 vs. 1490.3	87.6%	(83.6%, 91.7%)
AUC(0-inf) (ng.hr/ml)	1 x 60 mg vs. 3 x 20 mg	1315.0 vs. 1500.7	87.6%	(83.6%, 91.9%)
Cmax (ng/ml)	1 x 60 mg vs. 3 x 20 mg	196.66 vs. 179.86	109.3%	(93.5%, 127.8%)
		Adjusted Means	Difference	
Tmax (hr)	1 x 60 mg vs. 3 x 20 mg	5.54 vs. 7.54	-2.00	(-2.69, -1.31)
Kel (/hr)	1 x 60 mg vs. 3 x 20 mg	0.151 vs. 0.158	-0.007	(-0.049, 0.035)

Source Data: Appendix III, Tables 1-5 Date of Data Extraction: 03JUL96 Date of Table Generation: 23JUL96

5

Figure 1.1 Mean Serum Ziprasidone Concentrations Versus Time Following Oral Administration of Three 20 mg Capsules (FID #CS-90-031) and a Single, 60 mg Capsule (FID #G00355AA) of Ziprasidone HCl To Healthy Male Volunteers Ziprasidone Protocol 018



Source Data: Appendix IV, Tables 1 and 2

Study 019: (BE of 1 X 80 mg vs 4 X 20 mg, single dose)

Study Design and Summary:

(see attachments 1 and 3)

Results:

(See attachments 4-6)

Reviewer's Comments:

1. This is a failed BE study since 90% CI were 72% to 98% for Cmax and 77% to 93% for AUC (attachments 4).

2. The mean and individual Cmaxs and AUCs were consistently higher in almost all subjects following the 4 X 20 mg than 1 X 80 mg capsules (attachments 5 and 6).

3. The variability in the data was similar following both treatments.

4. The dose was not tolerated due to the orthostatic/postural hypotension which was experienced by almost all subjects.

Conclusions:

1. In this study, the BE criteria were not met since the 90% CI for the Cmax was 72% to 98% and for the AUC was 77% to 93% which is outside the currently required limits (80% to 125%).

2. The blood level of ziprasidone was constantly higher after the 4 X 20 mg than the 1 X 80 mg. However, this difference may not be of clinical significance.

3. The 80 mg dose is intolerable and is not recommended for chronic therapy.

PROTOCOL 128-019: PHASE I OPEN PILOT STUDY TO COMPARE THE PHARMACOKINETICS OF A SINGLE 80 MG ORAL DOSE OF CP-88,059-1 ADMINISTERED AS FOUR 20 MG CAPSULES AND ONE 80 MG CAPSULE TO NORMAL, HEALTHY MALE VOLUNTEERS

Principal Investigator: G. Apseloff, M.D.

Study Publication: None

Study Dates: 22 November 1993 - 12 December 1993

Study Objective: To compare the pharmacokinetics of a single oral 80 mg dose of ziprasidone HCl administered as 4 x 20 mg capsules (FID #CS-90-031) and as one 80 mg capsule (FID #G00356AA), both under fed conditions.

Study Design: This was an open, randomized, two-way crossover pilot study comparing the pharmacokinetics of ziprasidone administered as 4 x 20 mg capsules and one 80 mg capsule, both under fed conditions. Subjects completing the study received both formulations as single doses separated by at least seven days.

Evaluation Groups:

Entered Study	11
Completed Study	8
Evaluated for Pharmacokinetics	8
Assessed for Safety	
Adverse Events	11
Laboratory Tests	2[a]

[a]Laboratory tests were performed at screening and prior to dosing only, unless follow-up was required. Two subjects required repeat laboratory tests which were done after dosing; one subject was not fasting at screening, and one subject had hemoglobin, basophil, and urinalysis values at screening which fell outside of normal limits.

Subjects: Healthy male volunteers ranging in age from 18 to 39 years.

Drug Administration:

Dosage Form	4 x 20 mg capsules (FID #CS-90-031) 80 mg capsule (FID #G00356AA)
Dosing	Subjects were administered single 80 mg doses of ziprasidone as either 4 x 20 mg capsules or one 80 mg capsule on the first treatment day immediately following a standard breakfast. After a washout period of at least seven days, subjects received the alternate treatment. All doses were administered with 50 ml of water.

Pharmacokinetic and Safety Evaluations: Blood samples for the determination of serum ziprasidone concentrations were collected prior to and up to 48 hours after each dose of study drug. 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 and changes in vital signs.

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}, 90% confidence limits were calculated for the ratio of geometric means.

Pharmacokinetic Results:

Mean ± Coefficients of Variation (%CV) of Pharmacokinetic Parameters (n=8)

	Ziprasidone			
Parameter	1 x 80 mg capsule		4 x 20 mg capsules	
$AUC_{0-\infty}$ (ng•hr/ml)[a]	1393.9	± 40	1615.5	± 37
C_{max} (ng/ml)a	179.5	± 47	205.9	± 29
T_{max} (hours)	5.8	± 36	6.1	± 27
K_{el} (hr^{-1})	0.196	± 24	0.217	± 17
$T_{1/2}$ (hours)[b]	3.5	--	3.2	--

[a] geometric mean
[b] mean $T_{1/2}$ = 0.693/mean K_{el}

Safety Results:

	Ziprasidone	
	1 x 80 mg capsule	4 x 20 mg capsules
Adverse Events (All Causality)[a]	9/9 (1)[b]	10/10 (2)[b]
Clinically Significant Laboratory Test Abnormalities	N/A[c]	1/2 (0)[c]

() subjects discontinued
[a] All reported adverse events were treatment-related.
[b] Three subjects withdrew consent due to multiple adverse events.
[c] Laboratory tests were performed at screening and prior to dosing only, unless follow-up was required. Two subjects required repeat laboratory tests after receiving 4 x 20 mg capsules.

Summary and Conclusions: After administration of a single dose of ziprasidone, the extent of absorption was less following one 80 mg capsule than that following four 20 mg capsules. Mean C_{max} and $AUC_{0-\infty}$ values for the 80 mg capsule were 13% and 14% lower, respectively, compared to the values following four 20 mg capsules. The eight subjects who were analyzed for pharmacokinetics in this pilot study did not provide enough power to demonstrate bioequivalency.

Mean T_{max} was similar for both treatments. Terminal phase half-lives were also similar, with mean values of 3.5 and 3.2 hours following a single 80 mg capsule and four 20 mg capsules, respectively.

Three subjects withdrew consent due to multiple adverse events which were considered related to treatment. One subject withdrew from the study due to orthostatic dizziness and somnolence of mild to moderate severity after receiving the 80 mg capsule. Two subjects withdrew from the study following administration of four 20 mg capsules. One of these subjects experienced 3 instances of orthostatic dizziness (2 mild, 1 severe), moderate to severe back pain, and mild somnolence and dry mouth. The other subject had 3 occurrences of mild to severe orthostatic dizziness, and experienced mild to severe somnolence, headache, vomiting, and insomnia.

All subjects in the study experienced adverse events, and all were considered treatment-related. Mild to severe somnolence was reported in all subjects following both treatments. Orthostatic dizziness, including postural hypotension (mild to severe) occurred with the next greatest frequency, with similar incidences following both treatments. Other adverse events following the 80 mg capsule were isolated and of mild to moderate severity. Following four 20 mg capsules, other reported adverse events were isolated and mild to severe, with instances of headache, back pain, agitation, and insomnia noted as severe. No serious adverse events were reported.

In summary, the exposure to ziprasidone was less following one 80 mg capsule as compared to four 20 mg capsules in this pilot study. Ziprasidone 80 mg was associated with somnolence, orthostatic dizziness, and postural hypotension. Subject toleration of a single 80 mg oral dose of ziprasidone was similar following either treatment under fed conditions.

Table 5.2
Summary of Statistical Analyses of Pharmacokinetic Parameters (AUC, Cmax, Tmax, and Kel)
Ziprasidone Protocol 019

Pharmacokinetic Parameter	1x80mg Capsule	4x20mg Capsules		90% Confidence Limits
	Adjusted Geometric Means		Ratio	
AUC (0-inf) (ng.hr/ml)	1340	1579	84.8%	(77.2%, 93.3%)
Cmax (ng/ml)	170	202	84.0%	(71.9%, 98.2%)
	Adjusted Means		Difference	
Tmax (hr)	5.5	6.0	-0.5	(-2.0, 1.0)
Kel (1/hr)	0.197	0.219	-0.022	(-0.039, -0.004)

The adjusted means are displayed because of the unequal number of subjects in each sequence.
Source Data: Appendix III Tables 1-4 Date of Data Extraction: 23SEP95. Date of Table Generation: 23SEP95.

5

(5) Table 5.1.1 Summary of Pharmacokinetic Parameters for Ziprasidone Following Oral Administration of Ziprasidone HCl as Four 20 mg Capsules and as a Single, 80 mg Capsule To Healthy Male Volunteers
Ziprasidone Protocol 019

Treatment		N=8	AUC(0-t) (ng•hr/ml)	AUC(0-∞) (ng•hr/ml)	Cmax (ng/ml)	Tmax (hr)	Kel (hr^{-1})	T1/2[a] (hr)
Four 20 mg Capsules - 20C FID #CS-90-031	MEAN[b]		1607.2	1615.5	205.9	6.1	0.217	3.2
	SD		585.7	592.3	60.3	1.6	0.036	---
	CV%		36	37	29	27	17	---
One 80 mg Capsule 80C FID #G00356AA	MEAN[b]		1385.4	1393.9	179.5	5.8	0.196	3.5
	SD		572.0	558.1	83.8	2.1	0.047	---
	CV%		41	40	47	36	24	---

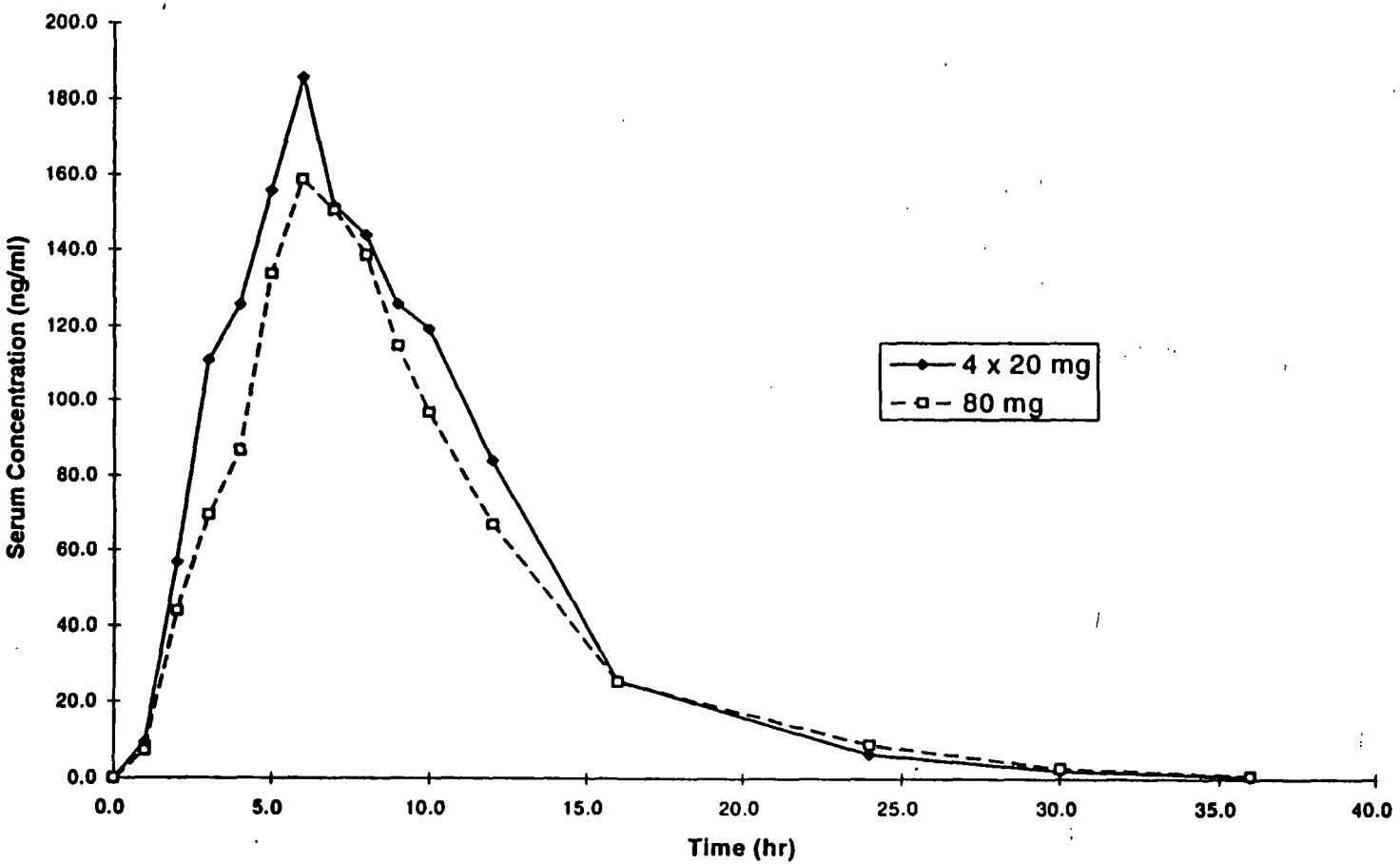
[a] = Calculated as 0.693/mean Kel
[b] = Geometric mean and standard deviation for AUC(0-t), AUC(0-∞), and Cmax; arithmetic mean and standard deviation for Tmax and Kel.

Source Data: Appendix IV, Tables 1 and 2

6

(6)

Figure 1. Mean Serum Ziprasidone Concentrations Versus Time Following Oral Administration of Four 20 mg Capsules and a Single 80 mg Capsule of Ziprasidone HCl To Healthy Male Volunteers
Ziprasidone Protocol 019



Source Data: Appendix IV, Tables 1 and 2

Study 027: (Mass-Balance):

Study Design and Summary:

(see attachments 1-5)

Results:

(See attachments 6-22)

Reviewer's Comments:

1. In this study the data are very tight for the parent, ziprasidone, and for the 3H and 14C radioactivity (attachments 6-11).

2. Overall about 90% of the radioactivity was recovered from urine (~20%) and feces (~70%)-attachments 6 and 11.

3. The major metabolic pathways are N-dealkylation and oxidation to form sulfoxide and sulfone (attachments 21 and 22). According to the sponsor, all the metabolites are inactive.

4. In serum, approximately 50% of the total radioactivity is represented by the parent drug, ziprasidone (attachment 7).

5. It should be noted that, ziprasidone, which is also labeled as M13, is the major component (~25%) in the serum (attachment 10). However, ziprasidone (M13) was not present in urine (attachment 8). Overall, there were 12 metabolites found in serum in which 11 of these were also found in urine. About 60 to 70% of the radioactivity was found in serum (attachment 10).

