Table 1 (Cont.)
Summary of CP-88,059 Protein Binding Calculations

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

	Cpe (ng/ml)	Cbe (ng/ml)	Vpe (ml)	Vpi (ml)	Fb (Zip.) (%)
Propranolol Concentration: 0 ng/ml; CP-88,059 Concentration 400 ng/ml					
Human #1	207	0.185	1.43	1.00	99.94
	207	0.157	1.41	1.00	99.95
Average	207	0.171	1.42	1.00	99.95
Human #2	219	0.297	1.37	1.00	99.90
	214	0.218	1.39	1.00	99.93
Average	217	0.258	1.38	1.00	99.92
Human #3	212	0.200	1.34	1.00	99.93
	230	0.201	1.34	1.00	99.93
Average	221	0.201	1.34	1.00	99.93
Propranolol Concentration: 50 ng/ml; CP-88,059 Concentration 400 ng/ml					
Human #1	246	0.183	1.37	1.00	99.95
	243	0.196	1.38	1.00	99.94
Average	244	0.190	1.38	1.00	99.95
Human #2	248	0.164	1.38	1.00	99.95
	257	0.169	1.39	1.00	99.95
Average	252	0.167	1.39	1.00	99.95
Human #3	245	0.164	1.27	1.00	99.95
	258	0.183	1.33	1.00	99.95
Average	252	0.174	1.30	1.00	99.95
Propranolol Concentration:500 ng/ml; CP-88,059 Concentration:400 ng/ml					
Human #1	222	0.292	1.38	1.00	99.90
	235	0.284	1.41	1.00	99.91
Average	229	0.288	1.40	1.00	99.91
Human #2	219	0.298	1.35	1.00	99.90
	244	0.334	1.39	1.00	99.90
Average	231	0.316	1.37	1.00	99.90
Human #3	228	0.239	1.37	1.00	99.92

(7)

Table 2
Summary of CP-88,059 Protein Binding Calculations

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

CP-88,059 Concentration: 0 ng/ml; Warfarin Concentration: 7.4 µg/ml					
	DTe (DPM)	DF (DPM)	Vpe (ml)	Vpi (ml)	Fb (Warfarin) (%)
Human #1	22018	189	1.47	1.00	99.41
	20173	147	1.44	1.00	99.49
Average	21096	168	1.46	1.00	99.45
Human #2	25546	244	1.45	1.00	99.34
	24927	173	1.49	1.00	99.53
Average	25237	209	1.47	1.00	99.44
Human #3	26509	177	1.41	1.00	99.52
	30234	176	1.25	1.00	99.54
Average	28372	177	1.33	1.00	99.53

CP-88,059 Concentration: 200 ng/ml; Warfarin Concentration: 7.4 µg/ml					
	DTe (DPM)	DF (DPM)	Vpe (ml)	Vpi (ml)	Fb (Warfarin) (%)
Human #1	26915	167	1.48	1.00	99.58
	26393	151	1.45	1.00	99.61
Average	26654	159	1.47	1.00	99.60
Human #2	25703	520	1.39	1.00	98.54
	26069	170	1.49	1.00	99.56
Average	25886	345	1.44	1.00	99.05
Human #3	26476	179	1.45	1.00	99.53
	25336	197	1.51	1.00	99.48
Average	25906	188	1.48	1.00	99.51

CP-88,059 Concentration: 400 ng/ml; Warfarin Concentration: 7.4 µg/ml					
	DTe (DPM)	DF (DPM)	Vpe (ml)	Vpi (ml)	Fb (Warfarin) (%)
Human #1	26211	160	1.44	1.00	99.57
	25955	150	1.47	1.00	99.60
Average	26083	155	1.45	1.00	99.59
Human #2	26615	223	1.43	1.00	99.41
	25944	171	1.39	1.00	99.52
Average	26280	197	1.41	1.00	99.47
Human #3	26919	180	1.42	1.00	99.53
	26498	219	1.44	1.00	99.43
Average	26709	200	1.43	1.00	99.48

Table 2 (Cont.)
Summary of CP-88,059 Protein Binding Calculations

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

CP-88,059 Concentration: 0 ng/ml; Propranolol Concentration: 50 ng/ml					
	DTe (DPM)	DF (DPM)	Vpe (ml)	Vpi (ml)	Fb (Prop.) (%)
Human #1	6141	1143	1.27	1.00	84.69
	6386	964	1.34	1.00	88.26
Average	6263	1054	1.30	1.00	86.48
Human #2	6484	702	1.32	1.00	91.58
	6578	683	1.38	1.00	92.28
Average	6531	692	1.35	1.00	91.93
Human #3	6363	755	1.43	1.00	91.39
	6298	716	1.39	1.00	91.57
Average	6331	735	1.41	1.00	91.48

CP-88,059 Concentration: 200 ng/ml; Propranolol Concentration: 50 ng/ml					
	DTe (DPM)	DF (DPM)	Vpe (ml)	Vpi (ml)	Fb (Prop.) (%)
Human #1	5901	735	1.50	1.00	91.32
	5950	760	1.54	1.00	91.31
Average	5926	747	1.52	1.00	91.32
Human #2	6282	618	1.41	1.00	92.83
	6296	627	1.42	1.00	92.76
Average	6289	622	1.41	1.00	92.80
Human #3	6015	639	1.49	1.00	92.61
	6188	663	1.47	1.00	92.45
Average	6102	651	1.48	1.00	92.53

CP-88,059 Concentration: 400 ng/ml; Propranolol Concentration: 50 ng/ml					
	DTe (DPM)	DF (DPM)	Vpe (ml)	Vpi (ml)	Fb (Prop.) (%)
Human #1	5866	720	1.52	1.00	91.56
	5801	1037	1.46	1.00	87.00
Average	5833	878	1.49	1.00	89.28
Human #2	6388	589	1.49	1.00	93.60
	6272	578	1.46	1.00	93.50
Average	6330	584	1.47	1.00	93.55
Human #3	6218	642	1.49	1.00	92.83
	6106	891	1.49	1.00	89.74
Average	6162	766	1.49	1.00	91.29
	80	176	0.00	0.00	2.18

Table 3

Binding of CP-88,059 to Human Albumin

Sample	Initial Plasma Conc. (ng/ml)	Cpe (ng/ml)	Cbe (ng/ml)	Recovery (%)	Vpl (ml)	Vpe (ml)	Fb (%)
1	478	435	18.59	118.1	1.00	1.30	96.68
2	478	472	2.10	121.4	1.00	1.23	99.64
3	478	434	11.34	90.8	1.00	1.00	97.39
4	478	469	5.12	124.6	1.00	1.27	99.14
Mean		452	9.29	113.7	1.00	1.20	98.21
S.D.		21	7.30	15.5	0.00	0.14	1.41

Binding of CP-88,059 to Human α–1 Acid Glycoprotein

Sample	Initial Plasma Conc. (ng/ml)	Cpe (ng/ml)	Cbe (ng/ml)	Recovery (%)	Vpl (ml)	Vpe (ml)	Fb (%)
1	454	415	9.11	89.5	1.00	0.98	97.76
2	454	416	9.55	91.5	1.00	1.00	97.70
3	454	476	7.41	102.6	1.00	0.98	98.41
Mean		435	8.69	94.6	1.00	0.99	97.96
S.D.		35	1.13	7.1	0.00	0.01	0.39

Study 015: (PK/PD-Akathisia, 40 mg QID vs 80 mg BID, Patients)

Study Design and Summary:

(see attachments 1-3)

Results:

(See attachments 4-23)

Reviewer's Comments:

1. The major draw backs of this study are the small sample size (i.e., n= 3 or 4) and the high variability in the data (attachments 4-11). Therefore, the data is inconclusive.

2. In general, the Cmaxs and AUCs are comparable after 40 mg QID and 80 mg BID (attachment 3). However, on day 22, the Cmax and AUC were doubled after 80 mg dose compared to 40 mg dose (attachment 18).

3. The relationship between the serum drug concentration and the degree of akathisia is not conclusive, possibly, due to the small sample size (i.e., 3 and 4). However, it should be noted that the mean number of lower limb movements appears to be significantly higher in the treatment groups than the placebo group (attachment 19 and 23). In addition, there is no apparent difference in the degree of sedation between the different treatment sequences (attachment 21).

Conclusions:

1. Inconclusive data in terms of the PK/PD relationship due to the high variability and the limited sample size (i.e., 3 and 4).

2. In general, the Cmaxs and AUCs after 40 mg QID are comparable to that after 80 mg BID.

Attachment 1

PROTOCOL 128-015: PHASE I DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO COMPARE THE PHARMACOKINETICS OF CP-88,059 TO AKATHISIA EVALUATIONS FOLLOWING 80 MG BID OR 40 MG QID DOSING IN SUBJECTS WITH CHRONIC OR SUBCHRONIC SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER

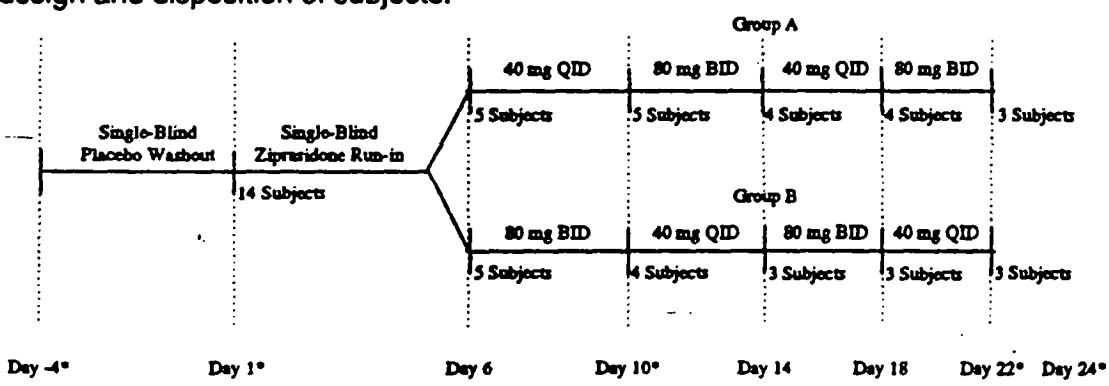
Principal Investigators: S. Stahl, M.D., S. Preskorn, M.D.

Study Publication: None.

Study Dates: 4 August 1993 - 30 December 1993

Study Objective: To evaluate the relationship between serum concentrations of ziprasidone and the degree of akathisia in subjects with chronic or subchronic schizophrenia or schizoaffective disorder receiving two different dosing regimens (40 mg QID or 80 mg BID).

Study Design: This was a 22 day, double blind, two-center, two-treatment, four-period crossover randomized study in subjects with chronic or subchronic schizophrenia or schizoaffective disorder. The following chart illustrates the study design and disposition of subjects:



* indicates laboratory tests were performed

Note: Only the morning dose was to be given on day 22. In addition, subjects were inadvertently administered the opposite formulation on day 22.

Evaluation Groups:

	Single Blind Run-in	40 mg QID	80 mg BID
Entered	14	9	10
Completed	10	8	7
Discontinued	4	1	3
Analyzed for Pharmacokinetics	14	9	10
Analyzed for Pharmacodynamics	14	9	10
Analyzed for Safety:			
Adverse Events	14	9	10
Laboratory Tests*	14	--	--

* Laboratory tests were performed as scheduled for all subjects who received ziprasidone.

Subjects: Male and female subjects diagnosed with chronic or subchronic schizophrenia or schizoaffective disorder. Subjects ranged in age from 23 to 62 years. There were 12 male and 2 female subjects.

Drug Administration:

Dosage Form	20 mg ziprasidone capsules	FID# CS-90-031
	Placebo capsules	FID# BK-87-007

Dosing — Subjects completing the 5-day single-blind washout period entered a 5-day single-blind active treatment period. Each subject received ziprasidone 20 mg BID on day 1, 40 mg BID on day 2, and 80 mg BID for three days (days 3-5). The double-blind treatment period consisted of 17 days. Subjects were randomly assigned, in equal numbers, to one of the two treatment sequences by a computer-generated randomization. During the double-blind legs, study drug (ziprasidone and/or placebo) was administered 4 times daily with meals (breakfast, lunch, dinner, and snack at bedtime) for a total of 21 days and only with breakfast on day 22. On day 22, subjects were inadvertently administered the alternate dose from the schedule.

Pharmacokinetic and Safety Evaluations: Serum concentrations were used to estimate $AUC_{0\text{-}12}$, C_{max}, T_{max}, K_{el}, and $T_{1/2}$ on days 1, 5, 9, 13, 17, 21, and 22. Adverse events and laboratory tests were monitored. Assessments of extrapyramidal system effects, akathisia, and abnormal movements were made daily at specified times.

Analytical Methods:

Statistical Methods: Geometric means were calculated for $AUC_{0\text{-}12}$ and C_{max}. Arithmetic means were calculated for T_{max} and K_{el}. Mean $T_{1/2}$ was calculated as 0.693/mean K_{el}.

Safety Results:

	Ziprasidone		
	Single Blind Run-in (80 mg BID)	40 mg QID	80 mg BID
Treatment-emergent Adverse Events (All Causality)	12/14 (2)	9/9 (1)	10/10 (1)
Treatment-emergent, Treatment-related Adverse Events	11/14	7/9	9/10
Clinically Significant Laboratory Abnormalities	8/14 (0)[a]	–	–

() Subjects discontinued

[a] - Laboratory tests were pooled across treatments

Pharmacokinetic Results: (values are Mean ± %CV)

Treatment Group	Study Day	Dose Regimen	n	AUC_{0-12} (ng•hr/ml)	C_{max} (ng/ml)	T_{max} (hours)	K_{el} (hr^{-1})	$T_{1/2}$ (hours)
Single Blind Ziprasidone	Day 1	20 mg	14	298.0 ± 73	58.5 ± 35	6.1 ± 66		
	Day 5	80 mg BID	11	1668.4 ± 35	246.6 ± 39	3.6 ± 81		
Group A[e]	Day 9	40 mg QID	5	1567.5 ± 48[b]	173.6 ± 39[a] 156.5 ± 66[b]	4.0 ± 50[a] 3.6 ± 23[b]		
	Day 13[c]	80 mg BID	4	1655.2 ± 42	237.9 ± 40	3.0 ± 38		
	Day 17[c]	40 mg QID	3	1742.9 ± 28[b]	191.2 ± 40[a] 183.2 ± 29[b]	4.0 ± 50[a] 3.0 ± 0[b]		
	Day 21[c]	80 mg BID	2	2266.8[d]	403.5[d]	7.0		
	Day 22[c]	40 mg	2	633.0[d]	112.6[d]	2.5	0.054	12.8
Group B[e]	Day 9	80 mg BID	4	1437.3 ± 62	196.7 ± 58	7.5 ± 70		
	Day 13	40 mg QID	4	1738.9 ± 18[b]	159.2 ± 33[a] 196.9 ± 4[b]	3.0 ± 38[a] 3.0 ± 22[b]		
	Day 17	80 mg BID	3	1542.8 ± 30	203.2 ± 37	6.0 ± 88		
	Day 21	40 mg QID	3	1278.0 ± 22[b]	154.2 ± 5[a] 110.3 ± 33[b]	4.0 ± 50[a] 9.3 ± 25[b]		
	Day 22	80 mg	3	1490.0 ± 42	233.2 ± 56	3.7 ± 42	0.104 ± 45	6.7

a - after first dose (0-6 hours)

b - after second dose (6-12 hours)

c - excludes Subject 557-0004 who had unusually low exposure

d - arithmetic mean (n=2) and no %CV calculated

e - Group A received ziprasidone single blind on days 1-5; double-blind 40 mg QID on days 6-9, 14-16, 22; and double-blind 80 mg BID on days 10-13, 18-21. Group B received single blind ziprasidone on days 1-5, double-blind 80 mg BID on days 6-9, 14-16, 22; and double-blind 40 mg QID on days 10-13, 18-21.