6. In serum, the metabolites were always higher than the parent drug and their half lives were similar suggesting that the metabolites were rapidly formed (attachments 16-20). It appears that these metabolites, possibly, formed during the absorption process and/or before. Therefore, it would be very interesting to know if the same metabolites will be formed at the same rate after IV administration.

7. In urine, 11 metabolites were identified and about 97% of these were recovered (attachments 8, 21, and 22). The parent drug (M13) was not found in urine (attachment 8.)

8. In feces, only one metabolite (M9) was identified, in addition to the parent drug, M13 (attachment 9), which both were completely recovered (100%).

9. All subjects had similar cumulative urinary and fecal plots for the total radioactivity (attachments 12-15)

Conclusions:

1. The drug is extensively metabolized after oral administration with approximately 3% excreted unchanged in feces and <1% unchanged in urine.

2. There were 13 metabolites identified in this study.

3. Most of the metabolites, were excreted in urine. Unchanged drug and/metabolites accounted for 64%, 97%, and 100% of the total radioactivity extracted from serum, urine, and feces, respectively.

PROTOCOL 128-027: PHASE I OPEN STUDY TO EXAMINE THE METABOLISM AND EXCRETION OF $^{14}C/^{3}H$-CP-88,059-1 IN NORMAL HEALTHY MALE VOLUNTEERS (REPEAT)

Principal Investigator: B. Levy, M.D.

Study Publication: None

Study Dates: 31 May 1994 - 24 June 1994

Study Objective: To elucidate the ultimate routes of excretion and the metabolic profile of radiolabelled ziprasidone HCl (CP-88,059-1) in man.

Study Design: This was an open, non-randomized, single group study designed to examine the metabolism and excretion of ziprasidone. All subjects received a single oral dose of $^{14}C/^{3}H$-ziprasidone as a 20 mg suspension following consumption of a standard breakfast.

Evaluation Groups:

Entered Study	4
Completed Study	4
Evaluated for Pharmacokinetics	4
Assessed for Safety	4
Adverse Events	4
Laboratory Tests	0[a]

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

Subjects: Healthy male volunteers ranging in age from 37 to 45 years.

Drug Administration:

Dosage Form	20 mg CP-88,059-1 powder for constitution (FID #G00414AA)
Dosing	Ziprasidone was administered as a 20 mg suspension containing a total of 47.8 µCi of ^{14}C and 90.3 µCi of ^{3}H immediately following consumption of a standard breakfast. The suspension was prepared according to the instructions provided.

Pharmacokinetic and Safety Evaluations: Serum samples for the determination of ziprasidone concentrations, metabolites, and radioactivity were collected immediately prior to and up to 168 hours after dosing, and if necessary, every 24 hours thereafter until 2 consecutive fecal samples had radioactivity levels less than 1% of total radioactivity. Serum ziprasidone concentrations were used to estimate pharmacokinetic parameters (AUC_{∞}, C_{max}, T_{max}, K_{el}, half-life). Urine specimens were collected just prior to and up to 168 hours after dosing, and if necessary, continuing in

24-hour intervals until 2 consecutive fecal samples had radioactivity levels less than 1% of total radioactivity. Fecal specimens were collected as passed from the time of dosing until 168 hours after dosing or until fecal samples had radioactivity levels that were less than 1% of total radioactivity, whichever was greater. Urine and fecal samples were analyzed for metabolites and radioactivity. Subjects were monitored for adverse events and changes in vital signs.

Analytical Methods:

Statistical Methods: Pharmacokinetic and safety results were summarized using data tabulations, descriptive statistics, and graphical presentations.

Pharmacokinetic Results:

Percentage of $^{3}H/^{14}C$ Excreted in Urine and Feces From 0-264 Hours (n=4)

	Urine			Feces			Unused Dose*			Total		
	^{3}H	^{14}C	Avg.	^{3}H	^{14}C	Avg.	^{3}H	^{14}C	Avg.	^{3}H	^{14}C	Avg.
Mean	20.6	20.1	20.3	68.1	64.5	66.3	1.9	1.8	1.9	90.6	86.4	88.5
± SD	1.0	1.1	1.0	4.8	5.0	4.9	1.1	1.0	1.1	3.7	4.1	3.9

*dose recovered in containers

Mean ± Coefficients of Variation (%CV) of Serum Pharmacokinetic Parameters (n=4)

Parameter	Ziprasidone	^{3}H Radioactivity	^{14}C Radioactivity	Ziprasidone (%)
$AUC_{0-\infty}$ (ng•hr/ml)[a,b]	361.3 ± 11.2	876.6 ± 15.9	760.8 ± 15.6	44.1 ± 5.7
C_{max} (ng/ml)[a,c]	45.4 ± 31.5	94.5 ± 26	88.4 ± 25	49.6 ± 10
T_{max} (hours)	3.5 ± 54.7	5.5 ± 18.2	5.5 ± 18.2	--
K_{el} (hr^{-1})	0.197 ± 13.2	0.153 ± 10.9	0.175 ± 10.5	--
$T_{1/2}$[d] (hours)	3.5	4.5	4.0	--

[a]geometric mean; [b]values for radioactivity are expressed as ng equiv •hr/ml; [c]values for radioactivity are expressed as ng equiv/ml; [d]mean $T_{1/2}$ = 0.693/mean K_{el}

Safety Results:

Findings	Number of Subjects With/Evaluated 20 mg Suspension
Adverse Events (All Causality)	4/4 (0)
Adverse Events (Treatment-emergent, treatment-related)	3/4 (0)

0 subjects discontinued

Summary and Conclusions: Following study drug administration, approximately 89% of the administered dose was recovered in the urine and feces. The percentage of radioactive dose excreted in urine and feces was 20.3% and 66.3%, respectively.

Both ^{14}C- and ^{3}H-labelled metabolites were excreted through urine and feces at similar rates.

Serum concentrations of the total radioactivity were greater than the parent compound at all time points, suggesting the early formation of metabolites. At C_{max}, serum ziprasidone concentrations accounted for approximately 50% of the total circulating radioactivity. Based on values for $AUC_{0-\infty}$, approximately 44% of the circulating radioactivity was attributable to unchanged drug.

Ziprasidone was extensively metabolized, with only a small percentage (approximately 3%) of the unchanged drug detected in feces and less than 1% detected in urine. A total of 12 metabolites were identified in this study. The serum metabolites were similar to those found in urine. Only one metabolite, resulted by reductive cleavage of the benzisothiazole ring, was detected in feces. This metabolite was also detected in urine and serum. The major routes of metabolism were due to N-dealkylation of the ethyl side chain attached to the piperazinyl nitrogen, oxidation at sulfur resulting in the formation of sulfoxide and sulfone, reductive cleavage of the benzisothiazole moiety followed by methylation on the resulting thiophenol, and hydration of the C=N bond and subsequent oxidation of the benzisothiazole moiety. The metabolites resulting from these primary routes were found to undergo further metabolism. Unchanged drug and/or identified metabolites accounted for 97%, 64%, and 100% of the total radioactivity extracted from urine, serum, and feces, respectively.

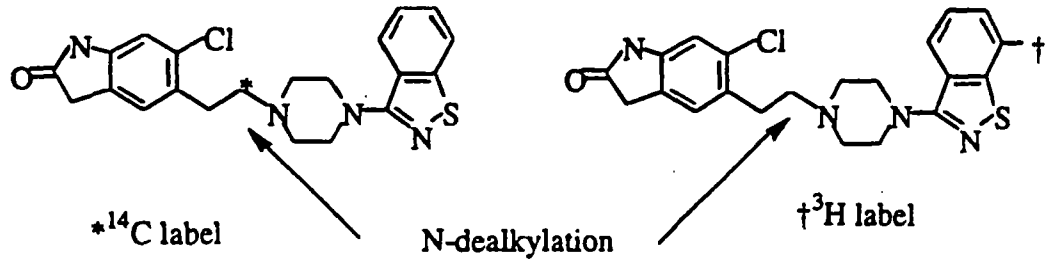
All four subjects experienced treatment-emergent adverse events of mild to moderate severity, with 3 subjects having adverse events considered related to treatment. One subject had treatment-related asthenia of moderate severity, and mild dizziness and sweating. Two subjects experienced moderate treatment-related somnolence. No serious adverse events were reported.

In conclusion, ziprasidone undergoes extensive metabolism in humans, with approximately 3% excreted unchanged in the feces and less than 1% excreted unchanged in the urine.

1. INTRODUCTION

Previous results from a $^{14}C/^{3}H$-ziprasidone HCl (CP-88,059-1) study in healthy male volunteers (study 128-020) indicated that two out of four subjects had greater than 4% radioactivity still present in fecal samples collected at the last time point (approximately 168 hours after dosing). Additionally, two out of four subjects had less than 70% total radioactivity recovered in urine and feces (see Appendix II.A, Sub-appendix V). The possibility existed that these subjects had incomplete fecal/urine collections. It was for these reasons that study 120-020 was repeated, as described in this report.

Radiolabelled ziprasidone HCl was prepared by labeling the ethyl side chain of the piperazinyl 6-chlorooxindole portion of the molecule with ^{14}C and labeling the benzisothiazole portion of the molecule with ^{3}H. This was done because the hypothesized oxidation of the ethyl side chain could result in metabolic cleavage of the molecule:



$^{14}C/^{3}H$-ziprasidone HCl was prepared with a specific activity of 2.39 µCi/mg for ^{14}C and 4.517 µCi/mg for ^{3}H. The radiochemical purity of both radiolabels was ≥98%. Since a single 20 mg dose of ziprasidone was to be administered to normal, healthy male volunteers, a total of 47.8 µCi of ^{14}C and 90.3 µCi of ^{3}H was to be consumed by each volunteer.

2. STUDY OBJECTIVES

The objective of this study was to elucidate the ultimate routes of excretion and the metabolic profile of radiolabelled ziprasidone HCl in man.

3. MATERIALS AND METHODS

3.1 Study Design

This was an open, non-randomized, single group study to examine the metabolism and excretion of ziprasidone HCl (CP-88,059-1) after a single oral dose of $^{14}C/^{3}H$-ziprasidone HCl as a 20 mg suspension. Four healthy male subjects were to enter the study. Administered doses are expressed as mg equivalents of the free base. Each subject was to receive a single 20 mg dose of ziprasidone containing a total of 47.8 µCi of ^{14}C and 90.3 µCi of ^{3}H. Study drug was to be administered under

fed conditions. The study had institutional review board approval and all subjects provided written informed consent.

Subjects were to fast for eight hours prior to consuming a standard breakfast (two eggs fried in butter, two strips of bacon, six ounces of hash brown potatoes, two pieces of toast with two pats of butter, and eight ounces of whole milk). Caffeinated or decaffeinated beverages were not to be permitted. The standard breakfast was to be consumed over a 20 minute period. Ziprasidone suspension was then to be immediately administered. Subjects were to refrain from lying down (except for blood pressure assessments), eating, or drinking caffeinated beverages during the first four hours after dosing to standardize experimental conditions. Under no circumstances were subjects to be allowed to ambulate or stand unattended for at least six hours after study drug was administered.

Serum samples were to be collected immediately prior to and up to 168 hours, and if necessary, every 24 hours until two consecutive fecal samples had radioactivity levels less than 1% of total radioactivity, after drug administration. They were to be analyzed for ziprasidone concentrations, metabolites, and radioactivity. Serum concentrations of ziprasidone were to be used to estimate pharmacokinetic parameters.

Urine specimens were to be collected immediately prior to and up to 168 hours after drug administration, and if necessary, continuing in 24-hour intervals until two consecutive fecal samples had radioactivity levels less than 1% of total radioactivity. Fecal specimens were to be collected as passed from the time of dosing until 168 hours after dosing or until fecal samples had radioactivity levels that were less than 1% of total radioactivity, whichever was greater. Urine and feces were to be analyzed for metabolites and radioactivity.

Subjects were to be monitored for adverse events and changes in vital signs, and were to be confined to the clinical research facility under continuous medical or paramedical observation for at least 12 hours prior to dosing and until 168 hours following dosing or until fecal samples had radioactivity levels that were less than 1% of total radioactivity, whichever was greater. Each subject was to undergo a final physical examination upon completion of or discontinuation from the study. Subjects discontinuing from the study were to be replaced by a substitute, at the discretion of investigator and sponsor clinician, who was to repeat the entire study.

Further details of the study design and procedures used are given in the protocol (Appendix II.A).

3.2 Study Population

Four healthy male subjects were to enter the study. Prior to inclusion in the study, subjects were to undergo a full clinical examination, including a 12-lead resting electrocardiogram (ECG), and provide a complete medical history. Blood samples were to be collected for clinical chemistry and hematological analyses. A urine sample was to be obtained for urinalysis and drug screen. An ethanol breath test was

(6) 6

Table 5.1. Radiolabelled Mass Balance of Ziprasidone in Four Male Subjects After a Single 20 mg dose of [^{14}C]- and [^{3}H]-Ziprasidone HCl

Ziprasidone Protocol 027

Percentage of ^{3}H/^{14}C Excreted in Urine and Feces from 0-264 hours

	Urine			Feces			Unused Dose*			Total		
Patient ID	^{3}H	^{14}C	Average	^{3}H	^{14}C	Average	^{3}H	^{14}C	Average	^{3}H	^{14}C	Average
610-0001			21.1			68.0			1.4			90.5
610-0002			19.2			71.7			1.4			92.3
610-0003			21.3			65.5			1.2			88.0
610-0004			19.7			60.1			3.5			83.2
Mean	20.6	20.1	20.3	68.1	64.5	66.3	1.9	1.8	1.9	90.6	86.4	88.5
±SD	1.0	1.1	1.0	4.8	5.0	4.9	1.1	1.0	1.1	3.7	4.1	3.9

* Dose recovered in containers

Source Data: Appendix IV, Table 1

Table 5.2. Serum Pharmacokinetic Parameters of Ziprasidone and Total Radioactivity in Four Male Subjects After a Single 20 mg Dose of [^{3}H]-and [^{14}C]-Ziprasidone HCl Ziprasidone Protocol 027

Subject ID	Unchanged drug & Radioactivity	PK parameters*				
		AUC (0-∞) ng•hr/ml	Cmax ng/ml	Tmax hr	Kel 1/hr	T1/2 hr
610-0001	Ziprasidone 3H radioactivity 14C radioactivity Ziprasidone (%)					
610-0002	Ziprasidone 3H radioactivity 14C radioactivity Ziprasidone (%)					
610-0003	Ziprasidone 3H radioactivity 14C radioactivity Ziprasidone (%)					
610-0004	Ziprasidone 3H radioactivity 14C radioactivity Ziprasidone (%)					
Mean[a]±CV(%)	Ziprasidone	361.3±11.2	45.4±31.5	3.5±54.7	0.197±13.2	3.53
	3H radioactivity	876.6±15.9	94.5±26	5.5±18.2	0.153±10.9	4.52
	14C radioactivity	760.8±15.6	88.4±25	5.5±18.2	0.175±10.5	3.96
	Ziprasidone (%)	44.1±5.7	49.6±10			

* Cmax and AUC (0-∞) values for radioactivity are expressed as ng equiv/mL and ng equiv•hr/mL, respectively

[a] geometric mean for AUC (0-∞) and Cmax and average for Tmax and Kel and Mean T1/2=0.693/Mean Kel

Source Data: Appendix IV, Table 2

Table 5.3. Percentages of Urinary Metabolites of Ziprasidone in Human Subjects After Oral Administration of [^{3}H]- and [^{14}C]-Ziprasidone HCl
Ziprasidone Protocol 027

Peak #	Metabolite #	% of Radioactivity in Urine									
		610-0001		610-0002		610-0003		610-0004		Average	
		3H	14C	3H	14C	3H	14C	3H	14C	3H	14C
I	M1+M2*									4.64	0.00
II	M3A									0.00	26.74
III	M4									0.00	34.49
IV	M4A									0.00	1.85
V	M5+M6+M7*									7.61	8.06
VI	M8+M9+M10*									34.82	25.63
	Total	99.9	92.6	88.4	95.5	100.0	99.0	100.0	100.0	97.1	96.8

* not separated

Source Data: Appendix IV, Sub-appendix 2

Table 5.4. Percentages of Fecal Metabolites of Ziprasidone in Human Subjects After Oral Administration of [^{3}H]- and [^{14}C]-Ziprasidone HCl Ziprasidone Protocol 027

Peak #	Metabolite #	% of Radioactivity in Feces									
		610-0001		610-0002		610-0003		610-0004		Average	
		^{3}H	^{14}C	^{3}H	^{14}C	^{3}H	^{14}C	^{3}H	^{14}C	^{3}H	^{14}C
I	M9									95.22	94.96
II	M13 parent									4.78	5.05
	Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Source Data: Appendix IV, Sub-appendix 2

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(9)

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Table 5.5. Percentages of Serum Metabolites of Ziprasidone in Human Subjects After Oral Administration of [^{3}H]- and [^{14}C]-Ziprasidone HCl
Ziprasidone Protocol 027

Peak #	Metabolite #	% of Radioactivity in Serum									
		610-0001		610-0002		610-0003		610-0004		Average	
		^{3}H	^{14}C	^{3}H	^{14}C	^{3}H	^{14}C	^{3}H	^{14}C	^{3}H	^{14}C
I	M1										
II	M2										
III	M3									21.53**	0.00
IV	M3A									4.05	0.00
V	M4									0.00	3.40
VI	M4A									0.00	2.03
VII	M5+M6+M7‡									0.00	1.60
VIII	M8									4.75	3.99
IX	M9+M10‡									0.83	1.80
X	parent M13									14.43	17.60
										24.20	27.70
	Total	**82.4**	**75.1**	**83.0**	**57.5**	**55.7**	**47.8**	**58.0**	**52.0**	**69.8**	**58.1**

* % could not be determined
** Both M1+M2
‡ not separated

Source Data: Appendix IV, Sub-appendix 2

Table 5.6. Average Percentages of Metabolites of Ziprasidone in Human Subjects After Oral Administration of [^{3}H]- and [^{14}C]-Ziprasidone HCl
Ziprasidone Protocol 027

Peak #	Metabolite #	% of Dose					
		Urine[a]		Feces[b]		Total	
		3H	14C	3H	14C	3H	14C
I	M1+M2*	11.25	0.00	ND	ND	11.25	0.00
II	M3A	0.00	5.38	ND	ND	0.00	5.38
III	M4	0.00	6.93	ND	ND	0.00	6.93
IV	M4A	0.00	0.37	ND	ND	0.00	0.37
V	M5+M6+M7*	1.39	1.62	ND	ND	1.39	1.62
VI	M8+M9+M10*	7.17	5.15	64.85	61.25	72.02	66.40
parent	M13	0.00	0.00	3.25	3.25	3.25	3.25
	Total	**19.82**	**19.45**	**68.10**	**64.50**	**87.92**	**83.95**

* not separated on Only M9 was detected in feces
a; based on 20.6% (^{3}H) and 20.1% (^{14}C) recovery in urine
b; based on 68.1% (^{3}H) and 64.5% (^{14}C) recovery in feces

Source Data: Appendix IV, Table 1 and Sub-appendix 2

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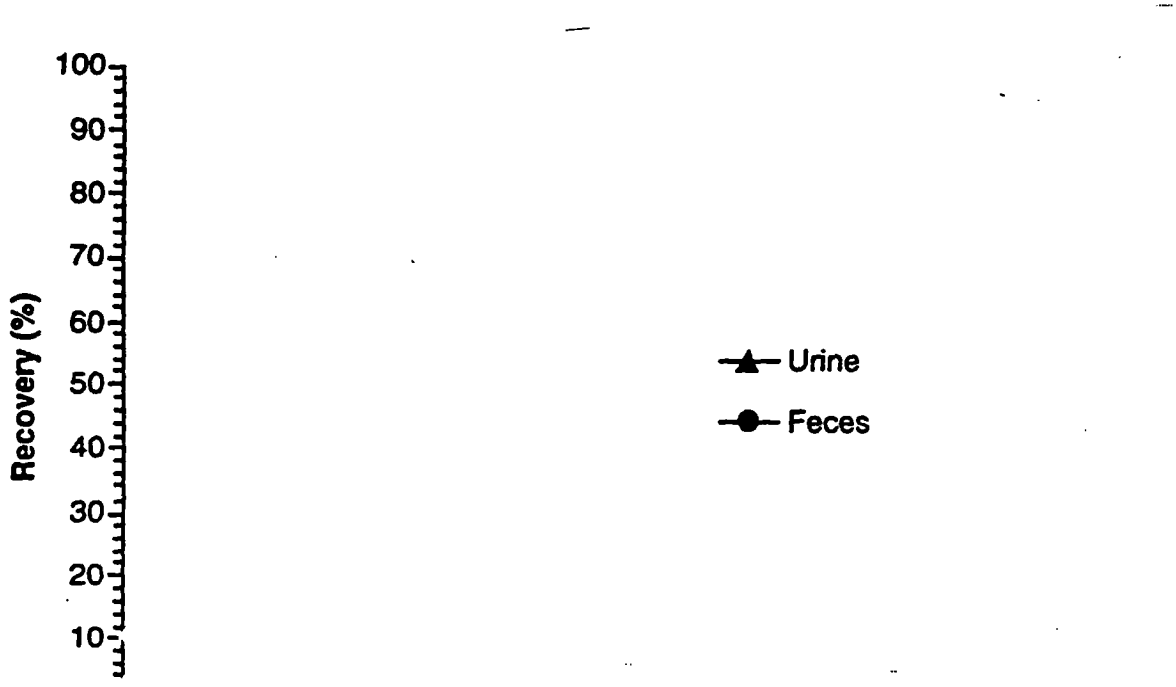

Figure 1. Cumulative Urinary and Fecal Excretion of Total Radioactivity in Male Volunteer (610-0001) After a Single 20 mg Oral Dose of [^{3}H]- and [^{14}C]- Ziprasidone HCl.

Ziprasidone Protocol 027

Source Data: Appendix IV, Table 1

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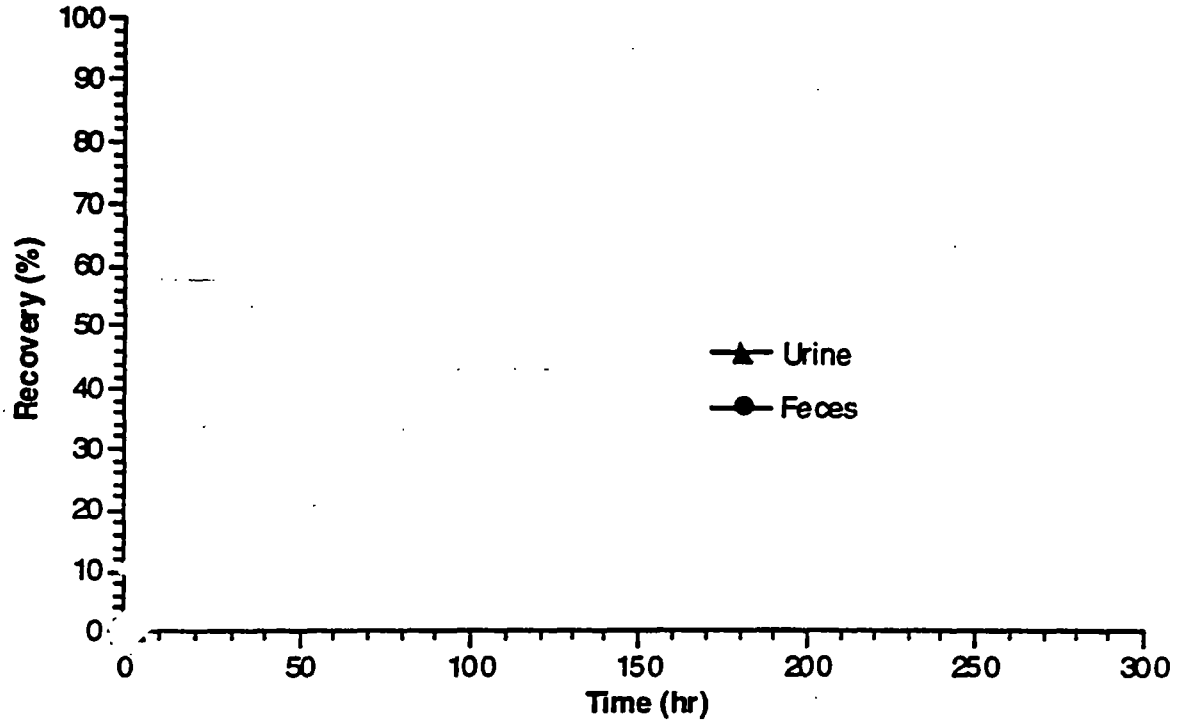

Figure 2. Cumulative Urinary and Fecal Excretion of Total Radioactivity in Male Volunteer (610-0002) After a Single 20 mg Oral Dose of [^{3}H]- and [^{14}C]- Ziprasidone HCl.

Ziprasidone Protocol 027

Source Data: Appendix IV, Table 1

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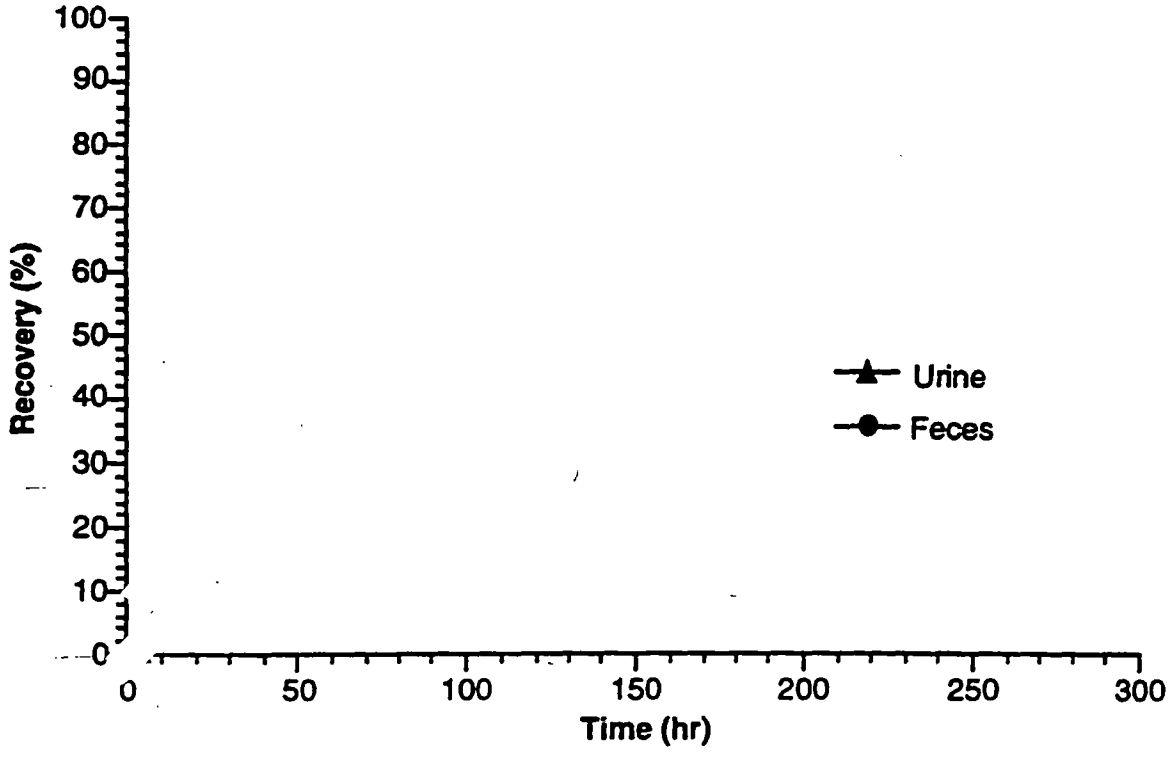

Figure 3. Cumulative Urinary and Fecal Excretion of Total Radioactivity in Male Volunteer (610-0003) After a Single 20 mg Oral Dose of [^{3}H]- and [^{14}C]- Ziprasidone HCl.

Ziprasidone Protocol 027

Source Data: Appendix IV, Table 1

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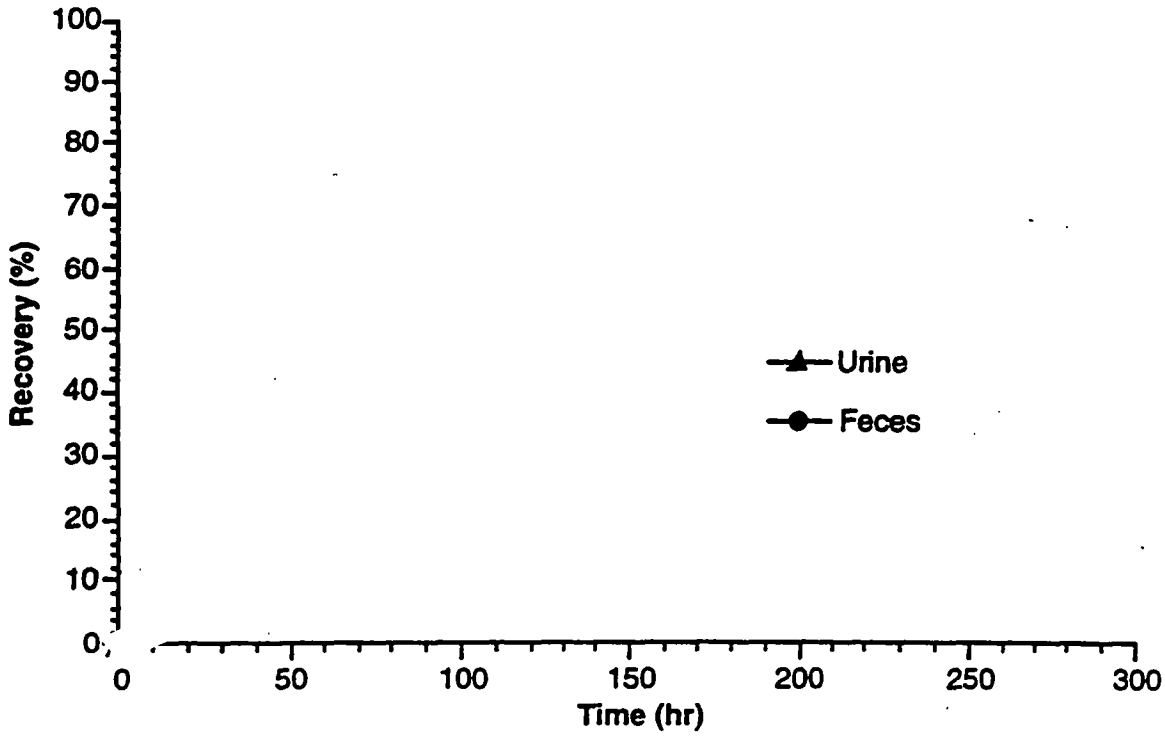

Figure 4. Cumulative Urinary and Fecal Excretion of Total Radioactivity in Male Volunteer (610-0004) After a Single 20 mg Oral Dose of [^{3}H]- and [^{14}C]- Ziprasidone HCl.