Summary and Conclusions: In this limited number of subjects, the data suggested that systemic exposure to ziprasidone was similar for the 40 mg QID and 80 mg BID dosage regimens based on AUC_{0-12} comparisons. C_{max} values were typically higher for the BID dosing regimen. T_{max} values were generally variable throughout the study, ranging from 2 to 12 hours.

The adverse event profiles were similar when subjects were taking ziprasidone 40 mg QID or 80 mg BID. Three subjects reported severe adverse events which began during the single-blind ziprasidone run-in period (dystonia, asthenia, somnolence, leg cramps). There were no serious adverse events reported during the study.

Based on Barnes' scores, the incidence and severity of akathisia was similar between 40 mg QID and 80 mg BID treatments. Because of the variability of the data and the limited number of subjects, no conclusions on the relationship between serum ziprasidone concentrations and akathisia can be made. No clinically significant differences between treatment groups were apparent for extrapyramidal symptoms, AIMS, or sedation.

Table 5.1
Ziprasidone Pharmacokinetic Parameters on Days 1 and 5
Ziprasidone Protocol 015

Day 1 20 mg bid

SUBJECT	GENDER	CODE[a]	AUC(0-12) (ng•hr/ml)	Cmax (ng/ml)	Tmax (hr)
557-0002	Male	A			
557-0004	Male	A			
557-0006	Male	A			
557-0007	Female	A			
5002-0014	Male	A			
557-0001	Male	B			
557-0003	Male	B			
557-0005	Male	B			
557-0008	Female	B			
5002-0013	Male	B			
557-9003	Male	C			
557-9015	Male	C			
557-9016	Male	C			
557-9017	Male	C			
MEAN[b]			298.0	58.5	6.1
SD			216.8	20.7	4.0
CV%			73	35	66

Day 5 80 mg bid

SUBJECT	CODE[a]	AUC(0-12) (ng•hr/ml)	Cmax (ng/ml)	Tmax (hr)
557-0002	A			
557-0004	A			
557-0006	A			
557-0007	A			
5002-0014	A			
557-0001	B			
557-0003	B			
557-0005	B			
557-0008	B			
5002-0013	B			
557-9016	C			
MEAN[b]		1668.4	246.6	3.6
SD		590.0	95.4	2.9
CV%		35	39	81

[a] = Group A: 20 mg bid (day 1)→40 mg bid (day 2)→80 mg bid (day 3 to 5)→40 mg qid (days 6-9)→80 mg bid (days 10-13) → 40 mg qid (days 14-17)→80 mg bid (days 18-21)→40 mg morning dose on day 22
Group B: 20 mg bid (day 1)→40 mg bid (day 2)→80 mg bid (day 3 to 5)→80 mg bid (days 6-9)→40 mg qid (days 10-13)→80 mg bid (days 14-17)→40 mg qid (days 18-21)→80 mg morning dose on day 22. Group C: Did not enter the double-blind portion of the study.

[b] = Geometric means are calculated for AUC(0-12) and Cmax.

Source Data: Appendix IV, Table 1

(5)

(5)

Table 5.2
Ziprasidone Pharmacokinetic Parameters in Group A[a]
Ziprasidone Protocol 015

Day 9 40 mg qid

	First Daily Dose		Second Daily Dose		
SUBJECT	Cmax (ng/ml)	Tmax (hr)	Cmax (ng/ml)	Tmax (hr)	AUC(0-12) (ng/ml)
557-0002					
557-0004					
557-0006					
557-0007					
5002-0014					
MEAN[b]	173.6	4.0	156.5	3.6	1567.5
SD	68.0	2.0	103.4	2.2	759.5
CV%	39	50	66	23	48

Day 13 80 mg bid

SUBJECT	AUC(0-12) (ng•hr/ml)	Cmax (ng/ml)	Tmax (hr)
557-0002			
557-0004			
557-0006			
557-0007			
5002-0014			
MEAN[b]	773.9	123.0	4.8
SD	1344.7	186.2	4.1
CV%	174	151	86
MEAN[b,c]	1655.2	237.9	3.0
SD	688.4	94.4	1.2
CV%	42	40	38

[a] = Group A: 20 mg bid (day 1)→40 mg bid (day 2)→80 mg bid (day 3 to 5)→40 mg qid (days 6-9)→80 mg bid (days 10-13) → 40 mg qid (days 14-17)→80 mg bid (days 18-21)→40 mg morning dose on day 22

[b] = Geometric mean and standard deviation for Cmax and AUC(0-12); arithmetic mean and standard deviation for Tmax.

[c] = Excludes data for subject 557-0004.

[d] = Geometric means are calculated for AUC(0-12) and Cmax.

Source Data: Appendix IV, Table 2

Table 5.2 (Cont'd)
Ziprasidone Pharmacokinetic Parameters in Group A[a]
Ziprasidone Protocol 015

Day 17 40 mg qid

	First Daily Dose		Second Daily Dose		
SUBJECT	Cmax (ng/ml)	Tmax (hr)	Cmax (ng/ml)	Tmax (hr)	AUC(0-12) (ng/ml)
557-0002					
557-0004					
557-0007					
5002-0014					
MEAN[b]	121.6	3.0	135.4	3.0	1226.6
SD	116.9	2.6	88.0	2.0	905.6
CV%	96	86	65	22	74
MEAN[b,c]	191.2	4.0	183.2	2.0	1742.9
SD	75.9	2.0	53.8	--	484.0
CV%	40	50	29	--	28

Day 18 80 mg

SUBJECT	AUC(0-12) (ng•hr/ml)	Cmax (ng/ml)	Tmax (hr)	Kel (hr^{-1})	T1/2 (hr)
557-0007[d]					

a = Group A: 20 mg bid (day 1)→40 mg bid (day 2)→80 mg bid (day 3 to 5)→40 mg qid (days 6-9)→80 mg bid (days 10-13) → 40 mg qid (days 14-17)→80 mg bid (days 18-21)→40 mg morning dose on day 22

b = Geometric mean and standard deviation for Cmax and AUC(0-12); arithmetic mean and standard deviation for Tmax.

c = Excludes data for subject 557-0004.

d = Subject 557-007 received 80 mg on the morning of day 18 and was discontinued from the study.

e = Geometric means are calculated for AUC(0-12) and Cmax.

Source Data: Appendix IV, Table 2

Table 5.2 (Cont'd)
Ziprasidone Pharmacokinetic Parameters in Group A
Ziprasidone Protocol 015

Day 21 80 mg bid

SUBJECT	AUC(0-12) (ng•hr/ml)	Cmax (ng/ml)	Tmax (hr)
557-0002			
557-0004			
5002-0014			
MEAN[a]	1455.2	235.7	6.7
SD	1109.5	218.1	5.0
CV%	76	93	75
MEAN[c]	2266.8	403.5	7.0
SD	--	--	--
CV%	--	--	--

Day 22 40 mg

SUBJECT	AUC(0-12) (ng•hr/ml)	Cmax (ng/ml)	Tmax (hr)	Kel (hr^{-1})	T1/2 (hr)
557-0002					
557-0004					
5002-0014					
MEAN[a]	278.5	46.5	2.0	0.062	11.2[b]
SD	429.3	74.1	1.7	0.021	--
CV%	154	159	87	35	--
MEAN[c]	633.0	112.6	2.5	0.054	12.8
SD	--	--	--	--	--
CV%	--	--	--	--	--

[a] = Geometric mean and standard deviation for AUC(0-12) and Cmax; arithmetic mean and standard deviation for all other parameters except T1/2.
[b] = Calculated as 0.693/mean Kel.
[c] = Arithmetic mean (N=2); data from Subject 557-004 excluded.
[d] = Geometric means are calculated for AUC(0-12) and Cmax.

Source Data: Appendix IV, Table 2.

(8) (8)

Table 5.3
Ziprasidone Pharmacokinetic Parameters in Group B[a]
Ziprasidone Protocol 015

Day 9 80 mg bid

SUBJECT	AUC(0-12) (ng•hr/ml)	Cmax (ng/ml)	Tmax (hr)
557-0001			
557-0003			
557-0008			
5002-0013			
MEAN[b]	1437.3	196.7	7.5
SD	887.7	114.8	5.3
CV%	62	58	70

Day 13 40 mg qid

	First Daily Dose		Second Daily Dose		
SUBJECT	Cmax(0-6) (ng/ml)	Tmax(0-6) (hr)	Cmax(6-12) (ng/ml)	Tmax(6-12) (hr)	AUC(0-12) (ng•hr/ml)
557-0001					
557-0003					
557-0008[c]					
5002-0013					
MEAN[c]	159.2	3.0	196.9	3.0	1738.9
SD	52.9	1.2	7.0	2.0	312.8
CV%	33	38	4	22	18

Day 17 80 mg bid

SUBJECT	AUC(0-12) (ng•hr/ml)	Cmax (ng/ml)	Tmax (hr)
557-0001			
557-0003			
5002-0013			
MEAN[b]	1542.8	203.2	6.0
SD	468.1	74.2	5.3
CV%	30	37	88

a = Group B: 20 mg bid (day 1)→40 mg bid (day 2)→80 mg bid (day 3 to 5)→80 mg bid (days 6-9)→40 mg qid (days 10-13)→80 mg bid (days 14-17)→40 mg qid (days 18-21)→80 mg morning dose on day 22.

b = Geometric mean and standard deviation for AUC(0-12) and Cmax; arithmetic mean and standard deviation for all other parameters.

c = Subject 557-0008 dropped from the study after day 13.

Source Data: Appendix IV, Table 3

Table 5.3 (Cont'd)
Ziprasidone Pharmacokinetic Parameters in Group B[a]
Ziprasidone Protocol 015

Day 21 40 mg qid

	First Daily Dose		Second Daily Dose		
SUBJECT	Cmax (ng/ml)	Tmax (hr)	Cmax (ng/ml)	Tmax (hr)	AUC(0-12) (ng•hr/ml)
557-0001					
557-0003					
5002-0013					
MEAN[b]	154.2	4.0	110.3	3.3	1278.0
SD	8.2	2.0	36.0	2.3	283.8
CV%	5	50	33	25	22

Day 22 80 mg

SUBJECT	AUC(0-12) (ng•hr/ml)	Cmax (ng/ml)	Tmax (hr)	Kel (hr^{-1})	T1/2 (hr)
557-0001					
557-0003					
5002-0013					
MEAN[b]	1490.0	233.2	3.7	0.104	6.7[c]
SD	620.6	131.0	1.5	0.047	--
CV%	42	56	42	45	--

a = Group B: 20 mg bid (day 1)→40 mg bid (day 2)→80 mg bid (day 3 to 5)→80 mg bid (days 6-9)→40 mg qid (days 10-13)→80 mg bid (days 14-17)→40 mg qid (days 18-21)→80 mg morning dose on day 22.
b = Geometric mean and standard deviation for AUC(0-∞), Cmax; arithmetic mean and standard deviation for all other parameters except T1/2.
c = Calculated as 0.693/mean Kel.

Source Data: Appendix IV, Table 3

Table 5.4.1
Mean Steady-State Ziprasidone Pharmacokinetic Parameters in Subjects Receiving a 80 mg Ziprasidone HCl BID Dosing Regimen
Ziprasidone Protocol 015

	80 mg BID[a]						
	Group A and B Day 5	Group A Day 13	Group A Day 21	Group B Day 9	Group B Day 17	Group B Day 22	Overall
AUC(0-12) (ng•h/ml)							
MEAN[b]	1668.4	1655.2	2266.8[c]	1437.3	1542.8	1490.0	1676.8
SD	590.0	688.4	--	887.7	468.1	620.6	275.4
CV%	35	42	--	62	30	42	16
Cmax (ng/ml)							
MEAN[b]	246.6	237.9	403.5[c]	196.7	203.2	233.2	253.5
SD	95.4	94.4	--	114.8	74.2	131.0	65.7
CV%	39	40	--	58	37	56	26
Tmax (h)							
MEAN[b]	3.6	3.0	7.0[c]	7.50	6.0	3.7	5.1
SD	2.9	1.2	--	5.3	5.3	1.5	1.9
CV%	81	38	--	70	88	42	38
N	11	4	2	4	3	3	--

[a] = Group A: 20 mg bid (day 1)→40 mg bid (day 2)→80 mg bid (day 3 to 5)→40 mg qid (days 6-9)→80 mg bid (days 10-13) → 40 mg qid (days 14-17)→80 mg bid (days 18-21)→40 mg morning dose on day 22
Group B: 20 mg bid (day 1)→40 mg bid (day 2)→80 mg bid (day 3 to 5)→80 mg bid (days 6-9)→40 mg qid (days 10-13)→80 mg bid (days 14-17)→40 mg qid (days 18-21)→80 mg morning dose on day 22. Group C: Did not complete entire study.
[b] = Geometric mean and standard deviation for AUC(0-∞) and Cmax; arithmetic mean and standard deviation for Tmax.
[c] = N of 2; arithmetic mean, no standard deviation calculated.
[d] = Geometric means are calculated for AUC(0-12) and Cmax.

Source Data: Appendix IV, Tables 1, 2, and 3

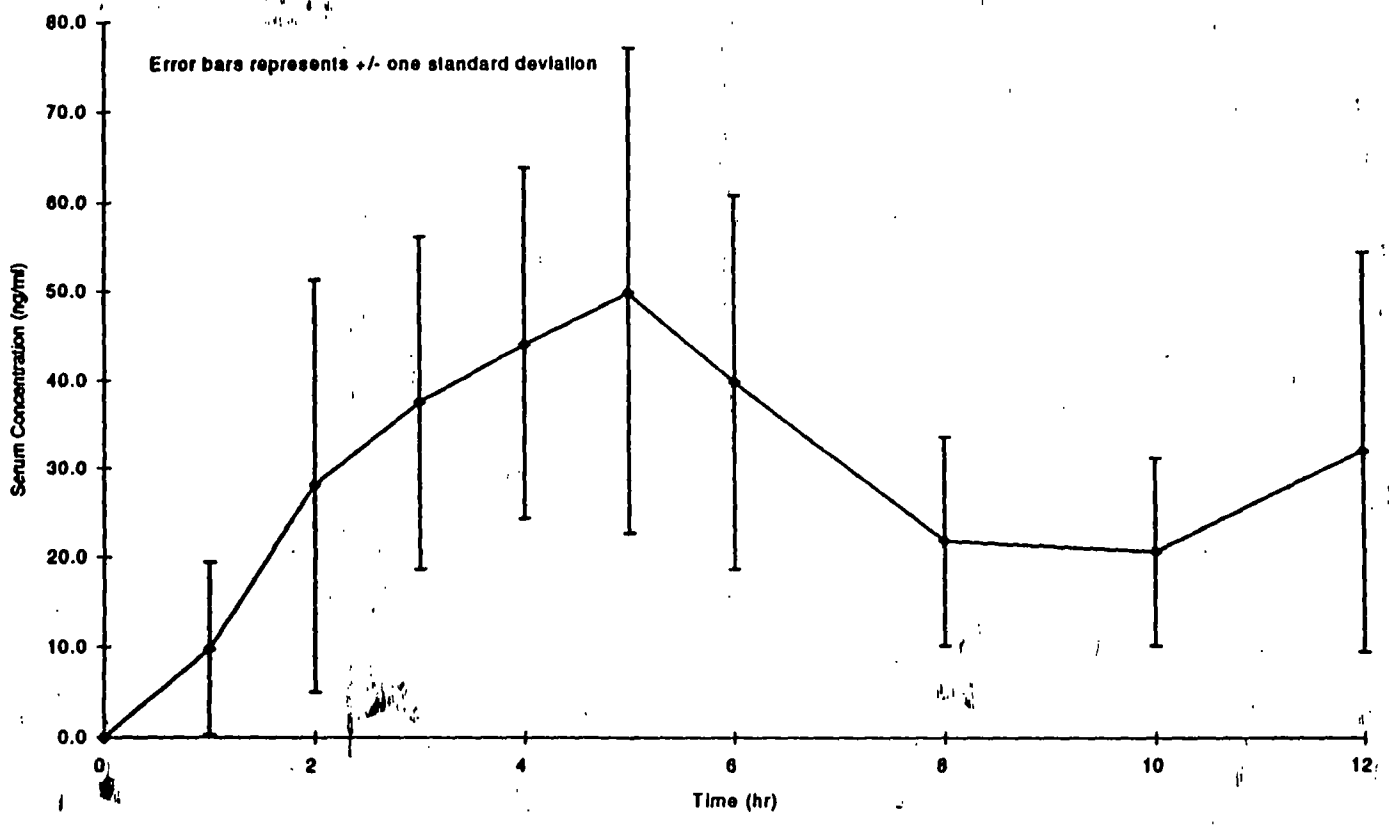
Table 5.4.2
Mean Steady-State Ziprasidone Pharmacokinetic Parameters in Subjects Receiving a 40 mg Ziprasidone HCl QID Dosing Regimen
Ziprasidone Protocol 015

	40 mg QID [a]				
	Group A Day 9	Group A Day 17	Group B Day 13	Group B Day 21	Overall
AUC(0-12) (ng•h/ml)					
MEAN [b]	1567.5	1742.9	1738.9	1278.0	1452.8
SD	759.5	484.0	312.8	283.8	241.3
CV%	48	28	18	22	17
	First Dose				
Cmax (ng/ml)					
MEAN [b]	173.6	191.2	159.2	154.2	169.9
SD	68.0	75.9	52.9	8.2	16.3
CV%	39	40	33	5	10
Tmax (h)					
MEAN [b]	4.0	4.0	3.0	4.0	3.8
SD	2.0	2.0	1.2	2.0	0.5
CV%	50	50	38	50	13
	Second Dose				
Cmax (ng/ml)					
MEAN [b]	156.5	183.2	196.9	110.3	161.7
SD	103.4	53.8	7.0	36.0	41.7
CV%	66	29	4	33	26
Tmax (h)					
MEAN [b]	3.6	2.0	3.0	3.3	3.0
SD	2.2	--	2.0	2.3	0.7
CV%	23	--	22	25	23
N	5	3	4	3	--

[a] = Group A: 20 mg bid (day 1)→40 mg bid (day 2)→80 mg bid (day 3 to 5)→40 mg qid (days 6-9)→80 mg bid (days 10-13) → 40 mg qid (days 14-17)→80 mg bid (days 18-21)→40 mg morning dose on day 22
Group B: 20 mg bid (day 1)→40 mg bid (day 2)→80 mg bid (day 3 to 5)→80 mg bid (days 6-9)→40 mg qid (days 10-13)→80 mg bid (days 14-17)→40 mg qid (days 18-21)→80 mg morning dose on day 22. Group C: Did not complete entire study.
[b] = Geometric mean and standard deviation for AUC(0-∞) and Cmax; arithmetic mean and standard deviation for Tmax.
[c] = Geometric means are calculated for AUC(0-12) and Cmax.

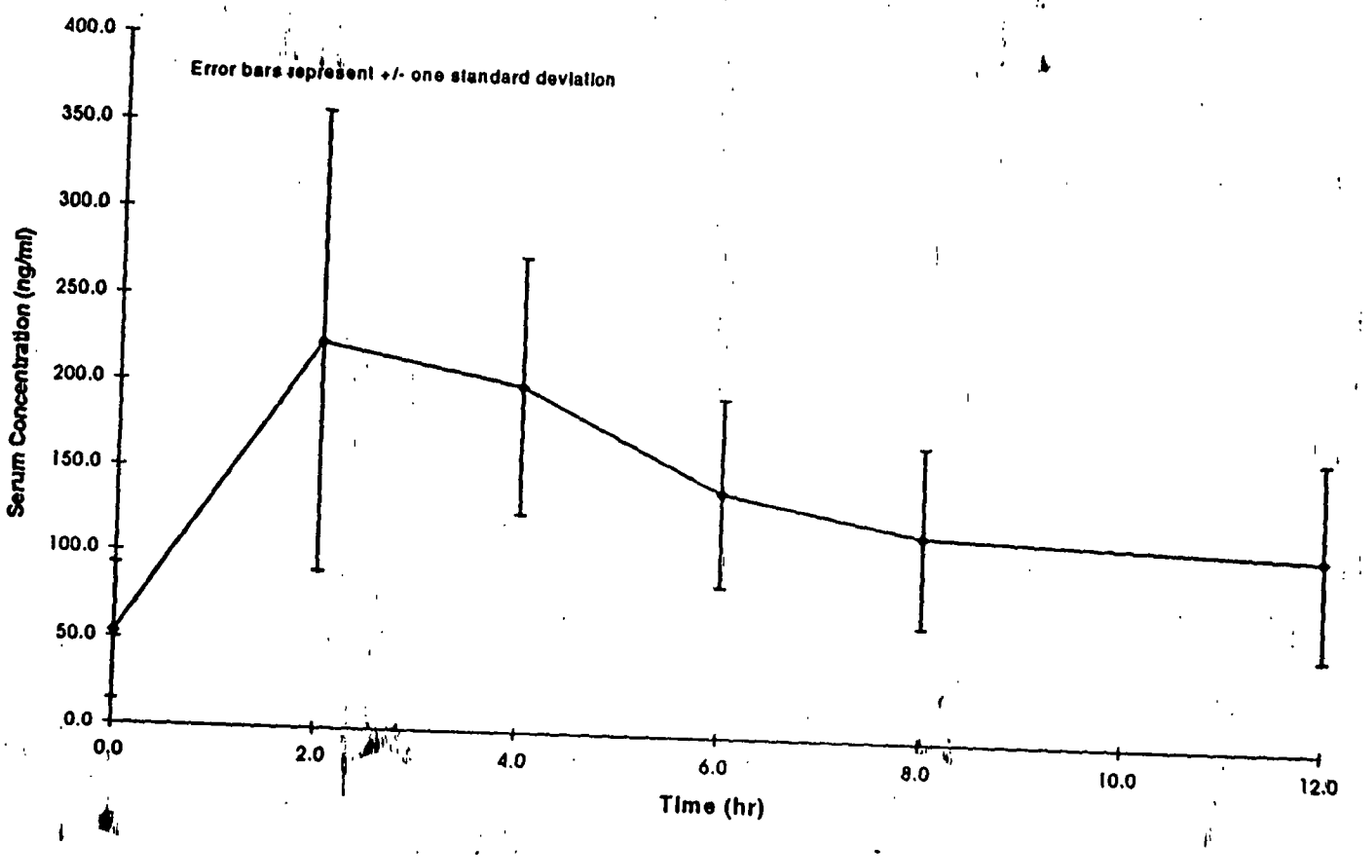
Source Data: Appendix IV, Tables 1, 2, and 3

Figure 1.1
Mean Serum Ziprasidone Concentrations on Day 1 Following Administration of 20 mg Ziprasidone HCl
Ziprasidone Protocol 015



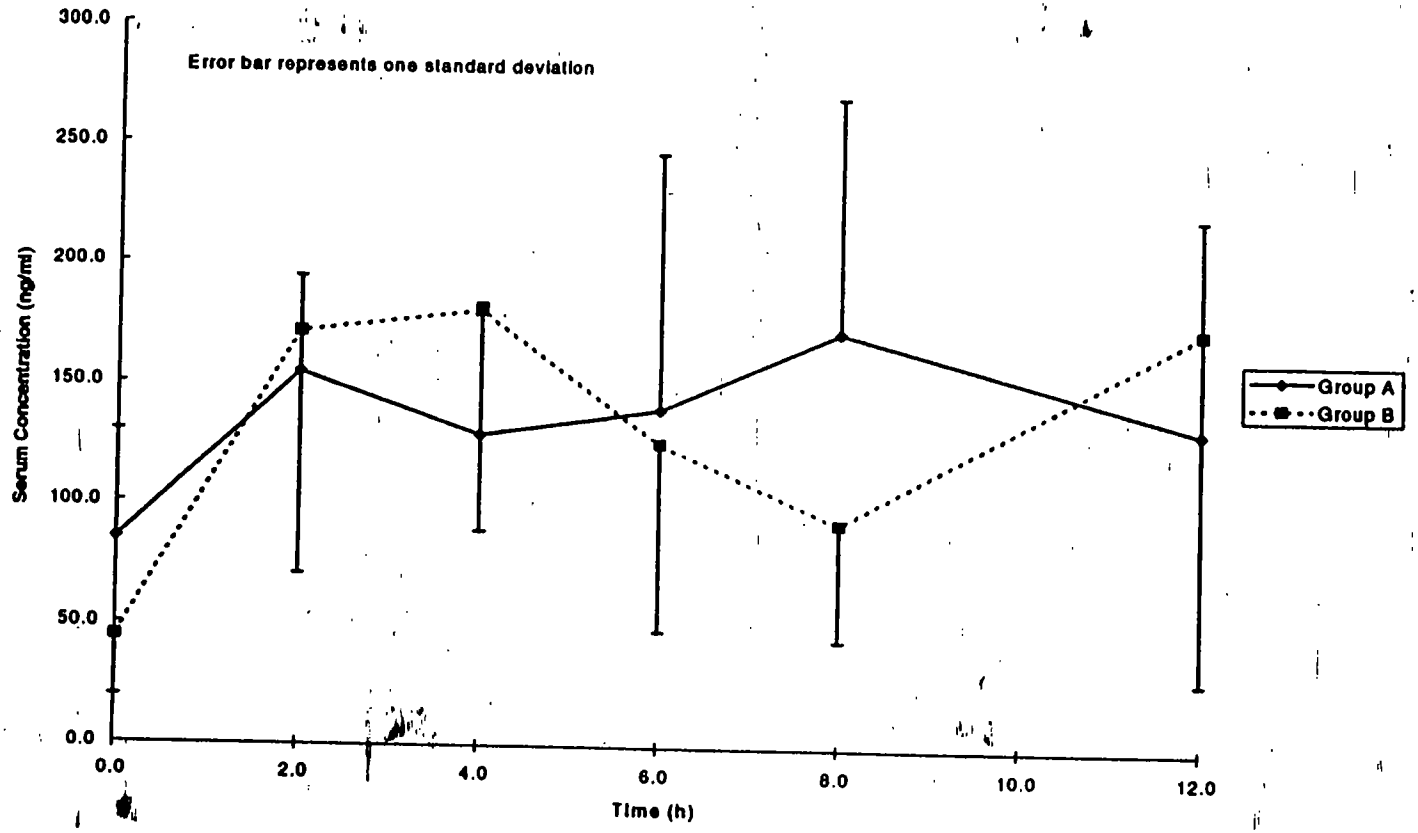
Source Data: Appendix IV, Table 1

Figure 1.2
Mean Serum Ziprasidone Concentrations on Day 5 Following Administration of 80 mg Ziprasidone
Ziprasidone Protocol 015



Source Data: Appendix IV, Table 1

Figure 1.3
Mean Serum Ziprasidone Concentrations on Day 9 in Subjects Receiving Ziprasidone HCl for 22 Days
Ziprasidone Protocol 015