Ziprasidone Protocol 027

Source Data: Appendix IV, Table 1

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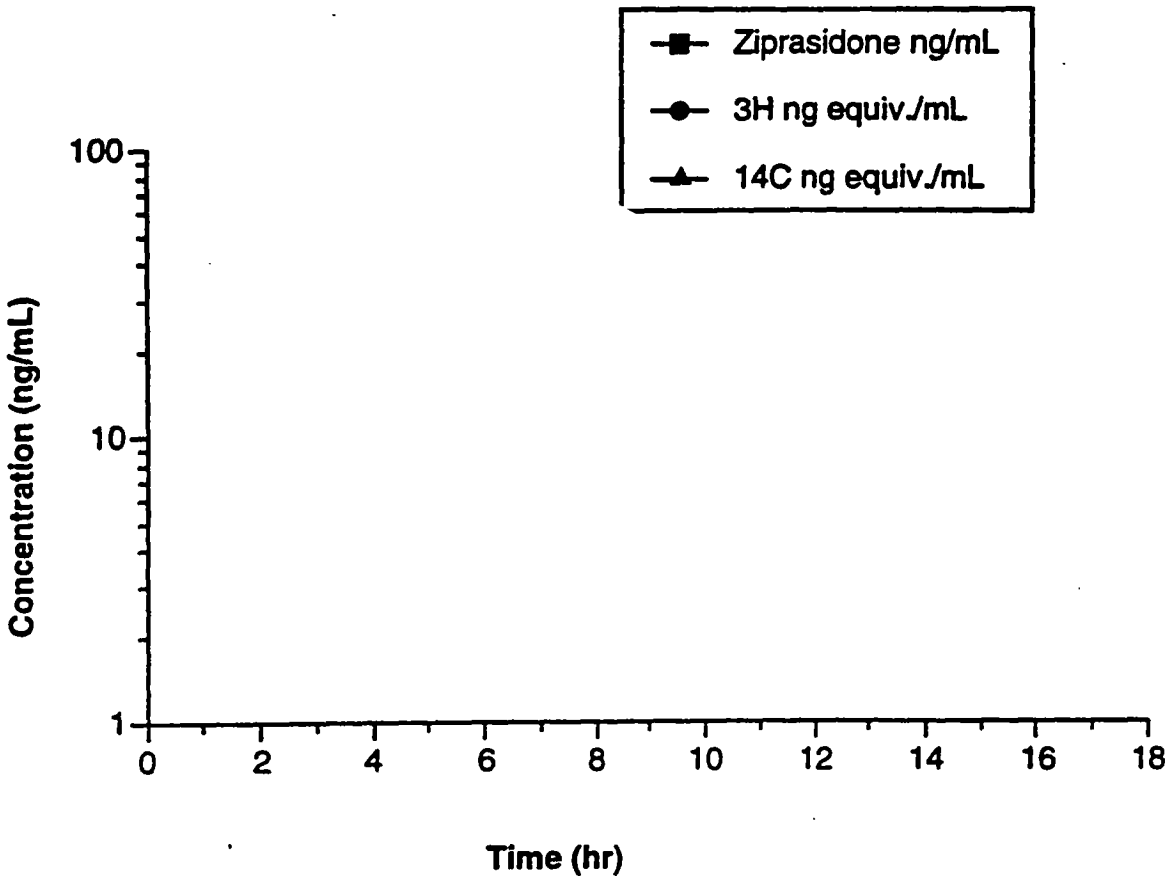

Figure 5. Serum Concentrations of Total Radioactivity and Ziprasidone in Male Volunteer (610-0001).

Ziprasidone Protocol 027

Source Data: Appendix IV, Table 2

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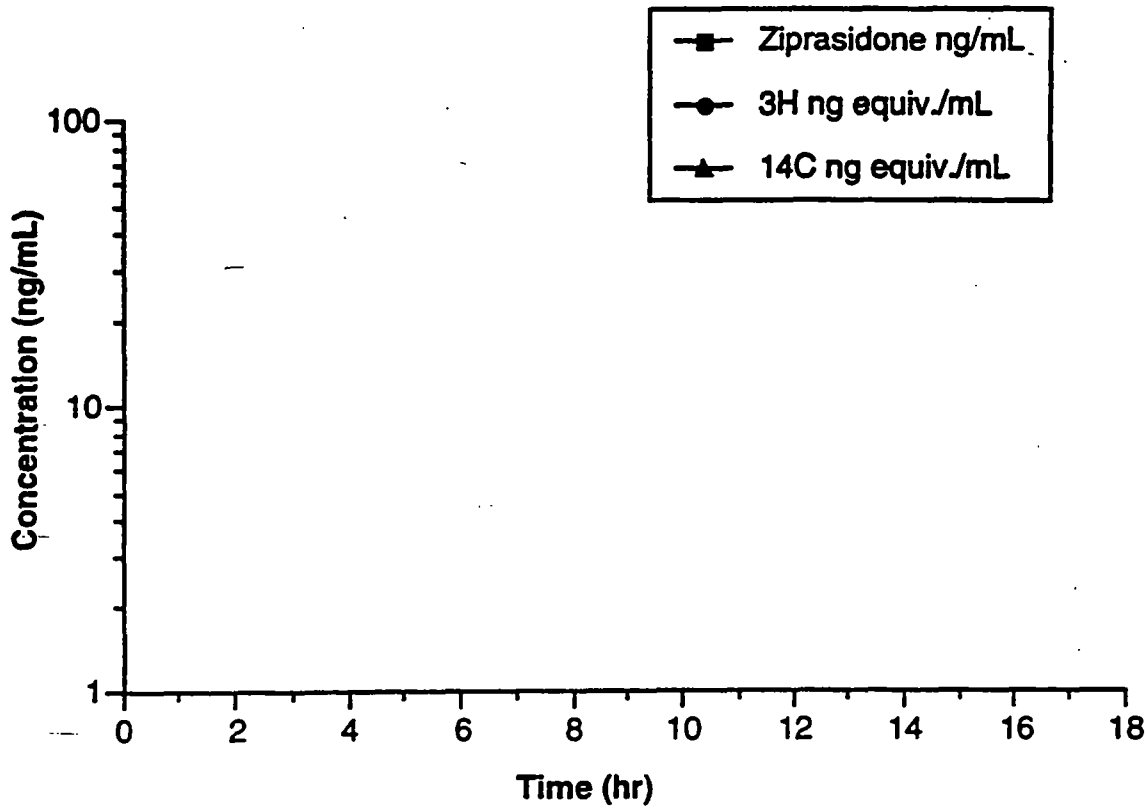

Figure 6. Serum Concentrations of Total Radioactivity and Ziprasidone in Male Volunteer (610-0002).

Ziprasidone Protocol 027

Source Data: Appendix IV, Table 2

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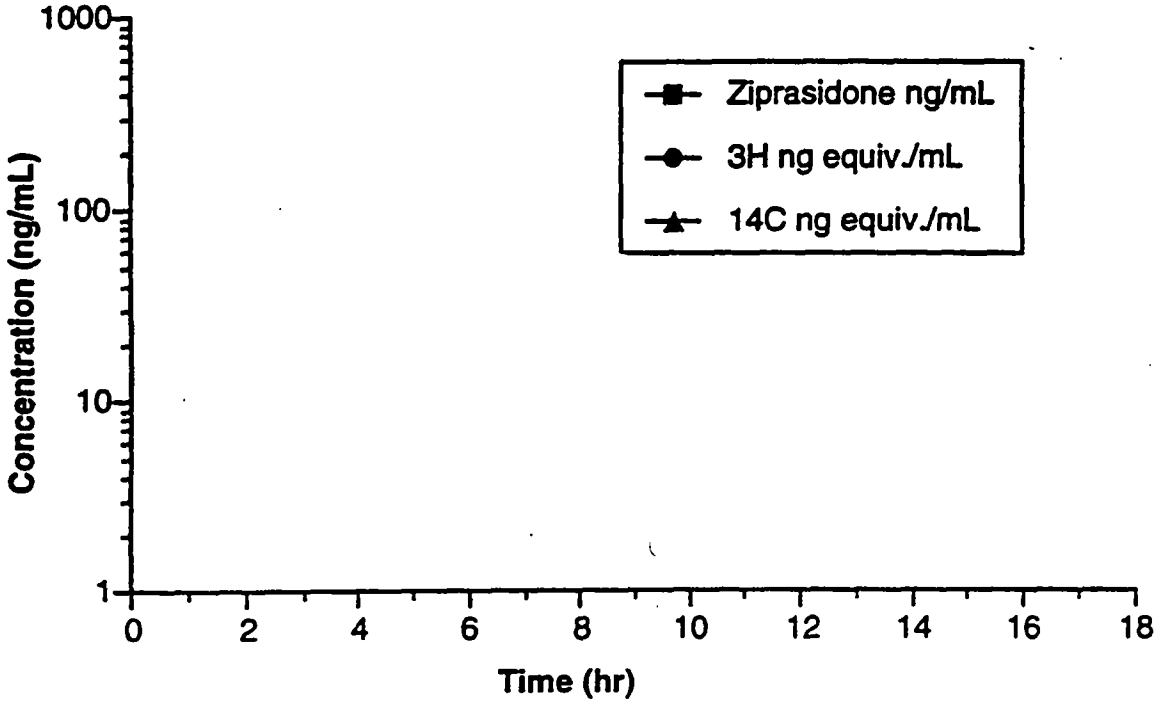

Figure 7. Serum Concentrations of Total Radioactivity and Ziprasidone in Male Volunteer (610-0003).

Ziprasidone Protocol 027

Source Data: Appendix IV, Table 2

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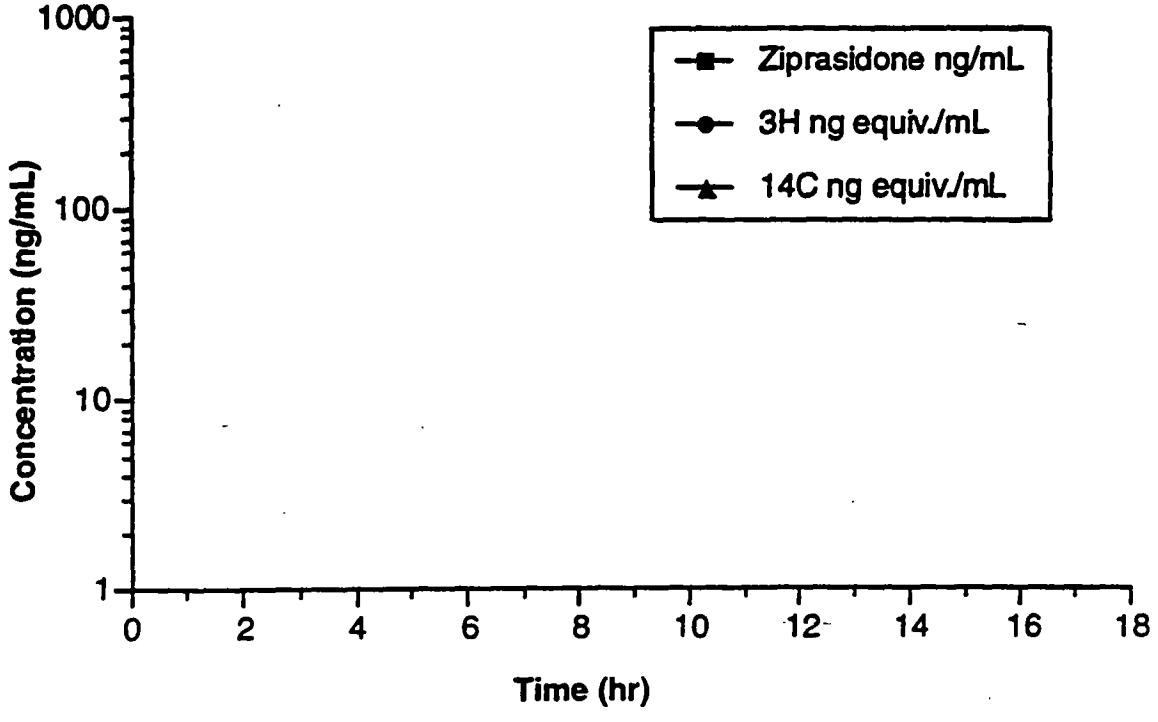

Figure 8. Serum Concentrations of Total Radioactivity and Ziprasidone in Male Volunteer (610-0004).