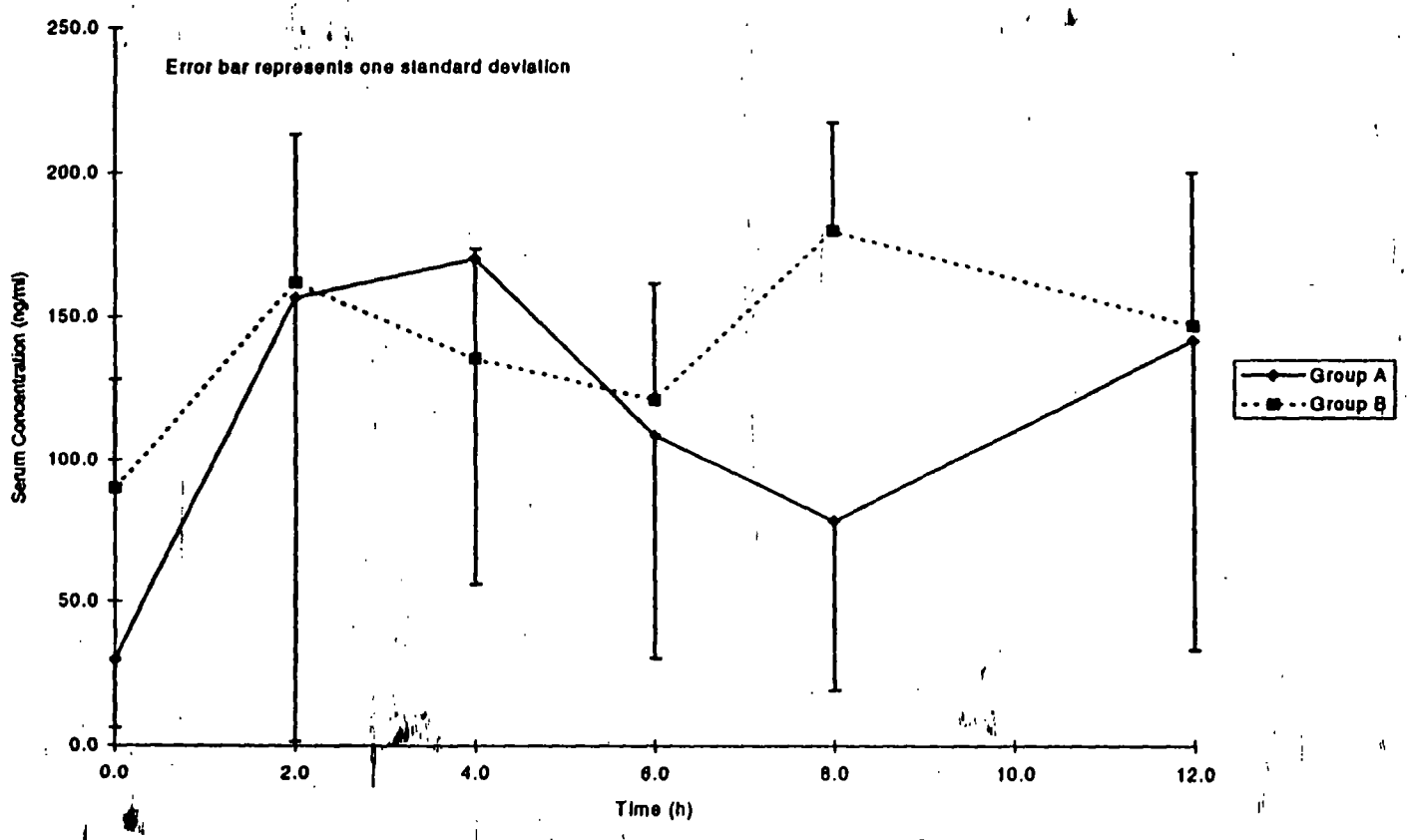


Group A: 20 mg bid (day 1) → 40 mg bid (day 2) → 80 mg bid (day 3 to 5) → 40 mg qid (days 6-9) → 80 mg bid (days 10-13) → 40 mg qid (days 14-17) → 80 mg bid (days 18-21) → 40 mg morning dose on day 22
Group B: 20 mg bid (day 1) → 40 mg bid (day 2) → 80 mg bid (day 3 to 5) 80 mg bid (days 6-9) → 40 mg qid (days 10-13) → 80 mg bid (days 14-17) → 40 mg qid (days 18-21) → 80 mg morning dose on day 22
Source Data: Appendix IV, Tables 2 and 3

(15)

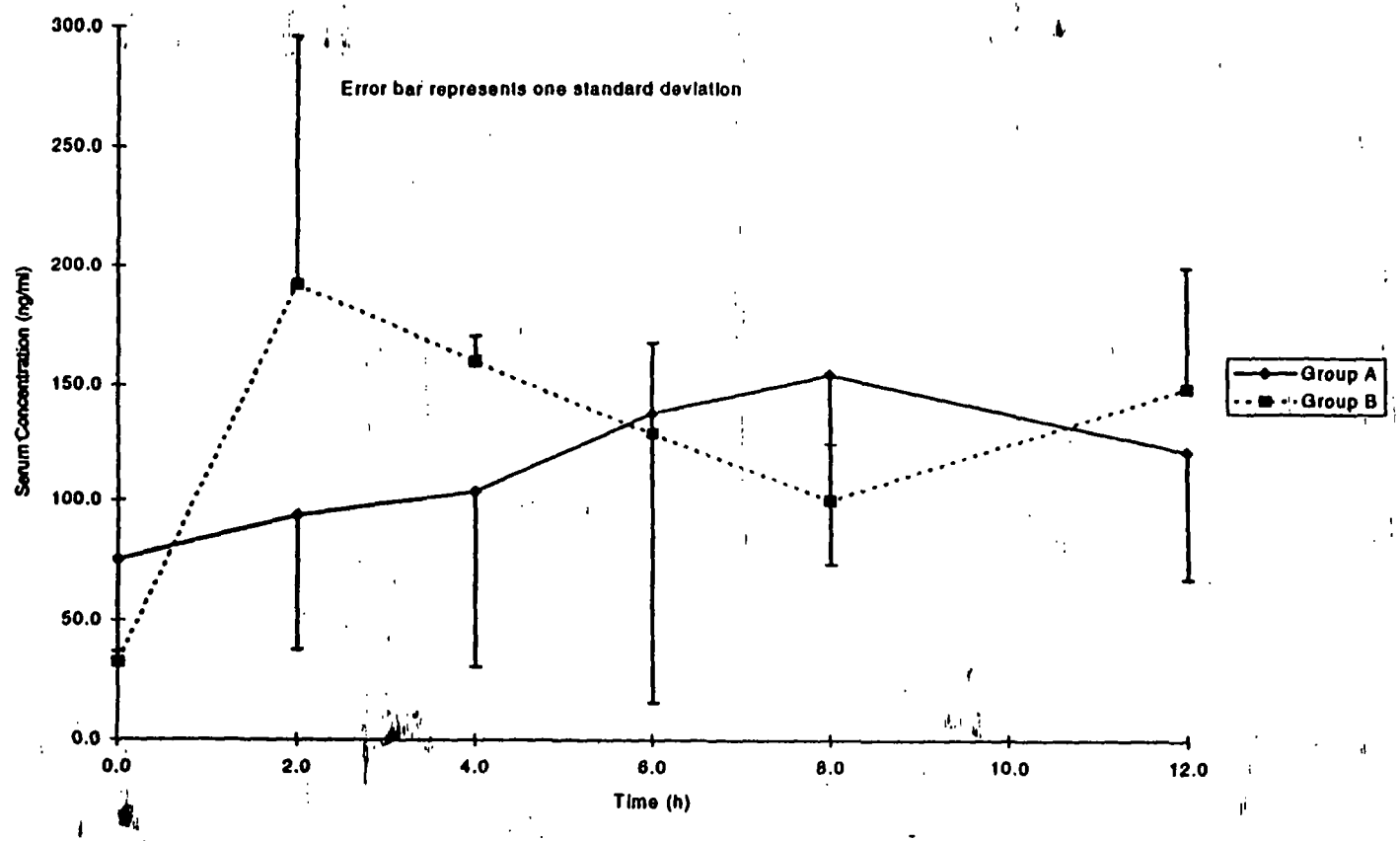
(15)

Figure 1.4
Mean Serum Ziprasidone Concentrations on Day 13 in Subjects Receiving Ziprasidone HCl for 22 Days
Ziprasidone Protocol 015



Group A: 20 mg bid (day 1) → 40 mg bid (day 2) → 80 mg bid (day 3 to 5) → 40 mg qid (days 6-9) → 80 mg bid (days 10-13) → 40 mg qid (days 14-17) → 80 mg bid (days 18-21) → 40 mg morning dose on day 22
Group B: 20 mg bid (day 1) → 40 mg bid (day 2) → 80 mg bid (day 3 to 5) 80 mg bid (days 6-9) → 40 mg qid (days 10-13) → 80 mg bid (days 14-17) → 40 mg qid (days 18-21) → 80 mg morning dose on day 22
Source Data: Appendix IV, Tables 2 and 3

Figure 1.5
Mean Serum Ziprasidone Concentrations on Day 17 in Subjects Receiving Ziprasidone HCl for 22 Days
Ziprasidone Protocol 015

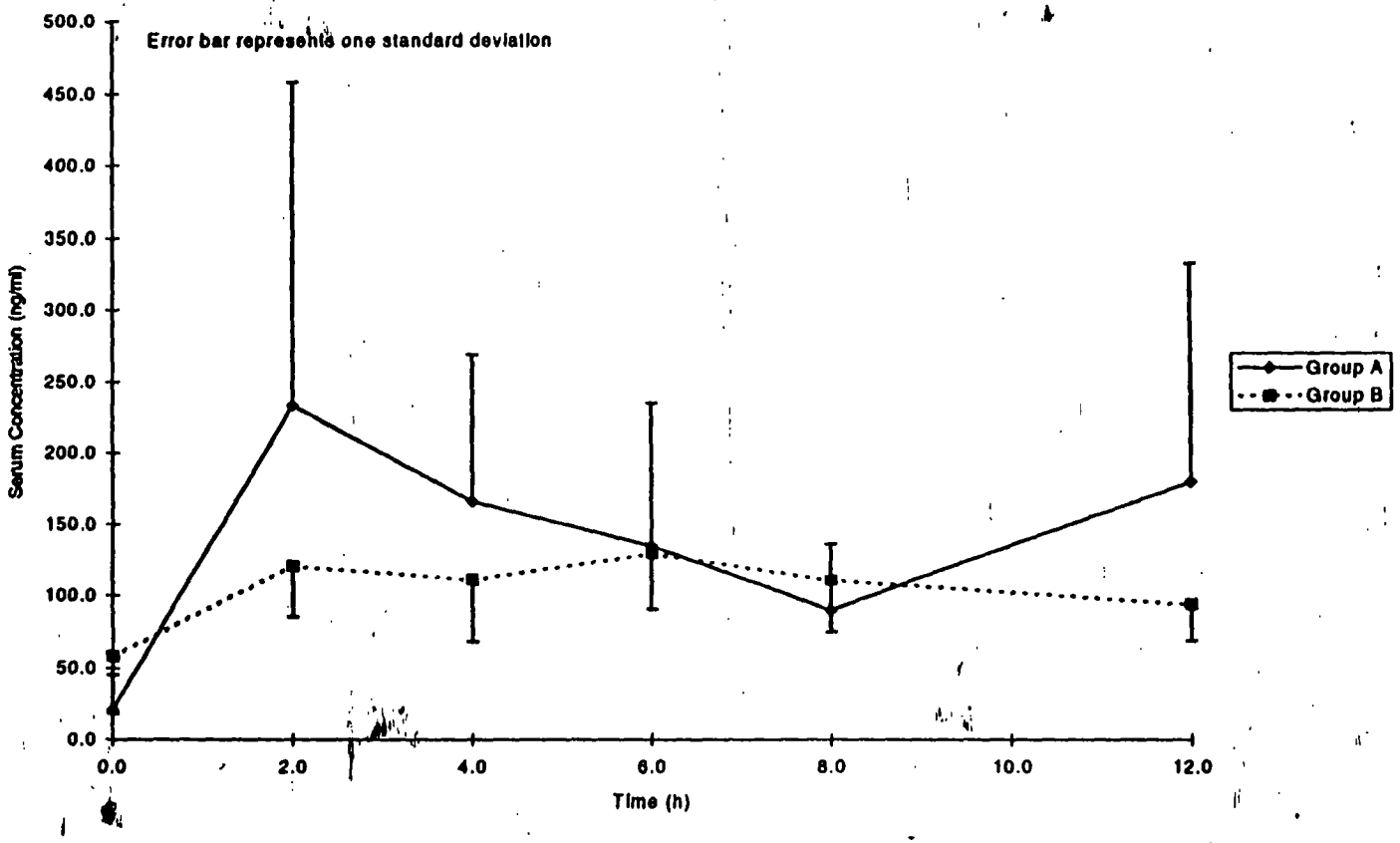


Group A: 20 mg bid (day 1) → 40 mg bid (day 2) → 80 mg bid (day 3 to 5) → 40 mg qid (days 6-9) → 80 mg bid (days 10-13) → 40 mg qid (days 14-17) → 80 mg bid (days 18-21) → 40 mg morning dose on day 22

Group B: 20 mg bid (day 1) → 40 mg bid (day 2) → 80 mg bid (day 3 to 5) 80 mg bid (days 6-9) → 40 mg qid (days 10-13) → 80 mg bid (days 14-17) → 40 mg qid (days 18-21) → 80 mg morning dose on day 22

Source Data: Appendix IV, Tables 2 and 3

Figure 1.6
Mean Serum Ziprasidone Concentrations on Day 21 in Subjects Receiving Ziprasidone HCl for 22 Days
Ziprasidone Protocol 015

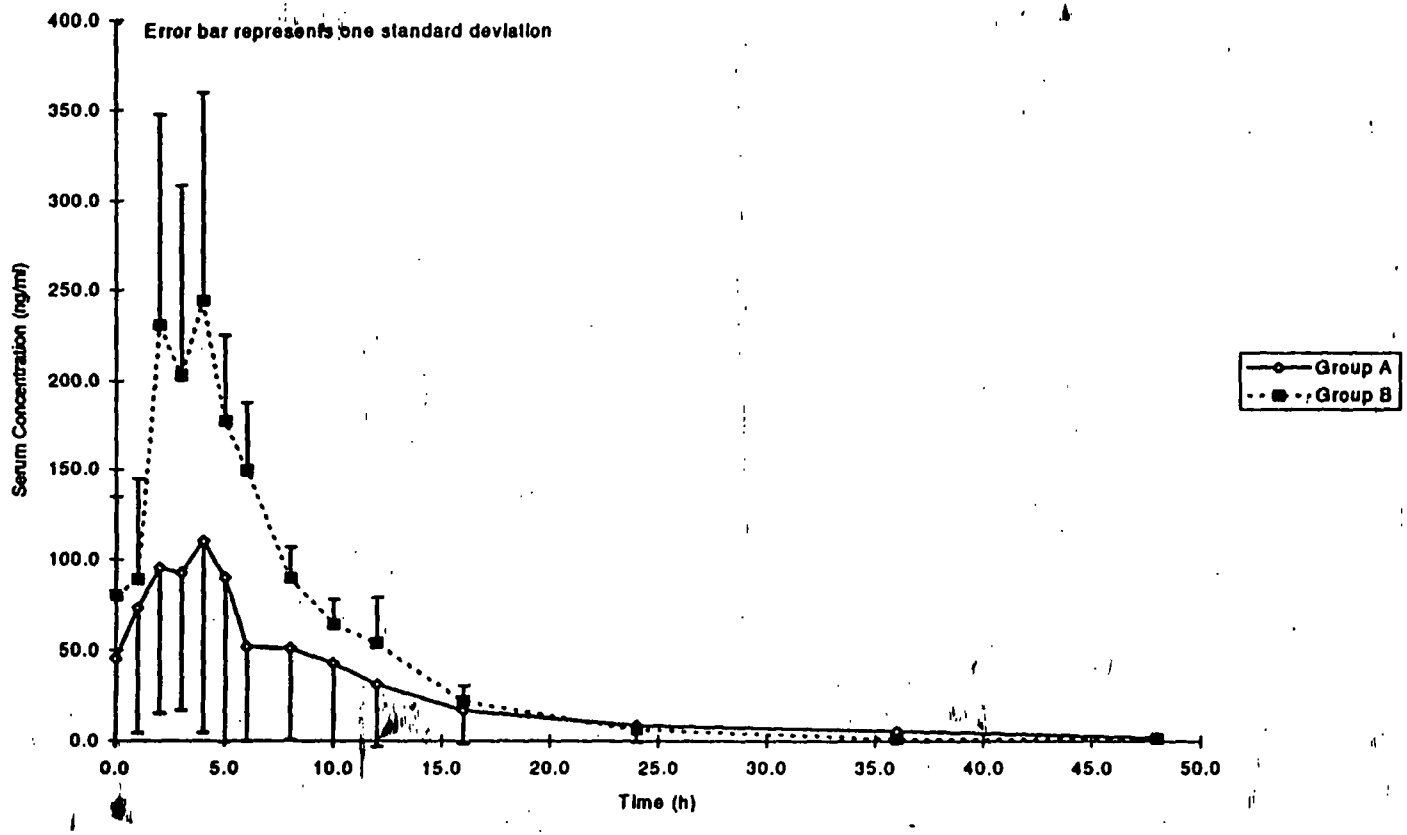


Group A: 20 mg bid (day 1) → 40 mg bid (day 2) → 80 mg bid (day 3 to 5) → 40 mg qid (days 6-9) → 80 mg bid (days 10-13) → 40 mg qid (days 14-17) → 80 mg bid (days 18-21) → 40 mg morning dose on day 22
Group B: 20 mg bid (day 1) → 40 mg bid (day 2) → 80 mg bid (day 3 to 5) 80 mg bid (days 6-9) → 40 mg qid (days 10-13) → 80 mg bid (days 14-17) → 40 mg qid (days 18-21) → 80 mg morning dose on day 22
Source Data: Appendix IV, Tables 2 and 3

(18)

(18)

Figure 1.7
Mean Serum Ziprasidone Concentrations on Day 22 in Subjects Receiving Ziprasidone HCl for 22 Days
Ziprasidone Protocol 015



Group A: 20 mg bid (day 1) → 40 mg bid (day 2) → 80 mg bid (day 3 to 5) → 40 mg qid (days 6-9) → 80 mg bid (days 10-13) → 40 mg qid (days 14-17) → 80 mg bid (days 18-21) → 40 mg morning dose on day 22

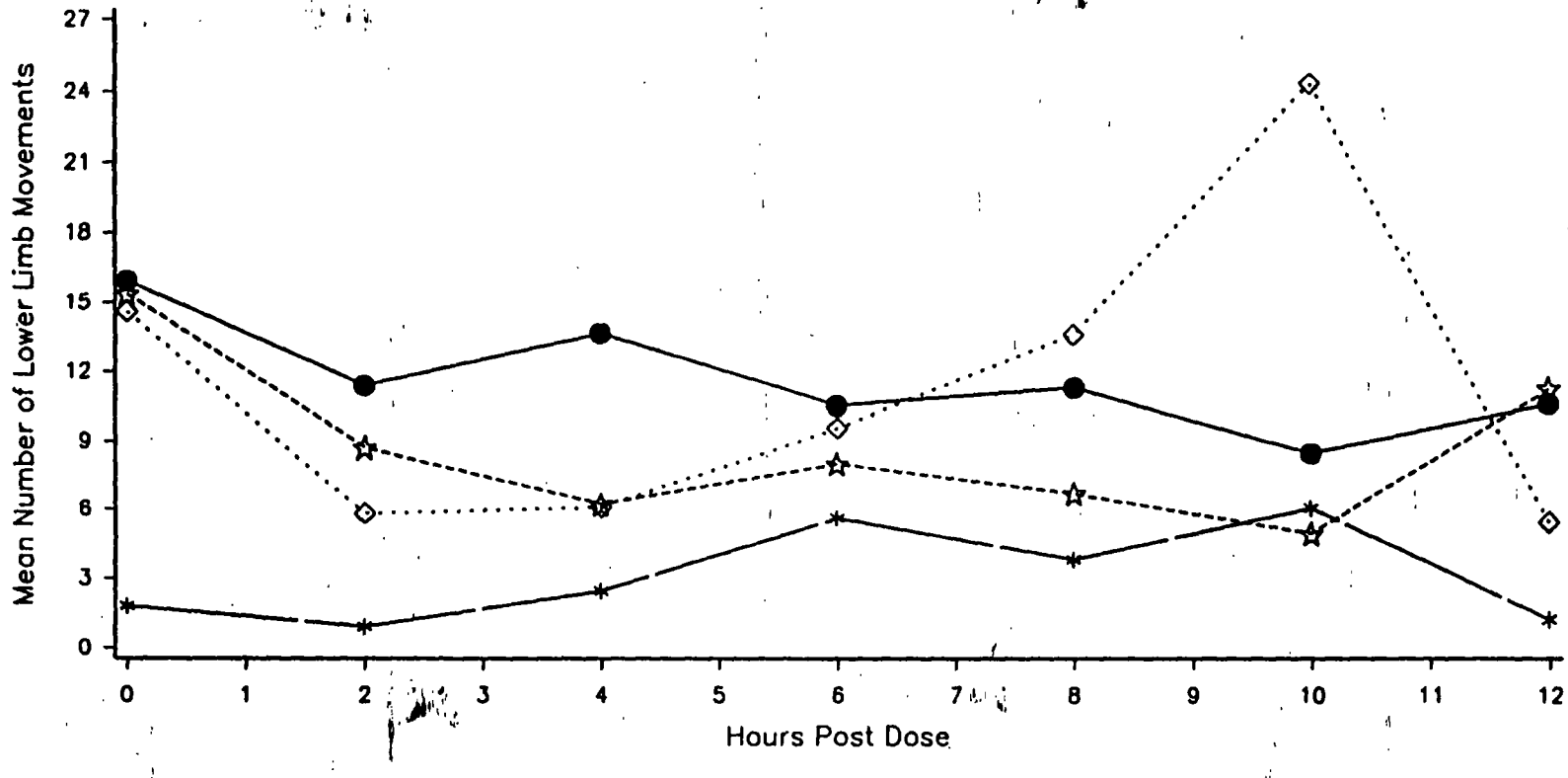
Group B: 20 mg bid (day 1) → 40 mg bid (day 2) → 80 mg bid (day 3 to 5) 80 mg bid (days 6-9) → 40 mg qid (days 10-13) → 80 mg bid (days 14-17) → 40 mg qid (days 18-21) → 80 mg morning dose on day 22

Source Data: Appendix IV, Tables 2 and 3

(19)

(5)

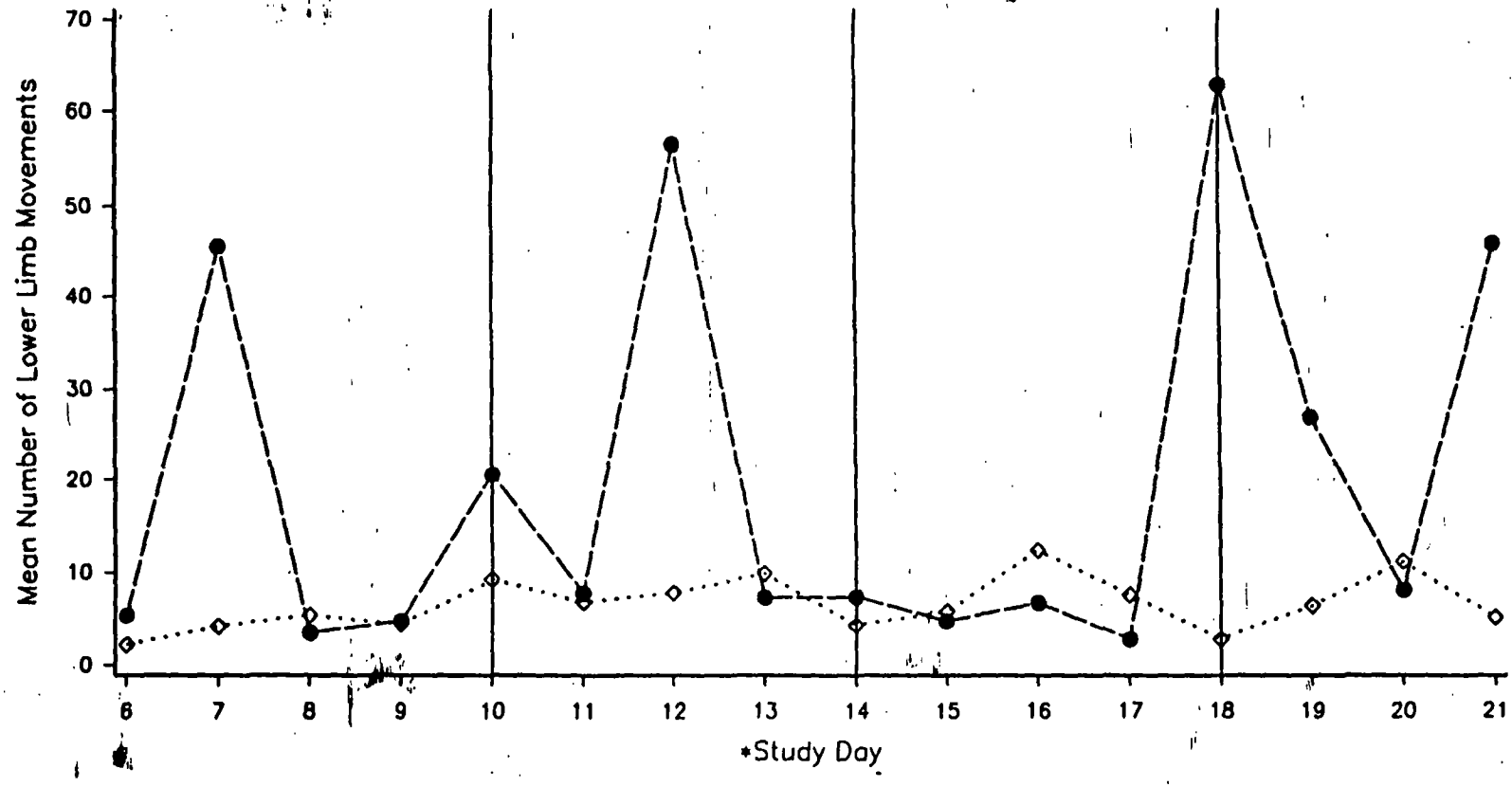
Figure 5
Mean Number of Lower Limb Movements by Dose and Time Post Dose
Ziprasidone Protocol 015



☆ ☆ ☆ SB Ziprasidone 80mg, bid, •day 5,(n=11) • • • Ziprasidone 40mg, qid, •days 9,13,17 and 21,(n=16)
◇ ◇ ◇ Ziprasidone 80mg, bid, •days 9,13,17 and 21,(n=15) * * * SB Placebo •day 0,(n=14)

• First day of Ziprasidone dosing is day 1
QID dosing was at 0, 6, 12 and 18 Hours post dose. BID dosing was at 0 and 12 hours post dose.
Source Data : Appendix III, Tables 1.5 – 1.8 Date of Data Extraction : 09NOV95 Date of Figure Generation : 15MAY96

Figure 6
Mean Number of Lower Limb Movements by Dose and Day for Four Hours Post First Dose
Ziprasidone Protocol 015



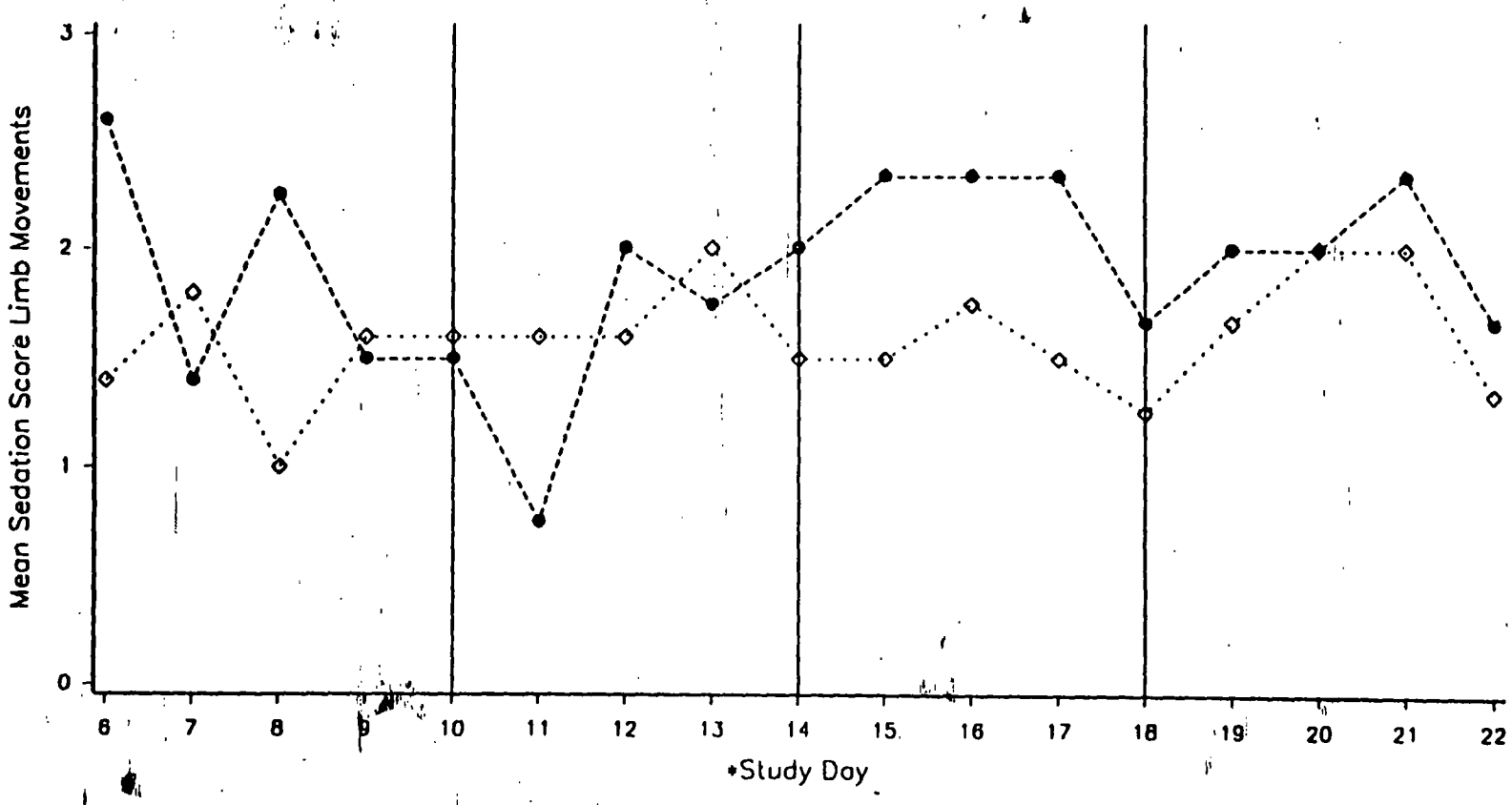
◇ ◇ ◇ Sequence 1: 40mg, qid ->80mg, bid ->40mg, qid ->80mg, bid
••• Sequence 2: 80mg, bid ->40mg, qid ->80mg, bid ->40mg, qid