Ziprasidone Protocol 027

Source Data: Appendix IV, Table 2

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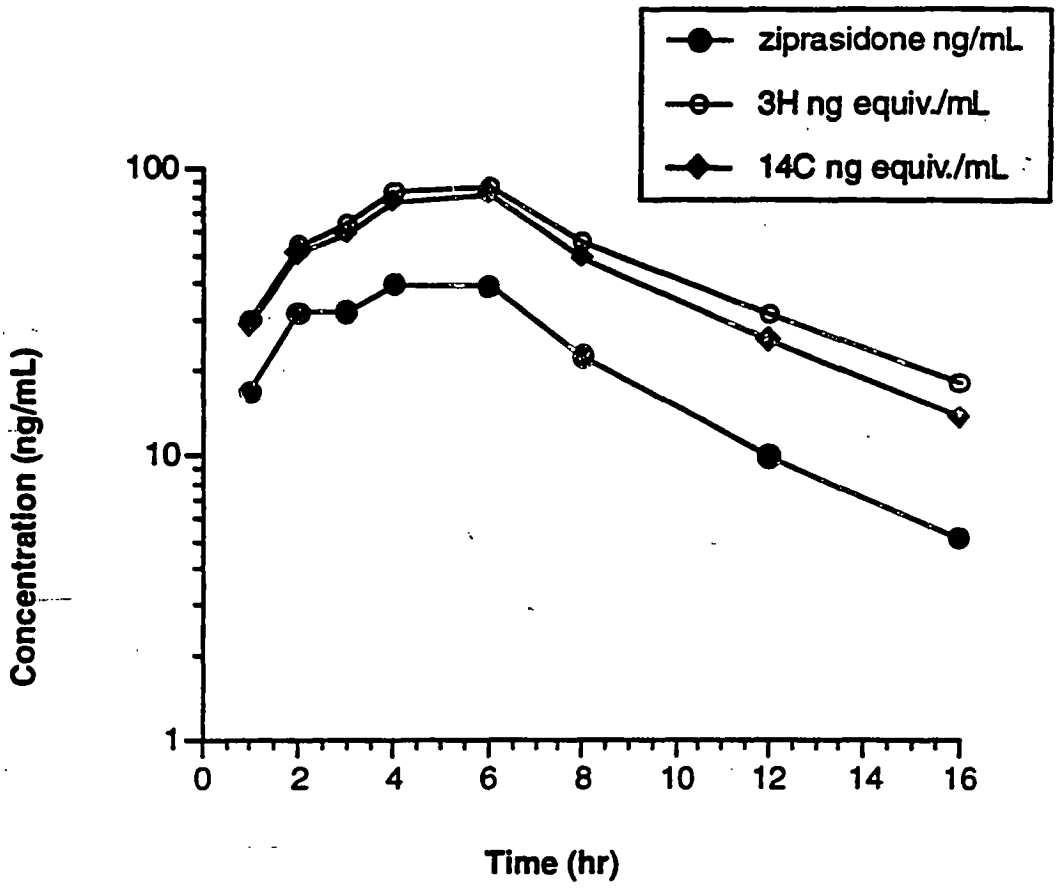


Figure 9. Mean Serum Concentrations of Total Radioactivity and Ziprasidone in Male Volunteers.

Ziprasidone Protocol 027

Source Data: Appendix IV, Table 2

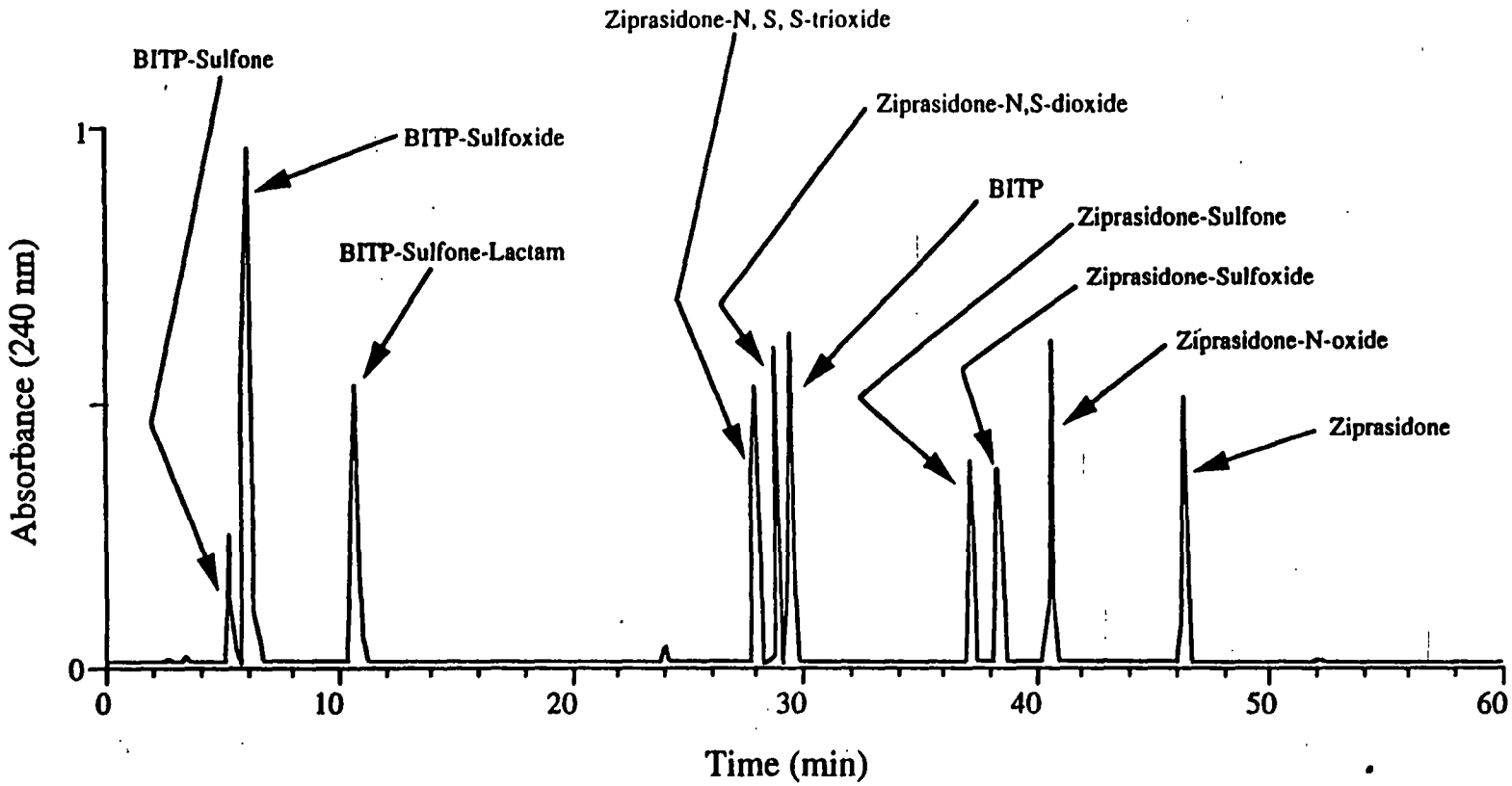
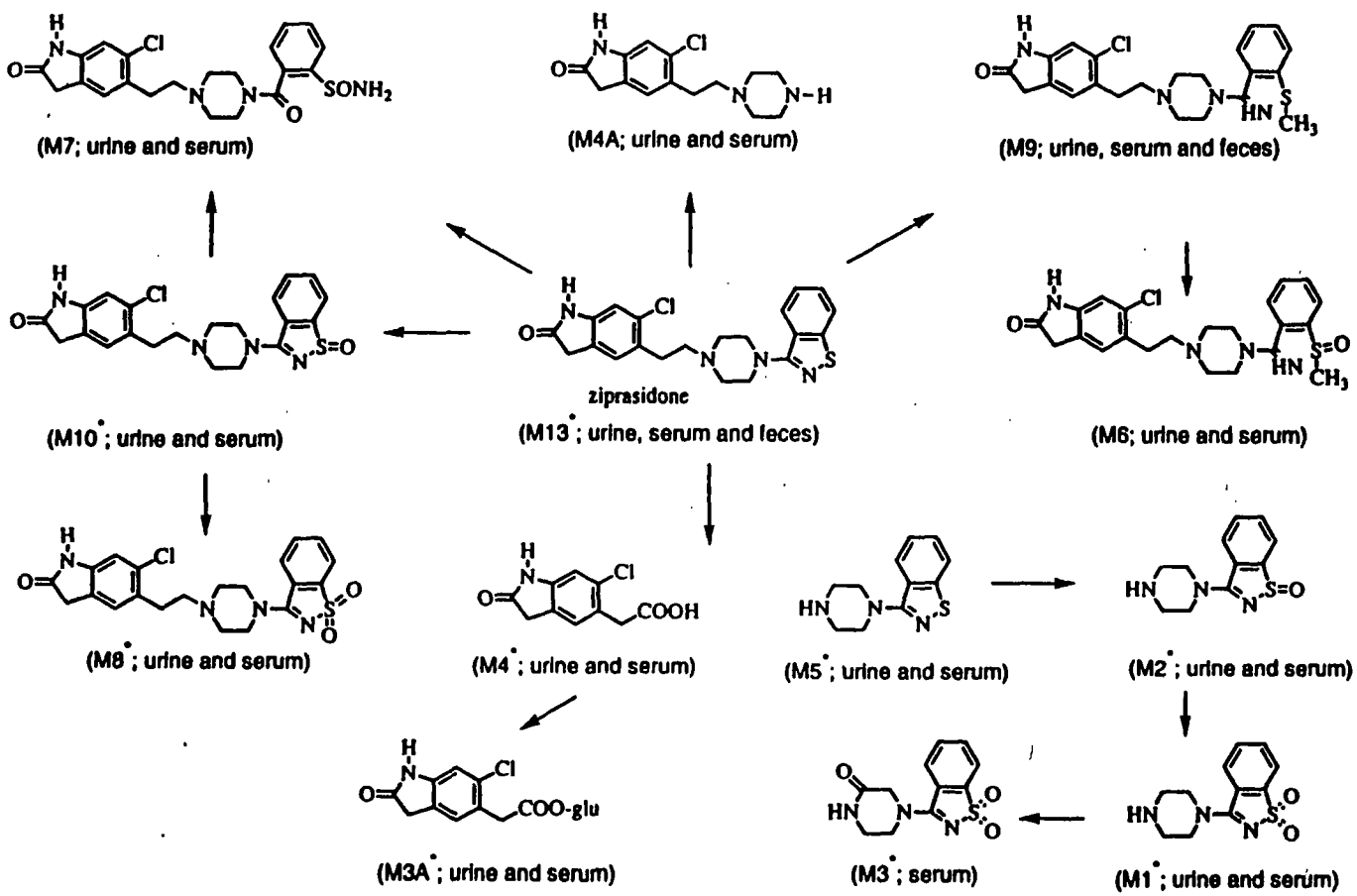


Figure10. a Standard Mixture of Ziprasidone and Its Synthetic Metabolites

Ziprasidone Protocol 027
Source Data: Appendix IV, Sub-appendix II



• Metabolites confirmed by comparing with synthetic standards

Figure 11. Proposed Routes for the Biotransformation of Ziprasidone in Man

Ziprasidone Protocol 027
Source Data: Appendix IV, Sub-appendix 2 and 3

Study DM-95-128-20: (Mass Balance in humans- ^{3}H and ^{14}C-single 20 mg PO dose)

Study Design and Summary:

(see attachment 1)

Results:

(See attachments 4-6)

Reviewer's Comments:

1. As shown in attachment 2, the drug undergoes extensive metabolism with the production of 13 metabolites.

2. The major routes of the metabolism are (attachment 2):

    a. N-dealkylation of ethyl side chain attached to piperazinyl nitrogen (M4 and M5). The M5 metabolite formed sulfoxides (M2), sulfone (M1) and M4 metabolite was conjugated to form glucuronide (M3A).

    b. Oxidation at sulfur to form ziprasidone-sulfoxide and ziprasidone sulfone (M10 and M8).

3. In serum, most of the recovered radioactivity was for M2 (22%) and a combination of M9 and M10 (15%). However, about 25% were for the intact ziprasidone, which constitute about half of the total radioactivity in serum (attachment 3).

4. The percent of radioactivity in urine for the metabolites was highest for the combination of M1 and M2 (55%) followed by M4 (35%). The total radioactivity for urinary metabolites was fully recovered (attachment 4).

5. In feces, most of the recovered radioactivity was for M9 metabolite (95%). (attachment 5)

6. Several metabolites were found in urine, but only few in feces (mainly M9). The percentage of the metabolites found in urine and feces were about 30% and 63% of the dose, respectively (attachment 6).

Conclusions:

1. The drug is extensively metabolized, and most of the metabolites were clearly identified.

2. The major metabolites were sulfone and sulfoxide.

3. Several metabolites were found in urine, but only few in feces.

4. In serum, the concentration of the parent drug, ziprasidone, was about 50% of the metabolites.

(1)

Identification of Metabolites in Urine, Feces and Serum of Human subjects After Oral Administration of [^{3}H]- and [^{14}C]-labeled CP-88,059-1 (protocol # 128-027-610)

(Study # DM-95-128-20)

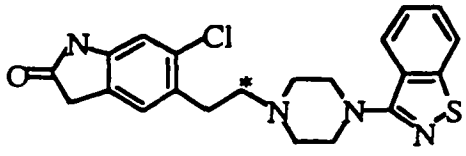
Purpose

To identify the metabolites of CP-88,059 in humans after oral administration of [^{3}H]- and [^{14}C]-labeled CP-88,059-1.

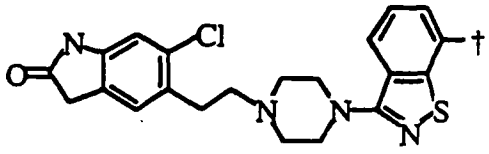
Materials and Methods

1. General

A mixture of [^{3}H]- and [^{14}C]-labeled CP-88,059-1 (HCl salt, Lot # ED-G-329-x93), specific activity 2.11 mCi for ^{3}H and 1.12 mCi for ^{14}C per mmol) was prepared by Dr. K. McCarthy. It showed a radio purity of 99%.



* ^{14}C-label



† ^{3}H-label

Four normal healthy male volunteers were confined to the Clinical Research Facility under continuous medical observation for 12 hr prior to dosing and until 264 hr after dosing. CP-88,059-1 was administered as a 20 mg suspension in water containing a total of 47.8 µCi of ^{14}C and 90.3 µCi of ^{3}H. Drug was administered in an open fashion as a single oral dose in the morning following a standard meal. Subjects were fasted for eight hours prior to consuming a standard breakfast.

Urine, blood, and feces were collected by standard techniques from each subject (1). Blood samples were centrifuged and serum was transferred to clean tubes.