*First day of Ziprasidone dosing is day 1.
On days 10, 14, and 18 subjects switched from qid to bid, or bid to qid therapy depending on the sequence
Source Data : Appendix III, Tables 1.3 and 1.4 Date of Data Extraction : 09NOV95 Date of Figure Generation : 12JUN96

(21)

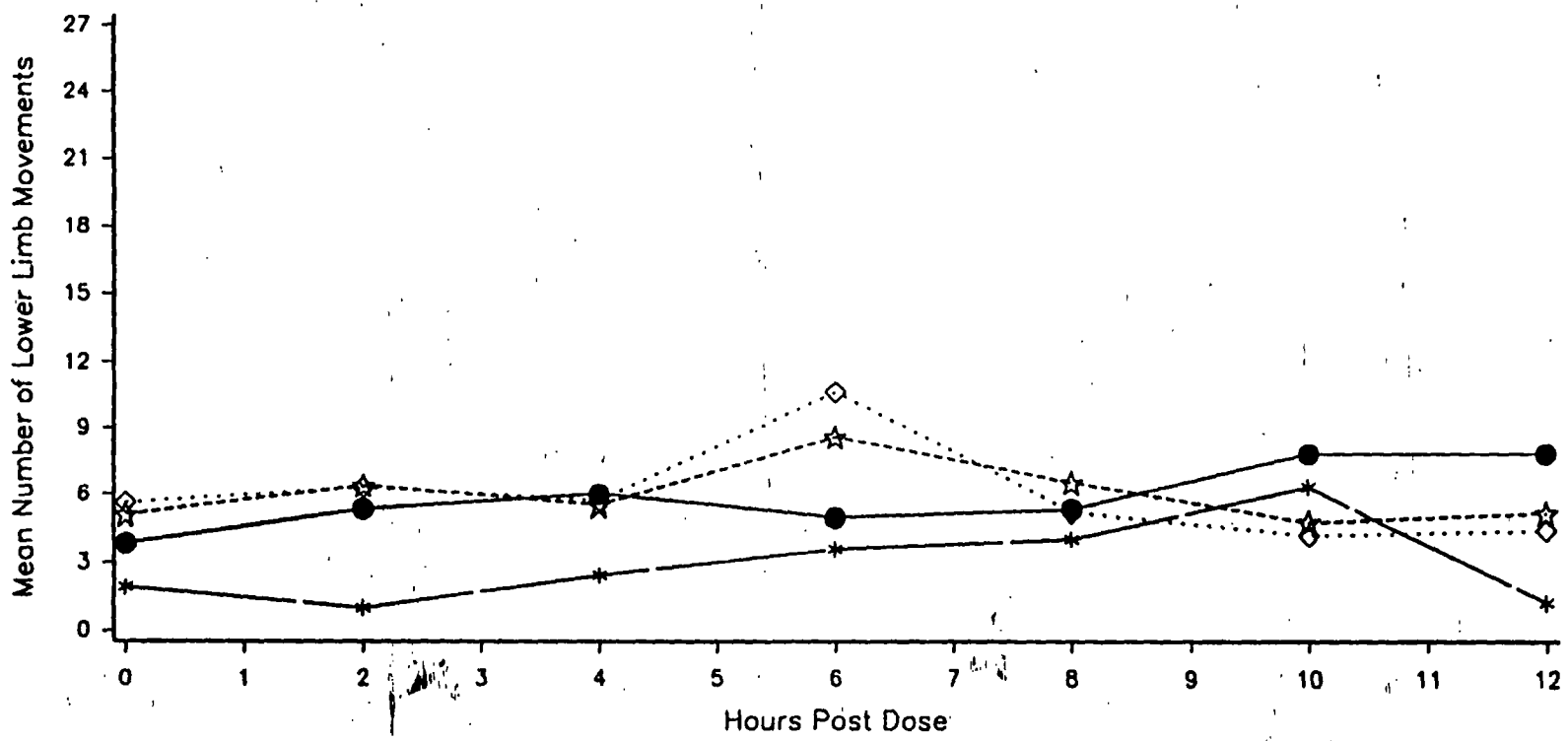
(21)

Figure 7
Mean Sedation by Dose and Day for Four Hours Post First Dose
Ziprasidone Protocol 015



◇ ◇ ◇ Sequence 1: 40mg, qid ->80mg, bid ->40mg, qid ->80mg, bid
••• Sequence 2: 80mg, bid ->40mg, qid ->80mg, bid ->40mg, qid
*First day of Ziprasidone dosing is day 1.
On days 10, 14, and 18 subjects switched from qid to bid, or bid to qid therapy depending on the sequence
Source Data : Appendix III, Tables 2.3 and 2.4 Date of Data Extraction : 09NOV95 Date of Figure Generation : 12JUN96

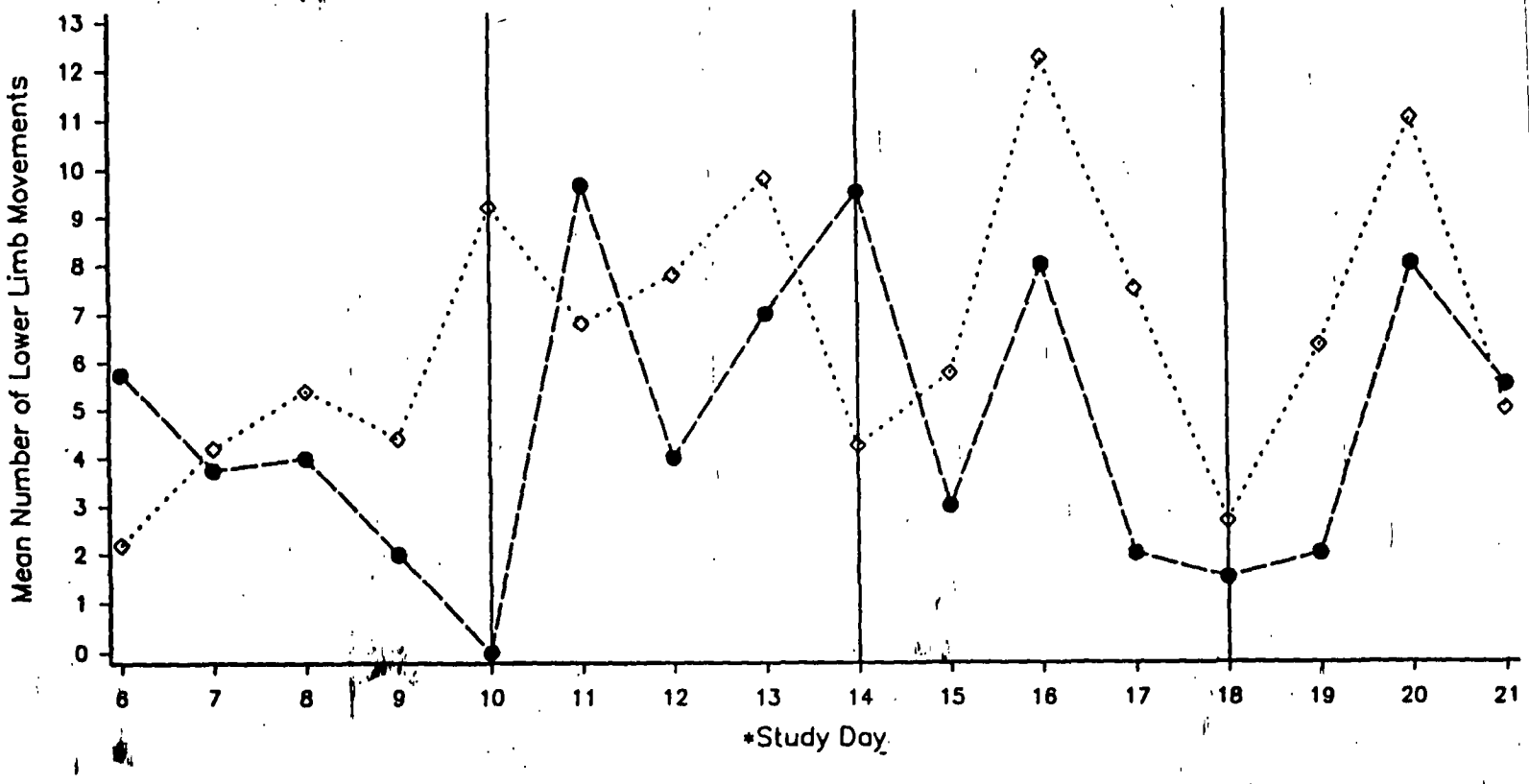
Figure 8
Mean Number of Lower Limb Movements by Dose and Time Post Dose
(Without Outlier: Subject #50020013)
Ziprasidone Protocol 015



☆ ☆ ☆ SB Ziprasidone 80mg, bid, •day 5,(n=10) • • • Ziprasidone 40mg, qid, •days 9,13,17 and 21,(n=14)
◇ ◇ ◇ Ziprasidone 80mg, bid, •days 9,13,17 and 21,(n=13) * * * SB Placebo •day 0,(n=13)

• First day of Ziprasidone dosing is day 1
QID dosing was at 0, 6, 12 and 18 Hours post dose. BID dosing was at 0 and 12 hours post dose.
Source Data : Appendix III, Tables 3.4 – 3.7 Date of Data Extraction : 09NOV95 Date of Figure Generation : 09JUL96

Figure 9
Mean Number of Lower Limb Movements by Dose and Day for Four Hours Post First Dose
(Without Outlier: Subject #50020013)
Ziprasidone Protocol 015



◇ ◇ ◇ Sequence 1: 40mg, qid –>80mg, bid –>40mg, qid –>80mg, bid
••• Sequence 2: 80mg, bid –>40mg, qid –>80mg, bid –>40mg, qid

*First day of Ziprasidone dosing is day 1.
On days 10, 14, and 18 subjects switched from qid to bid, or bid to qid therapy depending on the sequence
Source Data : Appendix III, Tables 1.3 and 3.3 Date of Data Extraction : 09NOV95 Date of Figure Generation : 12JUN96

Study 032: (Different Infusion Rates, 2.5 to 40 mg, patients)

Study Design and Summary:

(see attachments 1-4)

Results:

(See attachments 5-20)

Reviewer's Comments:

1. Clearly the PK of the drug is linear within the tested IV doses in this study (5 to 40 mg) since the PK parameters (CL, Vd and half-life) remain constant and the Cmax and AUC increased proportionally with the dose (attachments 5-8 and 10-13).

2. There is anti-clock hysteresis relationship between sedation and serum ziprasidone concentration at 10, 20 and 40 mg dose levels (examples are shown for two subjects in attachments 14 and 15). This suggests a delay effect for the drug which can be due to several facts such as delay in distribution or delivery to the site of action. However, according to the sponsor, all the metabolites are inactive. No explanations were made by the sponsor on this observed hysteresis relationship. In addition, there was relatively good correlation between the observed and predicted sedation scores with the dose (attachments 16-20).

3. The saliva/plasma ratio was extremely low (0.001 to 0.025) which is consistent with its high degree of plasma protein binding (~99.9 %). No clear relationship between the plasma and the saliva concentration was observed (attachment 9).

4. The drug appears to cause postural hypotension and tachycardia at the IV dose >10 mg.

Conclusions:

1. The drug follows linear PK within the study dose range (5 and 40 mg)

2. In general, there is no clear relationship between the sedation and the serum concentration.

3. The tolerable dose is 10 to 20 mg.

PROTOCOL 128-032: PHASE I OPEN PILOT STUDY TO EVALUATE THE EFFECT OF THE INFUSION RATE AND DOSE ON THE SAFETY, TOLERATION AND PHARMACOKINETICS OF ZIPRASIDONE IN SUBJECTS WITH CHRONIC OR SUBCHRONIC SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER

Principal Investigator: S. Preskorn, M.D.

Study Publication: None

Study Dates: 09 January 1995 - 22 March 1995

Study Objective: To explore the tolerability of various infusion rates of ziprasidone and to determine, for each infusion rate, whether sedation would occur in the absence of clinically significant hypotension.

Study Design: This was an open non-randomized, 2- to 3- way crossover inpatient study to evaluate ziprasidone pharmacokinetics and pharmacodynamics in the same subjects. Various doses of ziprasidone were administered intravenously over 30 minutes under fasting conditions on 2 to 3 separate dosing days. This study included a 5-day washout period of previous neuroleptic treatment prior to each subject receiving his/her first infusion of ziprasidone. There was at least 3 days separating each infusion.

Evaluation Groups:

	Ziprasidone IV Infusion			
	5 mg	10 mg	20 mg	40 mg
Entered Study	1	8	7	2
Completed Study	1	8	5	2
Evaluated for Pharmacokinetics	1	8	7	2
Evaluated for Pharmacodynamics				
Blood Pressure and Pulse Rate	1	8	7	2
Sedation Evaluation	1	8	7	2
Assessed for Safety				
Adverse Events	1	8	7	2
Laboratory Tests[a]	0	0	0	0

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

Subjects: Male or female subjects with chronic or subchronic schizophrenia or schizoaffective disorder, between the ages of 38 and 50, inclusive.

Drug Administration:

Dosage Form

Ziprasidone for intravenous administration was supplied to the site at a concentration of 0.05 mg/ml isotonic, pH 3.5, pyrogen-free aqueous solution. The volume of the intravenous solution and infusion rate for each dose level is as follows:

Dose Level (mg)	Amount of IV Solution (ml)	Infusion Rate (ml/min)	Duration of Infusion (min)
2.5	50	1.67	30
5	100	3.33	30
10	200	6.67	30
20	400	13.3	30
40	800	26.7	30

Dosing: Subjects who completed the washout period entered the active treatment period. Two or three doses of ziprasidone infused over 30 minutes were evaluated. Each infusion was separated by at least 3 days. The first dose evaluated for each subject was 10 mg. If at any time point up to 24 hours after dosing a subject had clinically significant and symptomatic orthostatic hypotension, then succeeding dose levels for this subject were serially decreased until this postural hypotension was no longer observed or a maximum of two additional dose levels were evaluated. If no clinically significant and symptomatic postural hypotension was observed at the 10 mg dose level for a subject, then succeeding dose levels for this subject were serially increased until significant postural hypotension was observed or a maximum of two additional dose levels were evaluated. The order of the two possible alternatives for each subject are listed below:

(a) 10 mg → 5 mg → 2.5 mg
(b) 10 mg → 20 mg → 40 mg

Pharmacokinetic and Safety Evaluations: Blood samples for determination of serum ziprasidone concentrations were collected just prior to infusion and up to 36 hours after the start of each infusion. Saliva samples were collected just prior to infusion and at 0.5 hours after the infusion. A subject self-evaluation for the presence of sedation was performed prior to and up to 24 hours after drug administration. Subjects were monitored for adverse events and changes in vital signs.