2. Extraction of metabolites from biological samples

Urine (3 ml, 0-24 hour) from each subject was centrifuged and supernatant was transferred to a clean tube and concentrated on a The residue was dissolved in 200 µl of mobile phase and an aliquot (80 µl) was injected on without further purification. Serum (5 ml, 0-8 hr) was diluted with 2x5 ml of acetonitrile and the precipitated protein was removed by centrifugation. The pellet was washed with an additional 2 ml of acetonitrile and both the supernatants were combined. The supernatant was concentrated, dissolved in 200 µl of mobile phase and an aliquot (80 µl) was injected on the

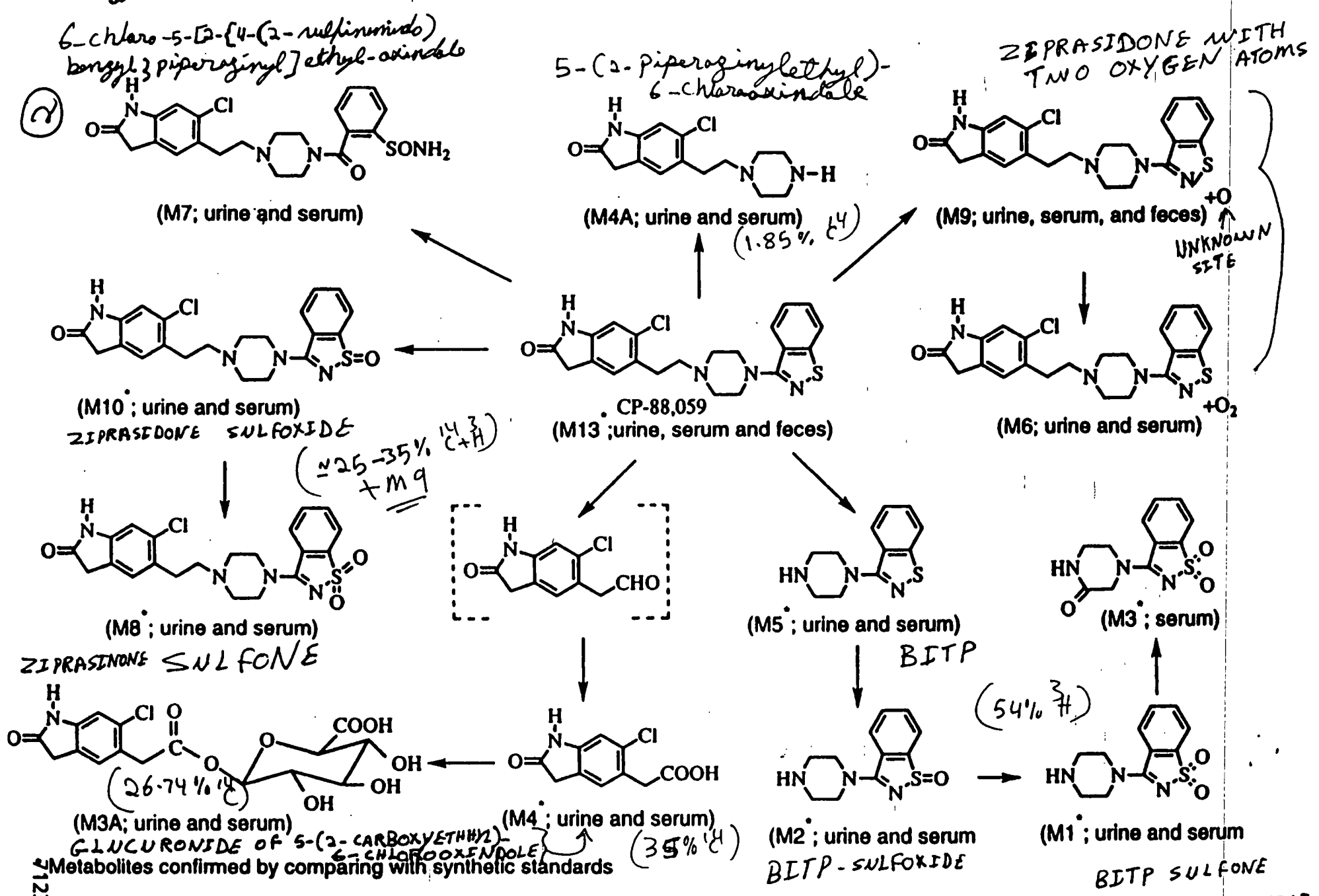


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Figure 33. Proposed routes for the biotransformation of CP-88,059 in man

In urine:-

M: M2 = 54% ^{3}H M4 = 35% ^{14}C M5+M1+M7 = 8% (^{14}C+^{3}H)

A: A = 27% ^{14}C M4A = 2% ^{14}C M8+ M10 = 27% (26-35%) ^{14}C+^{3}H

3

(3)

Table 3. Percentages of serum metabolites of CP-88,059-01 in human subjects after oral administration of [^{3}H]- and [^{14}C]-CP-88,059-01

Peak #	Metabolite #	% of Radioactivity in Serum									
		610-0001		610-0002		610-0003		610-0004		Average	
		^{3}H	^{14}C	^{3}H	^{14}C	^{3}H	^{14}C	^{3}H	^{14}C	^{3}H	^{14}C
I	M1										
II	M2									21.53**	0.00
III	M3									4.05	0.00
IV	M3A									0.00	3.40
V	M4									0.00	2.03
VI	M4A									0.00	1.60
VII	M5+M6+M7‡									4.75	3.99
VIII	M8									0.83	1.80
IX	M9+M10‡									14.43	17.60
X	parent M13									24.20	27.70
	Total	82.4	75.1	83.0	57.5	55.7	47.8	58.0	52.0	69.8	58.1

* % could not be determined
** Both M1+M2
‡ not separated on

Table 1. Percentages of urinary metabolites of CP-88,059 in human subjects after oral administration of [^{3}H]- and [^{14}C]-CP-88,059-01

Peak #	Metabolite #	% of Radioactivity in Urine									
		610-0001		610-0002		610-0003		610-0004		Average	
		3H	14C	3H	14C	3H	14C	3H	14C	3H	14C
I	M1+M2*									54.64	0.00
II	M3A									0.00	26.74
III	M4									0.00	34.49
IV	M4A									0.00	1.85
V	M5+M6+M7*									7.61	8.06
VI	M8+M9+M10*									34.82	25.63
	Total	**99.9**	**92.6**	**88.4**	**95.5**	**100.0**	**99.0**	**100.0**	**100.0**	**97.1**	**96.8**

* not separated on

Table 2. Percentages of fecal metabolites of CP-88,059-01 in human subjects after oral administration of [^{3}H]- and [^{14}C]-CP-88,059-01

Peak #	Metabolite #	% of Radioactivity in Feces									
		610-0001		610-0002		610-0003		610-0004		Average	
		^{3}H	^{14}C	^{3}H	^{14}C	^{3}H	^{14}C	^{3}H	^{14}C	^{3}H	^{14}C
I	M9									95.22	94.96
II	M13									4.78	5.05
	Total	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

b

(6) 6

Table 4. Percentages of metabolites of CP-88,059-01 in human subjects after oral administration of [^{3}H]- and [^{14}C]-CP-88,059-01

Metabolite	% of Dose[a]		
#	Urine[b]	Feces[c]	Total
M1+M2[d,e]	11.25	ND	11.25
M3A[f]	5.38	ND	5.38
M4[f]	6.93	ND	6.93
M4A[f]	0.37	ND	0.37
M5+M6+M7[e]	1.51	ND	1.51
M8+M9+M10[e]	6.16	63.05	69.21
parent M13	0.00	3.25	3.25

a; average of (^{3}H) and (^{14}C) labels.
b; based on 20.59% (^{3}H) and 20.07% (^{14}C) recovery.
c; based on 68.11 (^{3}H) and 64.52% (^{14}C) recovery.
d; only (^{3}H) label.
e; not separated on
f; only (^{14}C) label.

Study DM-95-128-19: (Mass Balance in humans- ^{3}H and ^{14}C-single 20 mg PO dose)

Study Design and Summary:

(see attachments 1 and 3)

Results:

(See attachments 4-8)

Reviewer's Comments:

1. Approximately 20 % of the radioactivity dose was recovered in urine which could reflect the percent of dose absorbed (attachment 4 and 5).

2. It appears that the fecal collection was incomplete due to two reasons:

    a. About 45% of the radioactivity was recovered in feces, making a total recovery of approximately 65% in urine and feces.

    b. The excretion of the radioactivity in feces has continued at a significant level for the last collection interval (see attachment 5 as a sample).

3. The AUC of the total radioactivity was approximately 50% higher than that of the ziprasidone (attachment 7 and 8).

Conclusions:

The complete mass-balance was not achieved in this study since there is approximately 20% of the radioactivity dose was not accounted for. Therefore, study # 128-027 should be considered instead.

Radiolabel Excretion, Circulating Radioactivity and Unchanged Drug in Humans After Oral Administration of [^{3}H]- and [^{14}C]-Labeled CP-88,059-1 (Protocol No. 128-020-5003)

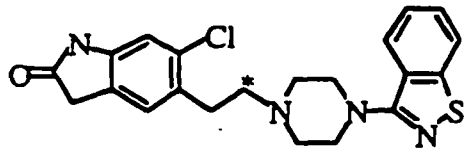
(Study # DM-95-128-19)

Purpose:

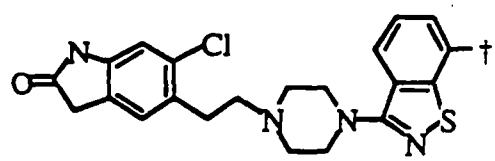
To determine the radiolabelled mass balance and routes of excretion of CP-88,059, and to compare total radioactivity versus unchanged drug level in serum of normal healthy male volunteers after a single 20 mg oral dose of a mixture of [^{3}H]- and [^{14}C]-labeled CP-88,059-1.

Materials and Methods:

A mixture of [^{3}H]- and [^{14}C]-labeled CP-88,059-1 (HCl salt, Lot # 24469-101, specific activity 2.26 mCi for ^{3}H and 1.13 mCi for ^{14}C per mmol) was prepared by Dr. K. McCarthy. It had a radio purity of 99%.



* ^{14}C-label



† ^{3}H-label

Four normal healthy male volunteers were confined to the Clinical Research Facility under continuous medical observation for 12 hr prior dosing and until 168 hr after dosing. CP-88,059-1 was administered as a 20 mg suspension in water containing a total of 48.6 µCi of ^{14}C and 96.9 µCi of ^{3}H. Drug was administered in an open fashion as a single oral dose in the morning following a standard meal. Subjects were fasted for eight hours prior to consuming a standard breakfast.

Urine was quantitatively collected from each subject for seven days (168 HPD) at 0-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours post dose. Feces were collected as passed from time of dosing until 168 hours after dosing. The weight of urine and fecal samples was recorded.

Blood was collected in tubes containing no preservatives, anticoagulant, or serum separator at the following times: 0 (just prior to dosing), 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96 and 120 hours after drug administration. Blood was centrifuged within 1 hour after collection and the serum was transferred to clean tubes.

Quantification of total radioactivity in urine, and serum was determined by counting sample aliquots (. µL, in triplicate) in a

counter utilizing a "dual-label" $^{3}H/^{14}C$ program.) was used for determination of radioactivity in the samples. were employed for determination of counting efficiencies for ^{3}H and ^{14}C.

Fecal samples were placed in and homogenized in water to a thick slurry using a Small aliquots (200 - 400 mg) were combusted using a Liberated $^{14}CO_2$ and $^{3}H_2O$ were trapped and the radioactivity in the trapped samples was determined by analysis. were used for ^{3}H and ^{14}C, respectively. Combustion efficiencies were determined by combustion of [^{14}C]- and [^{3}H]-standards in an identical manner.

Serum concentrations of unchanged CP-88,059 were determined by a validated (1). Pharmacokinetic parameters were determined using the , group procedure for The areas under CP-88,059 or total radioactivity serum concentration-time curves (AUC) were calculated from serum concentrations of CP-88,059 and total radioactivity using a trapezoidal approximation of area, using zero as the time zero concentrations. T_{max} was the time of the first occurrence of the maximal serum concentration (C_{max}).

Results:

The percentage of radioactivity excreted in urine and feces following administration of [^{3}H]- and [^{14}C]-CP-88,059-1 is shown in Table 1. The total radioactivity recovered from 0-168 hours post dose is summarized in Table 2. Separate plots for the cumulative recovery of the radioactivity, from 0-168 hours, in urine and feces of individual subject are shown in Figures 1-4.

Approximately, 68±9% of radioactive dose (average of ^{3}H and ^{14}C) was recovered in urine and feces (Table 2). The percentage of the radioactive dose excreted in urine and feces was 21±3 and 47±11%, respectively. Of all the radioactivity recovered in urine and feces, approximately 80 and 28% was excreted in the first 48 hours, respectively.

Serum concentrations of CP-88,059 are shown in Table 3 for all subjects. The total radioactivity in serum, expressed as ng equiv/mL, is also shown in Table 3. The profiles of total radioactivity vs unchanged CP-88,059 in the serum of individual subjects after administration of a 20 mg dose of [^{3}H]- and [^{14}C]-CP-88,059-1 at different time intervals are shown in Figures 5-8. The pharmacokinetic parameters for CP-88,059 and the total radioactivity are shown in Table 4. Absorption of CP-88,059 was rapid, as indicated by the early appearance of radioactivity in serum after oral administration. After a single oral dose of [^{3}H]- and [^{14}C]-CP-88,059-1, total serum radioactivity reached a peak concentration within 2-4 hr (Table 4). The mean serum concentration of unchanged drug reached a peak of 54 ng equiv./mL at approximately 4 hours post dose (Table 4). Based on area under the serum

concentration time curves (0-∞), approximately 54% of the circulating radioactivity (average of ^{3}H and ^{14}C) was attributable to unchanged drug.

Interpretation:

Sixty eight (68%) of the administered dose was recovered in the urine and feces of human subjects. The total amount excreted in urine was 21%. The urinary recovery of the dose was similar to total recovery in bile and urine of Beagle dogs suggesting that at least 21% drug was absorbed in human. The results indicated that two out of four subjects had greater than 5% radioactivity still present in fecal samples collected at the last time point. It is possible that these subjects may have had incomplete urine/fecal collections.

$AUC_{0-\infty}$ values of the unchanged drug and radiolabelled material were similar in three subjects. One subject had lower AUC value for unchanged drug and total radioactivity. Based on area under the serum concentration curves (0-∞), approximately 46% of the circulating radioactivity (average of ^{3}H and ^{14}C) was attributable to metabolites.

References:

1. Drug Metabolism Report: Study # DM-91-128-23.

Table 2. Radiolabelled mass balance of CP-88,059 in four male subjects after a single 20 mg dose of [^{14}C]- and [^{3}H]-CP-88,059-1

Percentage of ^{3}H/^{14} excreted in urine and feces from 0-168 hours

Subject ID	Urine ^{3}H	Urine ^{14}C	Feces ^{3}H	Feces ^{14}C	Total ^{3}H	Total ^{14}C
5003-0001					57.9	
5003-0002						
5003-0003						
5003-0004						
Average	19.6	21.8	44.1	49.6	63.6	71.4
±SD	3.1	3.5	10.0	11.6	8.4	9.6

(5)

(5)

Table 1. Percentage of radioactivity excreted in urine and feces from four male subjects after a single 20 mg dose of [^{14}C] and [^{3}H]-CP-88,059-1

Subject ID	HPD	Urine ^{3}H Recovery (%)	Urine ^{14}C Recovery (%)	HPD	Feces ^{3}H Recovery (%)	Feces ^{14}C Recovery (%)
5003-0001						
	Total	**18.5**	**20.4**	**Total**	**39.4**	**44.6**
5003-0002						
	Total	**21.1**	**23.2**	**Total**	**50.7**	**57.2**
5003-0003						
	Total	**22.9**	**25.7**	**Total**	**32.3**	**35.7**
5003-0004						
	Total	**15.9**	**17.7**	**Total**	**53.8**	**61.0**

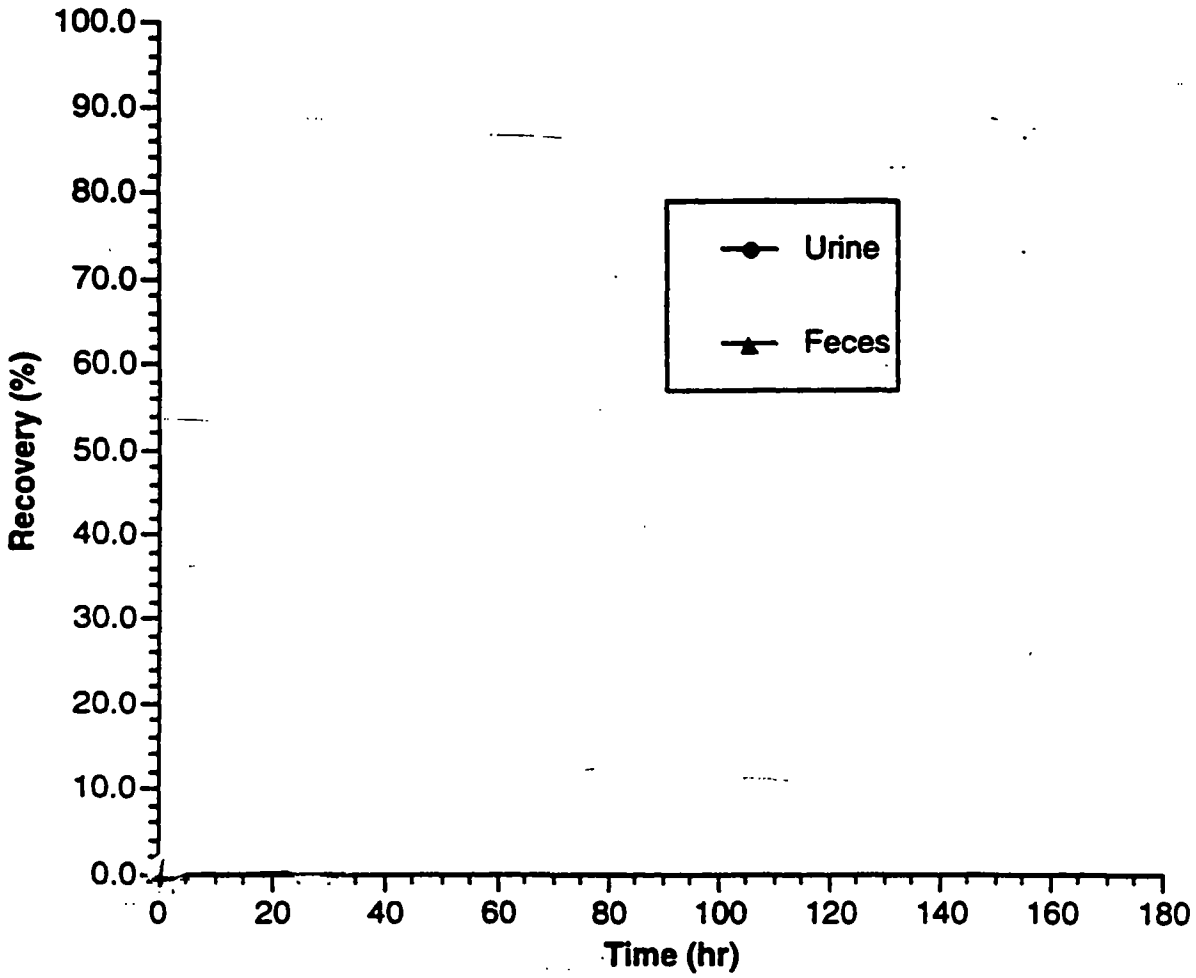


Figure 1. Cumulative urinary and fecal excretion of total radioactivity in male volunteer (5003-0001) after a single 20 mg oral dose of [^{3}H]- and [^{14}C]- CP-88,059-1.

(6) (7)

Table 4. Serum pharmacokinetic parameters of CP-88,059 and total radioactivity in four male subjects after a single 20 mg dose of [^{3}H]-and [^{14}C]-CP-88,059-1.

Subject ID	Unchanged drug & Radioactivity	PK parameters* AUC (0-∞) ng•hr/ml	Cmax ng/ml	Tmax (hr)	Kel (1/hr)	T1/2 (hr)
5003-0001	Ziprasidone					
	^{3}H radioactivity					
	^{14}C radioactivity					
	Ziprasidone (%)					
5003-0002	Ziprasidone					
	^{3}H radioactivity					
	^{14}C radioactivity					
	Ziprasidone (%)					
5003-0003	Ziprasidone					
	^{3}H radioactivity					
	^{14}C radioactivity					
	Ziprasidone (%)					
5003-0004	Ziprasidone					
	^{3}H radioactivity					
	^{14}C radioactivity					
	Ziprasidone (%)					
Mean[a]±CV(%)	Ziprasidone	488±30.6	53.8±28.9	3.50±16.7	0.166±19.3	4.17
	^{3}H radioactivity	931±27.8	75.1±30.2	3.25±30.6	0.103±13.9	6.73
	^{14}C radioactivity	871±32.1	83.6±27.2	3.75±13.4	0.126±17.2	5.50
	Ziprasidone (%)	54.1±16.9	67.8±18.6			

* Cmax and AUC (0-∞) values for radioactivity are expressed as ng equiv./mL and ng equiv.•hr/mL, respectively

[a] geometric mean for AUC (0-∞) and Cmax and average for Tmax and Kel and MeanT1/2= 0.693/mean Kel

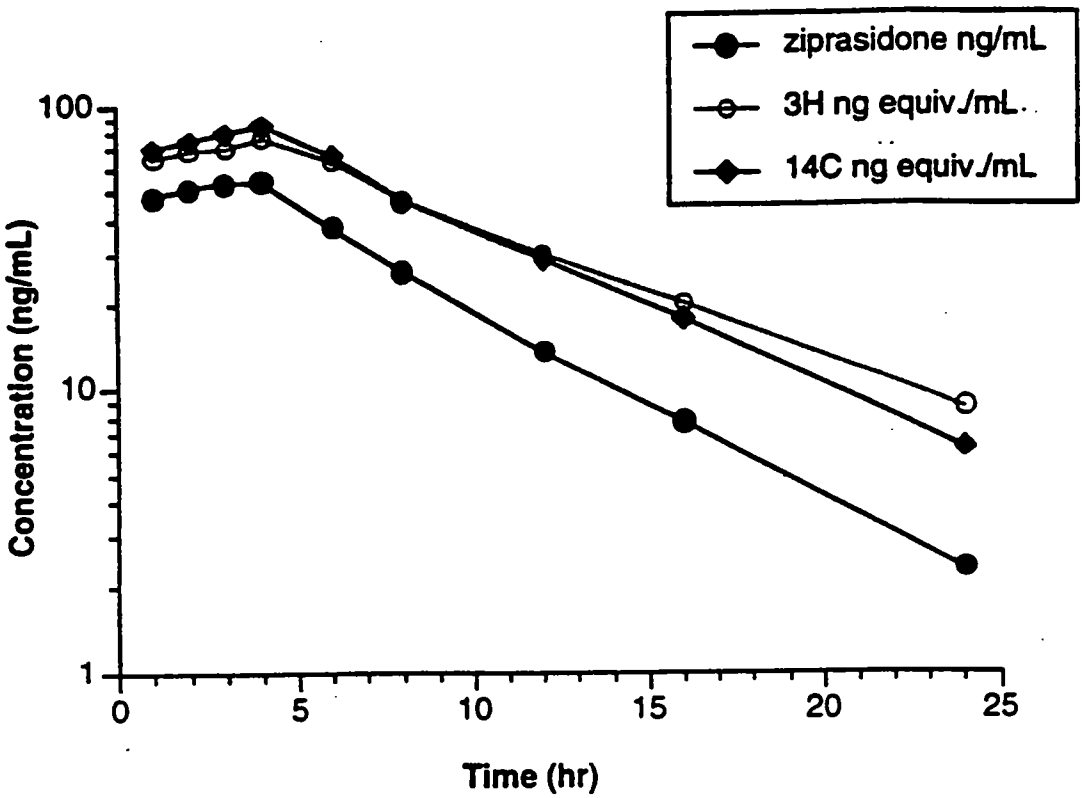


Figure 9. Mean serum concentrations of total radioactivity and CP-88,059 in male volunteers.

Study DM-95-128-29: (*In Vitro* Determination of Enzymes)

Study Design and Summary:

(see attachment 1-2)

Results:

(See attachments 3-8)

Reviewer's Comments:

1. The major metabolites were ziprasidone sulfoxide and sulfone (attachment 3). The formulation of these metabolites was non-linear (attachment 4). An additional metabolite was ziprasidone-desethylene.

2. The formation of these metabolites is mediated by CYP3A4 and CYP2C19:

   For CYP3A4:

   a. Ketoconazole, a potent inhibitor of CYP34A, produced 77% inhibition of the formation of sulfone and sulfoxide (attachment 5). However, the formation of desethylene was not affected (attachment 6).

   b. The formation of ziprasidone-sulfoxide (sum of sulfoxide and sulfone) was significantly correlated ($r = 0.83$) with testosterone 6β-hydroxylation rate (attachment 7).

   For CYP2C19:

   a. The formation of ziprasidone-sulfoxide (sum of sulfoxide and sulfone) was significantly correlated ($r = 0.7$) with mephenytoin 4'-hydroxylation rate (attachment 8).

4. The Cmax of ziprasidone after 80 mg dose was approximately 250 ng/ml (0.5 μM) and the concentration used in this study (50 μM) was about 100 times higher than the Cmax. In addition, ketoconazole concentration was relatively high (10 μM).

3. There was a poor correlation for other tested enzymes such as CYP2D6, CYP2C9 and CYP1A2.

Conclusions:

1. The main enzymes responsible for the metabolism of ziprasidone, particularly, the formation of sulfone and sulfoxide, are CYP3A4 and CYP2C19.

2. The relevance of the data is questionable due to the high concentrations of the drugs used.

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Study DM-95-128-33: (*In Vitro* Characterization of CYP-Isozymes)

Study Design and Summary:

(see attachment 1-2)

Results:

(See attachments 3-4)

Reviewer's Comments:

1. Addition of ABT (1-aminobenzotriazole), a potent nonspecific CYP inhibitor, to ketoconazole, caused about 88% reduction in the oxidation of ziprasidone to form sulfone and sulfoxide (attachment 3). However, ketoconazole alone caused 80% reduction.

2. In addition, ketoconazole alone caused 100% reduction in N-dealkylation process to form M4 Metabolite.

3. CY2C9/10 was not involved in the formation of sulfone and sulfoxide (attachment 3). This is based on the low inhibitory effects produced on sulfaphenazole (for CYP2C9/10). However, furafylline produced about 50% inhibition of the N-dealkylation, suggesting CYP1A2 involvement, in addition to CYP3A4 (see above), in the formation of M4 metabolites (OX-ethyl-COOH).

4. It should be noted that the metabolism of ziprasidone was not inhibited, but rather increased by quinidine, a CYP2D6 inhibitor (attachment 3). The reason for this is not clear.

5. Attachment 4 shows the comparison between the microsome and the homogenate in the metabolism of ziprasidone. The formation of the sulfoxide was higher in the microsome compared to homogenate. In addition, the total percentage of all metabolites formed in the microsomes was higher than in the homogenate (48% vs 40%). However, the inhibition study was performed with homogenate.

Conclusions:

1. This study demonstrates that the metabolism of ziprasidone is mediated mainly by CYP3A4 and to some extent by CYP1A2.

2. As stated in the previous study (DM-95-128-29) the relevance of the data is questionable

since the concentrations used are too high.

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Study 026: (Renal Impairmentt):

Study Design and Summary:

(see attachments 1-4)

Results:

(See attachments 5-12)

Reviewer's Comment:

1. From the data shown in attachment 5, it is not clear as to why there is a significant increase by ~40% in both the Cmax and AUC on day 8, only in Group 2 (moderate renal impairment). In contrary, Group 3 (severe renal impairment) is expected to have higher AUC and greater drug accumulation than Group 1 and 2. No explanations were given by the sponsor. It should also be noted that in the sponsor letter dated October 30, 1997 to the reviewer indicates that the reason for these observations is unknown.

2. It should be noted that in hemodialysis group, no evidence of drug adherence to the hemodialysis tubing was seen since the data is within the range seen in the rest of the group.

3. On day 8, the Cmaxs and AUCs are approximately 40% higher than on day 8 compared to day 1 in all groups. Based on these data drug accumulation does not seem to be of significance. However, accumulation may be greater after chronic use in subjects with low Clcr.

4. The study was conducted to measure only the parent drug in these groups of patients. However, this drug is extensively metabolized, and in renal failure, some of these metabolites may shunt off, and ultimately accumulate. It would be of great interest to conduct an additional study where "at least" the major metabolites are measured in this patient population.

5. Overall, it appears there is no clinically significant difference in the PK of this drug in these groups of renally impaired subjects.

Conclusions:

1. The PK of this drug is not significantly affected by the Clcr.

2. Based on this study, there is no significant drug accumulation.

PROTOCOL 128-026: PHASE I MULTIPLE DOSE OPEN STUDY DESIGNED TO EVALUATE THE EFFECTS OF VARYING DEGREES OF RENAL FUNCTION ON THE SAFETY AND DISPOSITION OF ORAL CP-88,059-1

Principal Investigators:

F. Aweeka, Pharm.D. M. Horton, Pharm.D. S. Swan, M.D.

Study Publication: None

Study Dates: 14 October 1994 - 19 October 1996

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

Study Design: This was an open, multicenter, multiple dose study evaluating the pharmacokinetics of ziprasidone (CP-88,059) in subjects with varying degrees of renal function. Four groups of subjects were studied:

Group 1: Subjects with creatinine clearance >70 ml/min. - sex, age, and weight of this group being matched as closely as possible to subjects in Groups 2 and 3.
Group 2: Subjects with creatinine clearance between 30 and 60 ml/min., inclusive.
Group 3: Subjects with creatinine clearance between 10 and 29 ml/min., inclusive.
Group 4: Subjects requiring hemodialysis - three times per week.

Subjects received ziprasidone 1 x 20 mg capsules orally BID for 7 days, and received a single 1 x 20 mg morning dose on day 8.

Evaluation Groups:

	Group 1	Group 2	Group 3	Group 4
Entered Study	10	9	11	9
Completed Study	9	9	10	8
Evaluated for Pharmacokinetics	9	9	9	9
Assessed for Safety				
Adverse Events	10	9	11	9
Laboratory Tests	10	9	11	9

Subjects: Male and female subjects with normal renal function or varying degrees of renal insufficiency, ranging in age from 26 to 73 years.

Drug Administration:

Dosage Form	20 mg research capsule (FID #CS-90-031) (three subjects in Group 2 at center 723 received FID #QC2327 [20 mg commercial capsule])
Dosing	Ziprasidone 20 mg was administered twice daily, under fed conditions, for seven days (days 1-7) with a single morning dose on day 8. For subjects in Group 4, ziprasidone was administered four hours prior to hemodialysis on days 1 and 8.