Analytical Methods:

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

Pharmacokinetic Results:

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

	Ziprasidone IV Infusion							
	5 mg		10 mg		20 mg		40 mg	
	Mean	CV%	Mean	CV%	Mean	CV%	Mean	CV%
$AUC_{(0-\infty)}$[a] (ng•hr/ml)	247		436	27	855	33	1646	26
C_{max}[a] (ng/ml)	113		218	19	360	21	621	42
T_{max} (hr)	0.33		0.44	20	0.43	30	0.33	0
K_{el}[b] (1/hr)	0.150		0.201	44	0.193	51	0.125	9
$T_{1/2}$[c] (hr)	4.6		3.5		3.6		5.5	
CL (ml/min/kg)	3.6		5.1	51	5.4	59	3.9	11
Vdss (L/kg)	0.9		1.1	13	1.2	20	1.2	12

a = Geometric means
b = Adjusted means are displayed for K_{el}.
c = Calculated as 0.693/mean K_{el}.

Safety Results:

	Number of Subjects [With/Evaluated (Discontinued)]			
	Ziprasidone IV Infusion			
Findings	5 mg	10 mg	20 mg	40 mg
Adverse Events (All Causality)	1/1(0)	8/8(0)	7/7(3)	2/2(0)
Adverse Events (Treatment-emergent, Treatment-related)	0/1(0)	8/8(0)	7/7(3)	2/2(0)

( ) Subjects discontinued
In the 20 mg group there were 2 subjects that completed the study as per protocol but did not continue on to the 40 mg dosing because of adverse events.

Summary and Conclusions: Following intravenous infusions of 5, 10, 20 and 40 mg of ziprasidone over 0.5 hours to eight subjects, exposure to drug as measured by both $AUC_{(0-\infty)}$ and C_{max} appeared to be proportional to dose. Systemic clearance and volume of distribution were similar across this dose range with mean values of 5.0 ml/min/kg (mean range 2.7 to 12.0 ml/min/kg) and 1.1 L/kg (mean range 0.8 to 1.6 L/kg), respectively. T_{max} was similar across doses and generally occurred at the end of the infusion. Terminal phase rate constants were similar across doses with corresponding mean $T_{1/2}$ values ranging from approximately 4 to 6 hours.

Saliva concentrations determined at the end of the infusion (0.5 hour) ranged from <0.1 to 9.4 ng/ml. The ratio of saliva concentration to the corresponding serum concentration generally ranged from 0.001 to 0.025 (0.007±116%CV ng/ml, n=12).

For the majority of subjects, no clear relationship was apparent in the plots of the change in sedation score from baseline versus observed ziprasidone serum concentration by dose. Changes from baseline in standing vital signs did not have any apparent direct or indirect relationship to the observed serum concentration.

The most frequently occurring adverse event reported was somnolence, mild to moderate in severity. There were no severe or serious adverse events reported. Two subjects in the 20 mg IV infusion group discontinued the study, one because of a treatment-related event (tachycardia). Two subjects in the 20 mg IV infusion treatment group were discontinued from dosing due to postural hypotension but were considered to have completed the study. One subject in the 10 mg IV infusion group had a dosage reduction due to postural hypotension.

In conclusion, multiple doses of ziprasidone given as an IV infusion over 30 minutes were well tolerated at 5, 10, and 20 mg. These results indicate that rapid administration of ziprasidone may be associated with a relatively rapid onset of sedation, in the absence of clinically significant hypotension.

(5) (5)

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Table 5.1. Summary of Pharmacokinetic Parameters for Ziprasidone IV Infusion of an Aqueous Solution of Ziprasidone at Various Infusion Rates to Subjects with Chronic or Subchronic Schizophrenia or Schizoaffective Disorder.

Ziprasidone Protocol #128-032-572

	Dose (mg)	Rate (mg/h)	AUC(0-∞) (ng•hr/ml)	AUMC(0-∞) (ng•hr/ml)	Cmax (ng/ml)	Tmax (hr)	Kel (hr^{-1})	T1/2 (hr)	CL (ml/min)	CL (ml/min/kg)	Vdss (L)	Vdss (L/kg)
	5	10										
Mean*	10	20	436	1747	218	0.44	0.201	3.5	395	5.1	87.5	1.1
S.D.			118	1028	41	0.09	0.088		105	2.6	18.6	0.1
CV%			27	59	19	20	44		27	51	21	13
Mean*	20	40	855	3585	360	0.43	0.193	3.6	407	5.4	94.3	1.2
S.D.			283	2258	76	0.13	0.099		126	3.2	24.6	0.2
CV%												
Mean*	40	80	1646	8627	621	0.33	0.125	5.5	412	3.9	123.8	1.2
S.D.			424	1933	259	0.00	0.011		105	0.4	35.8	0.1
CV%			26	22	42	0	9		26	11	29	12
All Doses												
Mean*						0.42	0.186	3.7	398	5.0	94.0	1.1
S.D.						0.10	0.085		105	2.6	23.7	0.2
CV%						25	46		26	52	25	17

* Geometric means and standard deviations are reported for AUC(0-∞), AUMC(0-∞) and Cmax.

Table 5.2. Individual and Mean Pharmacokinetic Parameters Following an Approximately 0.5 Hour IV Infusion of Ziprasidone HCl at Various Infusion Rates to Subjects with Chronic or Subchronic Schizophrenia or Schizoaffective Disorder.

Ziprasidone Protocol #128-032-572

Subject #	Wt (kg)	Treatment Day	Dose (mg)	Rate (mg/h)	AUC(0-∞) (ng•hr/ml)	AUMC(0-∞) (ng•hr/ml)	Cmax (ng/ml)	Tmax (hr)	Kel (hr^{-1})	T½ (hr)	CL (ml/min)	CL (ml/min/kg)	Vdss (L)	Vdss (L/kg)
5570006	93.0	4	5	10										
5570001	92.7	1	10	20										
5570002	115.0	1	10	20										
5570003	48.6	1	10	20										
5570004	85.5	1	10	20										
5570005	88.2	1	10	20										
5570006	93.0	1	10	20										
5570007	81.0	1	10	20										
5570008	73.0	1	10	20										
Mean*	84.6				436	1747	218	0.44	0.201	3.5	395	5.1	87.5	1.1
S.D.	19.0				118	1028	41	0.09	0.088		105	2.6	18.6	0.1
CV%	22				27	59	19	20	44		27	51	21	13
5570001	92.7	4	20	40										
5570002	115.0	4	20	40										
5570003	48.6	4	20	40										
5570004	85.5	4	20	40										
5570005	88.2	4	20	40										
5570007	81.0	4	20	40										
5570008	73.0	4	20	40										
Mean*	83.4				855	3585	360	0.43	0.193	3.6	407	5.4	94.3	1.2
S.D.	20.1				283	2258	76	0.13	0.099		126	3.2	24.6	0.2
CV%	24				33	63	21	30	51		31	59	26	20
5570001	92.7	7	40	80										
5570002	115.0	7	40	80										
Mean*	103.8				1646	8627	621	0.33	0.125	5.5	412	3.9	123.8	1.2
S.D.	15.8				424	1933	259	0.00	0.011		105	0.4	35.8	0.1
CV%	15				26	22	42	0	9		26	11	29	12
All Doses														
Mean								0.42	0.19	3.7	398	5.0	94.0	1.1
S.D.								0.10	0.09		105	2.6	23.7	0.2
CV%								25	46		26	52	25	17

* Geometric means and standard deviations are reported for AUC(0-∞), AUMC(0-∞) and Cmax.

(7)

(7)

Table 5.3. Summary of Pharmacodynamic Parameters Obtained for the Relationship Between Change in Sedation Score and Ziprasidone Effect Compartment Concentration Following an Approximately 0.5 Hour IV Infusion of Ziprasidone HCl at Various Infusion Rates to Subjects with Chronic or Subchronic Schizophrenia or Schizoaffective Disorder.

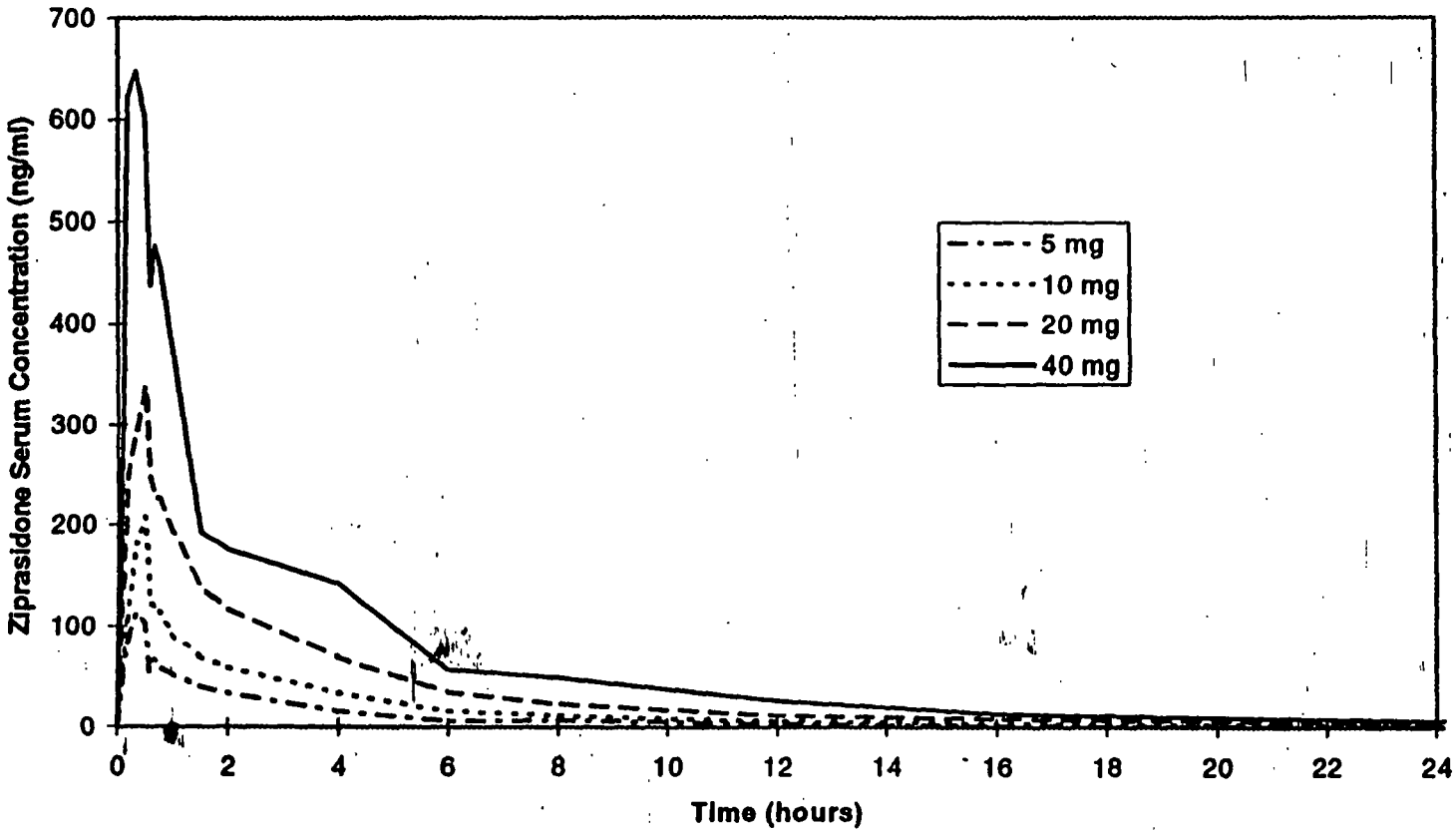
Ziprasidone Protocol #128-032-572

		EC50 (ng/ml)		Emax		Gamma		Keo (1/hr)	
Subject #	Dose (mg)	Estimate	StdError	Estimate	StdError	Estimate	StdError	Estimate	StdError
5770001	10	102	5	48	3	4.4	0.4	2.9	0.1
5770002	10	63	41	13	8	2.7	2.1	2.2	0.6
5770008	10	141	1118*	82	1744*	3.6	7.8	1.2	0.3
5770001	20	133	57	61	9	10.0	28.7	3.0	2.6
5770002	20	63	16	20	4	2.6	1.2	1.3	0.3
5770004	20	125	8	85	9	10.0	3.3	2.4	0.2
5770007	20	112	38	27	6	3.6	2.9	3.9	2.9
5770008	20	520	1562*	71	286*	1.9	0.9	2.0	0.3
5770001	40	160	13	79	4	9.8	3.9	4.5	0.5
5770002	40	160	64	61	19	2.1	0.8	2.3	0.4

* Note that the standard error is very high so the parameter estimate is unreliable.

Figure 1.1. Mean Serum Ziprasidone Concentrations Versus Time Following Administration of 5, 10, 20, and 40 mg IV Infusions over 0.5 Hour to Subjects with Chronic or Subchronic Schizophrenia or Schizoaffective Disorder.

Ziprasidone Protocol #128-032-572



FIRM PFIZER CENTRAL RESEARCH, PFIZER INC
DRUG ZIPRASIDONE HYDROCHLORIDE (CP-88,059-1)
NDA 20-825

PROPOSED DISSOLUTION METHOD AND SPECIFICATION[1]

1.	Dosage Form	Capsule
2.	Strength	20, 40, 60, 80 and mg
3.	Apparatus	USP Apparatus 2
4.	Media[2]	0.05 M sodium phosphate (NaH_2PO_4) with 2% sodium dodecylsulfate (SDS), pH = 7.5
5.	Volume	900 mL
6.	Speed	75 rpm
7.	Sampling Time	45 minutes
8.	Brief Description of Dissolution Analytical Method	
9.	Recommended Dissolution Specification	USP <711> Q value of % at 45 minutes

[1] Rationale for dissolution method and specifications is appended to this document.
[2] Ziprasidone capsules may be tested by a two-tiered method (see attached rationale). Represented in the table, above, is the Tier 1 test. The media used for the tests are different from Tier 1 to Tier 2. The incubation medium for the Tier 2 test is 700 mL 0.05 M NaH_2PO_4 adjusted to a pH of 7.5 and contains 1% pancreatin. The dissolving medium for the Tier 2 test is 200 mL 0.05 M NaH_2PO_4 adjusted to a pH of 7.5 and contains 9% sodium dodecylsulfate (SDS). Thus a total of 900 mL of media is used for this Tier 2 test.