Pharmacokinetic and Safety Evaluations: Blood samples for the determination of serum ziprasidone concentrations were collected immediately prior to and up to 12 hours following the morning dose on days 1 and 8. Additional serum samples were collected on day 8 from 18 to 96 hours after dosing. For subjects in Group 4, additional blood samples were collected 4 to 6 hours following dosing. Additional serum samples were collected prior to morning dosing on days 2, 3, 4, 5, and 7. For subjects in Group 4, serum samples were collected from 0.5 to 12 hours following the morning dose on day 7 (non-hemodialysis day). Serum concentrations were used to estimate pharmacokinetic parameters (AUC_{0-12}, C_{max}, T_{max}, K_{el}, and $T_{1/2}$). On day 8, a plasma sample was obtained from each subject prior to dosing for protein binding determinations (Fb). Subjects were monitored for adverse events, abnormal laboratory test results, and changes in vital signs and ECGs.

Analytical Methods:

Statistical Methods: An ANOVA was used to test for a renal group effect by using PROC GLM in SAS. A 5% level of significance was used to test for this effect. If a group effect was found to be significant, t-tests were then used to test for differences between each pair of renal function groups. A pairwise t-test comparing pre-(day 7) and post-hemodialysis (day 8) AUC_{0-12} values was used to examine if hemodialysis altered the pharmacokinetics of ziprasidone.

Pharmacokinetic Results:

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

Parameter	Group 1	Group 2	Group 3	Group 4
Screening CLcr (ml/min)	94.8 (13.7)	48.1 (23.6)	16.1 (31.1)	–
Day 1				
AUC_{0-12} (ng•hr/ml)[a]	272 (36)	370 (39)	250 (29)	297 (25)
C_{max} (ng/ml)[a]	47 (43)	61 (52)	41 (28)	50 (33)
T_{max} (hr)	5 (20)	6 (35)	5 (27)	5 (34)
Day 7[b]				
AUC_{0-12} (ng•hr/ml)[a]	–	–	–	334 (25)
C_{max} (ng/ml)[a]	–	–	–	51 (19)
T_{max} (hr)	–	–	–	4 (52)
Day 8				
AUC_{0-12} (ng•hr/ml)[a]	446 (33)	650 (27)	389 (29)	427 (43)
C_{max} (ng/ml)[a]	68 (38)	93 (30)	54 (30)	70 (41)
T_{max} (hr)	4 (31)	5 (24)	4 (35)	5 (17)
K_{el} (hr^{-1})	0.138 (32)	0.108 (39)	0.141 (36)	0.166 (40)
$T_{1/2}$ (hr)[c]	5.0	6.4	4.9	4.2
Fb (% bound)	99.88 (<1)	99.84 (<1)	99.87 (<1)	99.86 (<1)

[a]geometric mean and standard deviation
[b]non-hemodialysis day
[c]mean $T_{1/2}$ = ln 2/mean K_{el}

Safety Results:

Number of Subjects With/Evaluated For:	Group 1	Group 2	Group 3	Group 4
Adverse Events (All Causality)	10/10 (1)	9/9 (0)	11/11 (1)	9/9 (0)
Adverse Events (Treatment-emergent, treatment-related)	10/10 (1)	9/9 (0)	9/11 (1)	9/9 (0)
Clinically Significant Laboratory Test Abnormalities	6/10 (0)	6/9 (0)	11/11 (0)	9/9 (0)

() subjects discontinued

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 among the four renal function groups. By day 8, there was a 46 to 67% increase in mean AUC_{0-12}, and a 32 to 72% increase in mean C_{max}, in Group 2 compared to the other three groups. This led to a statistically significant difference among the four renal function groups for AUC_{0-12} and C_{max}, with Group 2 being statistically significantly different from the other three groups. There were no statistically significant differences in K_{el} and T_{max} among the four groups.

Based on AUC_{0-12} and C_{max} on days 7 (non-hemodialysis day) and 8 (hemodialysis day) for Group 4, hemodialysis did not have a clinically significant effect on the pharmacokinetics of ziprasidone. There was no statistically significant difference in percent plasma protein binding among the four treatment groups.

Three subjects discontinued from the study, two due to treatment-related adverse events (one subject with moderate drowsiness and orthostatic hypotension, and one subject with severe akathisia), and one for non-treatment-related reasons (subject was mugged). No serious adverse events were reported. All adverse events were of mild to moderate severity except for one incidence of severe non-treatment-related chest pain and one occurrence of severe treatment-related akathisia, both in Group 3. The most frequently reported adverse event in all four groups was treatment-related somnolence. Most of the clinically significant laboratory test abnormalities seen in Groups 2-4, including elevations in BUN and creatinine in particular, were a result of the subjects' underlying medical conditions. One subject in Group 3 had clinically significant elevations in SGOT and SGPT due to the onset of an acute hepatitis C infection which was considered non-treatment-related.

In summary, there were no statistically significant differences in the AUC_{0-12} and C_{max} of ziprasidone among subjects with normal renal function (Group 1) and those with moderate-to-severe impairment in renal function (Groups 3 and 4), suggesting that impaired renal function should not affect the pharmacokinetics of ziprasidone.

Attachment 1

(5)

Table 5.1.1 Summary of Ziprasidone Pharmacokinetic Parameters Following 20 mg BID Dosing
Ziprasidone 026

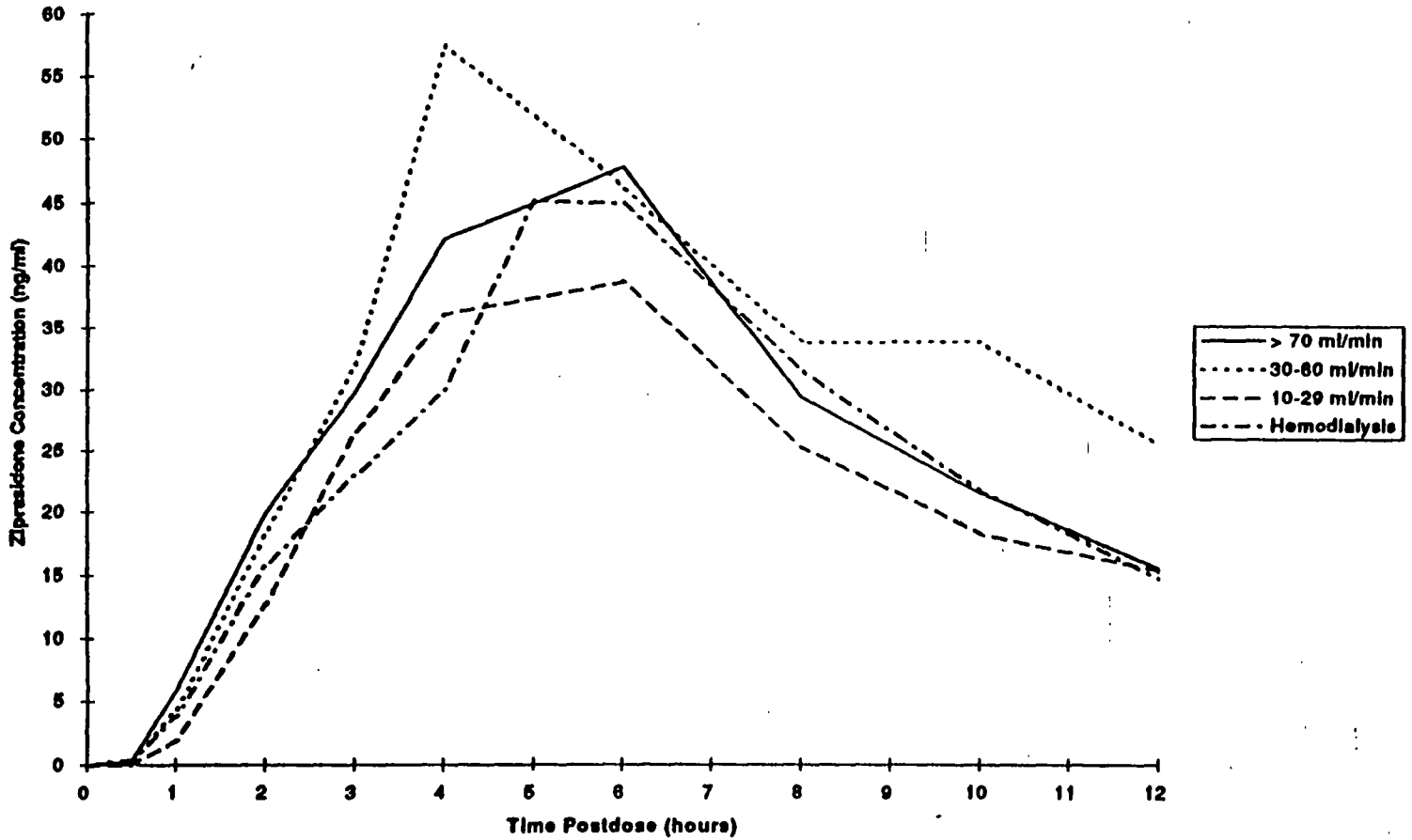
	CLcr	Day	AUC0-12 (ng•hr/ml)	Cmax (ng/ml)	Tmax (hr)	Kel (hr^{-1})	T1/2 (hr)	Fb (% bound)
Mean	> 70 ml/min	1	272[a]	47[a]	5			
S.D.			97	20	1			
CV%			36	43	20			
Mean	30-60 ml/min	1	370[a]	61[a]	6			
S.D.			145	32	2			
CV%			39	52	35			
Mean	10-29 ml/min	1	250[a]	41[a]	5			
S.D.			73	12	1			
CV%			29	28	27			
Mean	Hemodialysis	1	297[a]	50[a]	5			
S.D.			75	17	2			
CV%			25	33	34			
Mean	Hemodialysis[c]	7	334[a]	51[a]	4			
S.D.			84	10	2			
CV%			25	19	52			
Mean	> 70 ml/min	8	446[a]	68[a]	4	0.138	5.0[b]	99.88
S.D.			145	26	1	0.044		0.043
CV%			33	38	31	32		< 1
Mean	30-60 ml/min	8	650[a]	93[a]	5	0.108	6.4[b]	99.84
S.D.			174	28	2	0.042		0.152
CV%			27	30	54	39		< 1
Mean	10-29 ml/min	8	389[a]	54[a]	4	0.141	4.9[b]	99.87
S.D.			111	16	1	0.050		0.058
CV%			29	30	35	36		< 1
Mean	Hemodialysis	8	427[a]	70[a]	5	0.166	4.2[b]	99.86
S.D.			183	29	1	0.067		0.063
CV%			43	41	17	40		< 1

[a]Geometric mean and standard deviation
[b]Calculated as ln 2/mean Kel
[c]Non-dialysis day

Source Data: Appendix IV, Tables 1, 2, and 3; Appendix IV, Sub-appendix 2

(6) Attachment 7

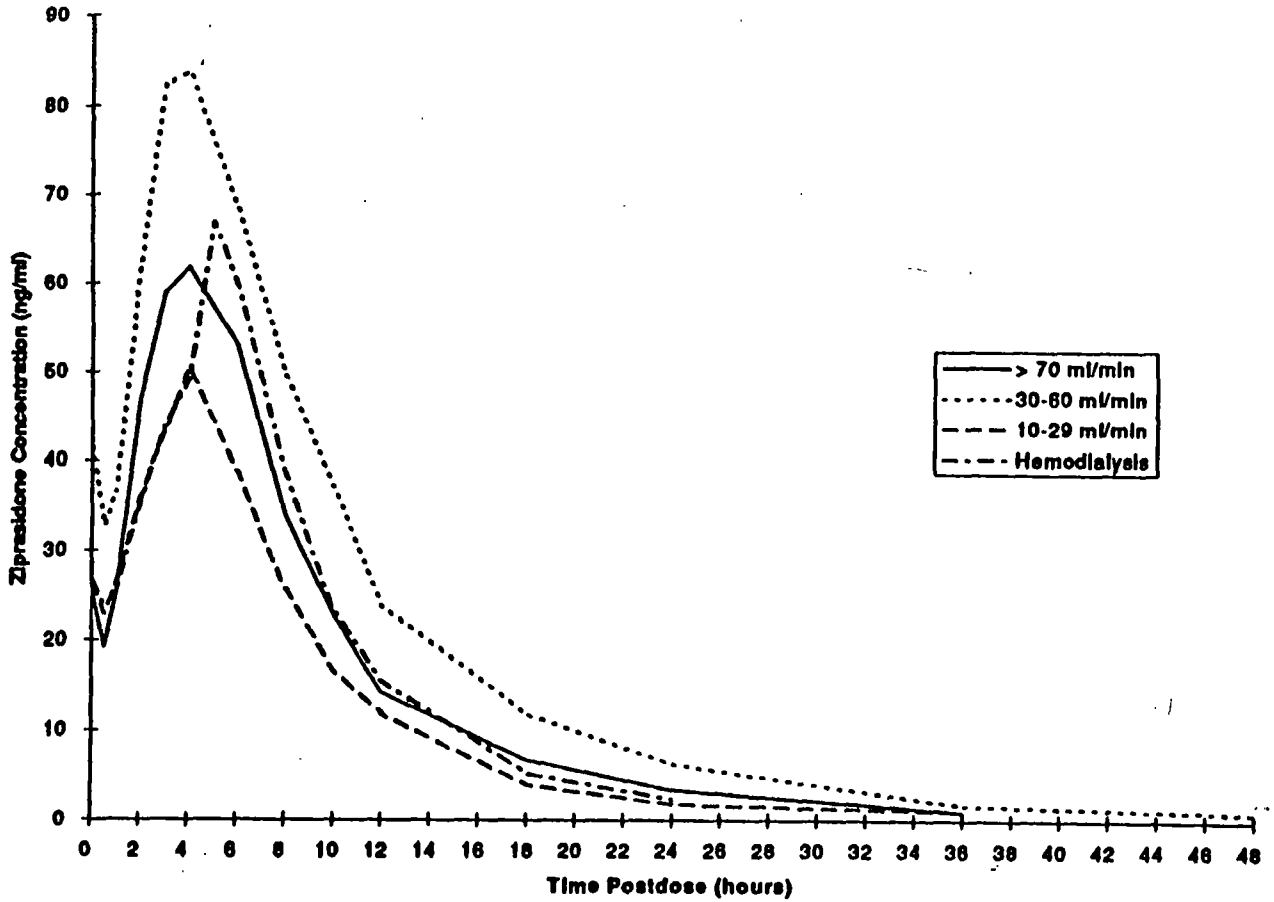
Figure 1.1 Mean Serum Ziprasidone Concentrations on Day 1 in Subjects with Varying Degrees of Renal Function
Ziprasidone 026



Source Data: Appendix IV, Table 1

(7) Attachment 8

Figure 1.2 Mean Serum Ziprasidone Concentrations on Day 8 in Subjects with Varying Degrees of Renal Function
Ziprasidone 026



Source Data: Appendix IV, Table 2