(6)

6

Table H.5.23.2 [Short Term] - Centrally Read 104,106,114, & 115
Change from Baseline to Last Observation in ECG Readings
Short-Term Fixed-Dose Placebo-Controlled Oral Dosing Phase II/III Studies
By BID Dose - Centrally Read Data

Variable	Treatment Group	N	Base Mean	Base Median	Base Range	Final Mean	Final Median	Final Range	Mean Change
*QTc int (msec)	Placebo	250	399.0	400.0					
	<40mg BID	230	396.9	396.0		396.5	396.0		-2.6
	40mg BID	138	397.6	396.5		397.5	396.5		0.6
	60mg BID	111	398.0	398.0		403.4	404.0		5.9
	80mg BID	100	394.6	394.5		405.7	404.0		7.7
	>-100mg BID	77	402.7	403.0		404.3	404.0		9.7
	Haloperidol	76	400.2	401.5		409.1	412.0		6.4
						398.6	398.5		-1.6
QT int (msec)	Placebo	250	348.6	344.5					
	<40mg BID	230	354.6	357.0		348.8	348.0		0.3
	40mg BID	138	351.2	349.0		350.2	350.5		-4.4
	60mg BID	111	352.5	356.0		351.5	350.0		-0.3
	80mg BID	100	352.4	351.0		359.6	357.0		7.1
	>-100mg BID	77	354.9	355.0		359.6	360.0		7.2
	Haloperidol	76	357.3	354.5		360.6	358.0		5.8
						354.9	354.5		-2.4
Heart Rate (bpm)	Placebo	250	80.4	78.0					
	<40mg BID	230	76.6	74.0		79.3	78.0		-1.1
	40mg BID	138	78.6	76.5		79.0	79.0		2.4
	60mg BID	111	78.5	77.0		80.8	79.0		2.2
	80mg BID	100	76.7	75.0		78.3	78.0		-0.2
	>-100mg BID	77	78.8	78.0		77.1	76.5		0.4
	Haloperidol	76	76.8	75.5		79.0	80.0		0.2
						77.2	77.0		0.4
PR int (msec)	Placebo	250	149.2	148.0					
	<40mg BID	230	148.8	147.0		148.9	146.0		-0.3
	40mg BID	138	148.4	146.0		147.8	146.0		-1.0
	60mg BID	111	149.2	146.0		146.5	146.0		-1.9
						148.3	145.0		-0.9

New data

Protocols: 104,106,114,115
BID dose is modal dose
*QTc int = QT int/SQRT(60/(Heart Rate))
Baseline = last ECG taken before the first day of study treatment.
Final = last ECG taken while on study treatment or within six days after the last day of study treatment.
Date of table generation: 21OCT97.

Nov 13, 1997
Submission

APPENDIX II

(Dosage Form Formulations)

D.2 Drug Product [Ziprasidone Hydrochloride Monohydrate Capsules (20, 40, 60, 80 and 100 mg)]

D.2.A Composition

The compositions of ziprasidone hydrochloride monohydrate capsules (20, 40, 60, 80 and are as follows:

Component (DFM #)	Reference	Function	20 mg
Ziprasidone Hydrochloride Monohydrate[a]	Pfizer	Active	
Lactose, Monohydrate[b]	NF		
Pregelatinized Starch	NF		
Magnesium Stearate	NF		
Hard Gelatin, Locking Capsule Shell	Pfizer		Blue/White
TOTAL (mg/capsule)			

Component (DFM #)	Reference	Function	40 mg	60 mg	80 mg	
Ziprasidone Hydrochloride Monohydrate[a]	Pfizer	Active				
Lactose, Monohydrate[b]	NF					
Pregelatinized Starch	NF					
Magnesium Stearate	NF					
Hard Gelatin, Locking Capsule Shell	Pfizer		Blue	White	Blue/White	Blue
TOTAL (mg/capsule)			150.0	225.0	300.0	375.0

(a) Based on a theoretical potency factor of
(b) The lactose, monohydrate weight is adjusted according to small potency changes in the ziprasidone hydrochloride monohydrate in order to maintain a constant capsule weight.

D.2.B Manufacturing and Packaging

Ziprasidone hydrochloride monohydrate capsules will be manufactured, labelled and packaged at the following site:

Pfizer Inc
630 Flushing Avenue
Brooklyn New York 11206

D.2.C Specifications and Analytical Methods

1. Components

The following compendial components are used in the manufacture of ziprasidone hydrochloride monohydrate capsules:

Component	Reference
Ziprasidone Hydrochloride Monohydrate	Pfizer
Lactose, Monohydrate	NF
Pregelatinized Starch	NF
Magnesium Stearate	NF
Hard Gelatin, Locking Capsule Shell	Pfizer

Specifications and test procedures for all components are provided or referenced in Section 3 III B.2.

2. Drug Product

The rationale for the quality control methodology and the associated specifications for ziprasidone hydrochloride monohydrate capsules are presented in this Section 3 III B.5. All specifications remain in effect throughout the shelf life of the product. Ziprasidone hydrochloride monohydrate capsules are assigned Pfizer Material Code Numbers FG-19612, -19614, -19616, -19618 and -19620 for the 20, 40, 60, 80 and mg capsules, respectively.

The appearance of the ziprasidone hydrochloride monohydrate capsules is determined by visual inspection in order to ensure the physical integrity of the product. The color and size of the capsule shells were chosen to allow drug product differentiation (between strengths).

The confirmation of identity of ziprasidone hydrochloride monohydrate capsules is achieved by is used because it is specific to the structural configuration of ziprasidone hydrochloride. The contents of the capsule are extracted and may be analyzed by

The assay is performed by an procedure which has been chosen because it is specific for ziprasidone in the presence of the excipients, drug substance impurities and potential degradation products. The range of % of label claim is well precedented for pharmaceutical products.

The content uniformity of the product is determined using the data obtained by the assay procedure. The criteria described in USP <905> are used to evaluate the data.

The water content of the dosage form is determined by . The dosage form is not hygroscopic and water does not affect product stability. The specification of % maximum is based on the data from manufacturing experience and stability studies.

The dissolution rate test for ziprasidone hydrochloride monohydrate capsules is a test employing a proteolytic enzyme in the tier to address the phenomenon of gelatin capsule cross-linking. Capsules are tested using a at rpm in a medium containing % sodium dodecylsulfate (SDS) thermostatted at °C. Test samples are assayed .

The conditions used to assess the dissolution rate of the capsules were developed to address the specific properties of ziprasidone hydrochloride monohydrate. Additional information regarding the selection of the dissolution conditions may be found in the validation package attached to the analytical method (Drug Product Analytical Methods Appendix) and in Section 3 III B.5.3.

The presence of impurities in ziprasidone hydrochloride monohydrate capsules can be attributed to two potential sources, drug substance process related impurities and degradation products formed upon storage. Stability studies reported in the application clearly rule out the possibility of any formation or increase in abundance of drug substance process related impurities. Therefore these materials are controlled at the drug substance stage and not monitored in the drug product. The methodology and the specifications applied to the drug products effectively monitor and control the abundance of the specified degradant. A complete discussion and table detailing the source of the potential impurities is provided in Section 3 III B.5.1. CP-356,567 is a process related impurity and the potential degradation product in ziprasidone hydrochloride monohydrate capsules. It is controlled in the drug substance specifications at %. No significant increase in CP-356,567 has been observed as a result of drug product manufacture nor throughout the drug product stability program. It is a degradant resulting only from treatment. The specification of % CP-356,567 is applied over the shelf-life of the product and is considered safe for administration to humans based on the results of drug safety studies.

The level of unspecified degradants allowed in the capsules is % (each).

A total degradants limit of not more than % is applied to the product. This limit is based on purity profile of the product as well as normal assay variations.

Analytical testing data on batches of ziprasidone hydrochloride monohydrate capsules are presented in Section 3 III B.5.4. All batches conform to the specification requirements.

D.2.D Packaging

Ziprasidone hydrochloride monohydrate 20, 40, 60, 80 and sules will be marketed in multiple container/closure systems. These systems are 1) :

foil blisters.

D.2.E Stability

Ziprasidone hydrochloride monohydrate capsules stored up to months show exceptionally good stability over the wide range of packaging alternatives and challenge conditions evaluated.

Summary of Phase II-III ECG (QTc) Data

Study Design and Summary:

(see attachments 1-2)

Results:

(See attachments 3-6)

Reviewer's Conclusion:

The graph shown in attachment 3 which is generated from the data shown in attachment 4, of the original submission, clearly demonstrates that the QTc prolongation is dose dependent. In patients with a placebo, there was a negative change in QTc (-2.6 msec) and in the haloperidol group, a well know anti-psychotic drug, was only 0.2 msec. However, in patients receiving ziprasidone, the mean change in QTc interval ranged from 4.0 to 12.1 as the dose increased from <40 mg BID to 100 mg BID.

In a subsequent submission dated November 13, 1997, the QTc data were further analyzed by the sponsor. Overall, it was concluded that in the original submission the observed dose dependent QTc prolongation was spurious which was due to the variability and the imprecision in QTc measurements. However, attachment 5, which is generated from the new data (attachment 6), still shows a dose dependent prolongation in QTc interval.

Based on the available data, it can be concluded that ziprasidone causes dose dependent prolongation in QTc intervals.

change from baseline. Subjects receiving either 80 mg or ≥100 mg of ziprasidone daily demonstrated median decreases in standing heart rate of -2.0 bpm. Measurement of sitting heart rate showed a median increase of 2.0 bpm among subjects receiving 40 mg ziprasidone daily and a median decrease of -3.0 bpm among subjects receiving 80 mg ziprasidone daily. Supine measurements of systolic and diastolic blood pressure showed median decreases of -8.0 mmHg and -10.0 mmHg, with a 2.0 bpm increase in supine heart rate in subjects receiving 60 mg BID of ziprasidone. Only small increases in body weight were observed across all doses of ziprasidone (0.5 to 0.7 kg).

Table H.5.21d displays median changes from baseline to last observation in vital signs with respect to gender for STFDPC trials. There appear to be no clinically meaningful differences between males and females.

Table H.5.21e displays median changes from baseline to last observation in vital signs with respect to age in STFDPC trials. Due to the small number of subjects aged 65 to 74 years, no meaningful conclusions can be drawn from these data.

Table H.5.21f displays median changes from baseline to last observation in vital signs with respect to race in STFDPC trials. There were no apparent clinically meaningful differences noted.

Median change from baseline to last observation for STFDAC, maintenance, North American and non-North American studies are presented in Tables H.5.21g, H.5.21h and H.5.21j. There are no remarkable findings.

H.5.H ECG Data

Electrocardiograms were recorded in all Phase II-III trials. Tracings collected in most trials (and in all STFDPC trials) were read at the site, and readings are recorded in the project database. Other clinical trials employed off-site third-party reading of ECG tracings, and those results are recorded in the project database. Tracings recorded in the 52-week placebo controlled Study 303 were initially read on-site, then delivered to , for blinded reading. The data collected on-site as well as the data provided by , are displayed in the 303 Study Report data listings, while that provided by has been summarized in 303 Study Report tables. This data has not been merged with the project database, so that H.5.23 tables include separate displays for data provided by , which is excluded from other H.5.23 tables.

Among ziprasidone treated subjects a mean increase in QTc interval of 3.8 msec was noted in all oral Phase II-III trials (Table H.5.23a). In STFDPC trials this increase appears to be dose-related, with a maximum mean increase of 12.1 msec measured in the 77 subjects receiving doses of 100 mg BID (Table H.5.23c). The mean increase was somewhat greater in females than males (Table H.5.23d). There are no apparently meaningful differences by race (Table H.5.23f).

However, this mean increase is not apparent in Study 303, where little mean change was seen in these ziprasidone-treated subjects (Section H.5.23m). In addition, no subjects in Study 303 exhibited a QTc interval of 500 msec or greater (Table H.5.22m).

Overall, the incidence of QTc prolongation to 500 msec or more was similar in ziprasidone-treated subjects (0.8%) compared to those treated with haloperidol (1.0%) or placebo (1.2%; Table H.5.22a). The proportion of female subjects reaching this threshold appeared to be numerically greater than for males. Overall, including Study 303, there were no ziprasidone-treated subjects and one placebo-treated subject with a QTc interval of at least 500 msec on more than one occasion.

None of the individuals who experienced syncope (N = 15 overall) were found to have a QTc of 500 msec or greater.

A QTc interval of 500 msec or greater was measured on one occasion in 13 ziprasidone-treated subjects (Table H.5.22a) (01505570008, 10105100053, 11506560036, 11506730408, 11507210511, 116B05560001, 116B05770005, 116B06040002, 116B0650003, 116B06690020, 30102190733, 10405210196, 11706480267). In these subjects, there were no adverse events experienced which would suggest that these QTc prolongations were of clinical significance (two subjects with dizziness and one with dizziness and transient postural hypotension from Days 1-3), and overall incidence in ziprasidone-treated subjects did not exceed that seen in controls.

Electrocardiographic data from all STFDPC trials was made available to Dr. , a third party consultant. Dr. after reviewing data listings and tables, requested and was provided individual tracings for overread. These data were then entered into a new ECG database, used by Dr. to support his report regarding the effect of ziprasidone upon the ECG. These tables and listings may be found with his report, located in Appendix X of Section 8 of this application. It is the conclusion of Dr. that ziprasidone has no clinically significant effect upon the ECG.

Phase I Studies

None of the 75 subjects receiving ziprasidone or the 33 subjects receiving placebo in multiple-dose clinical pharmacology studies had QTc intervals greater than 500 msec in duration (Table H.5.22n). Overall mean increases from baseline in both QTc interval and heart rate were observed in subjects receiving ziprasidone (9.2 msec and 4.5 bpm, respectively) or placebo (mean changes of 6.8 msec and 3.4 bpm, respectively) (Table H.5.23n). Similar mean decreases in QT interval were observed in both treatment groups (ziprasidone: -4.7 msec; placebo: -4.8 msec). Both treatment groups showed decreases in QRS interval (ziprasidone: -1.4 msec; placebo: -3.0 msec) and subjects receiving ziprasidone showed a very small mean decrease (-0.3 msec) in PR interval, whereas subjects receiving placebo showed no change.

H.5.I Ophthalmology Data

An ophthalmology (including slit lamp) examination was required by protocol in most long-term clincial trials. The incidence of clinically significant changes from baseline in ophthalmology data in Phase II/III studies was slightly greater in subjects receiving ziprasidone (8.0%) than those receiving haloperidol (6.0%), risperidone (5.4%), or placebo (6.1%) (Table H.5.24a). There was no particular pattern of abnormalities to suggest a toxic effect of ziprasidone upon the eye (Appendix V, Table 11.2).

H.5.J Concomitant Medications

Table H.5.25a lists all concomitant medications recorded by the investigators for all subjects receiving ziprasidone or comparative agents in Phase II/III clinical trials. The vast majority of subjects in this study population received concomitant medications, with no appreciable differences across treatment groups (84.5% to 92.1%) in the overall proportion of subjects receiving concomitant medications. Approximately 90% of the 2140 subjects receiving ziprasidone received a concomitant medication, most commonly hypnotics, sedatives, and anxiolytics (70.2%).

H.5.K Medical History

Table H.5.26a is a tabular presentation of the medical history of all subjects enrolled in oral dosing Phase II/III studies.

Mean Change in QTc After Administration of Ziprasidone in Phase II-III
(From Table H.5.23c in the Original Submission)

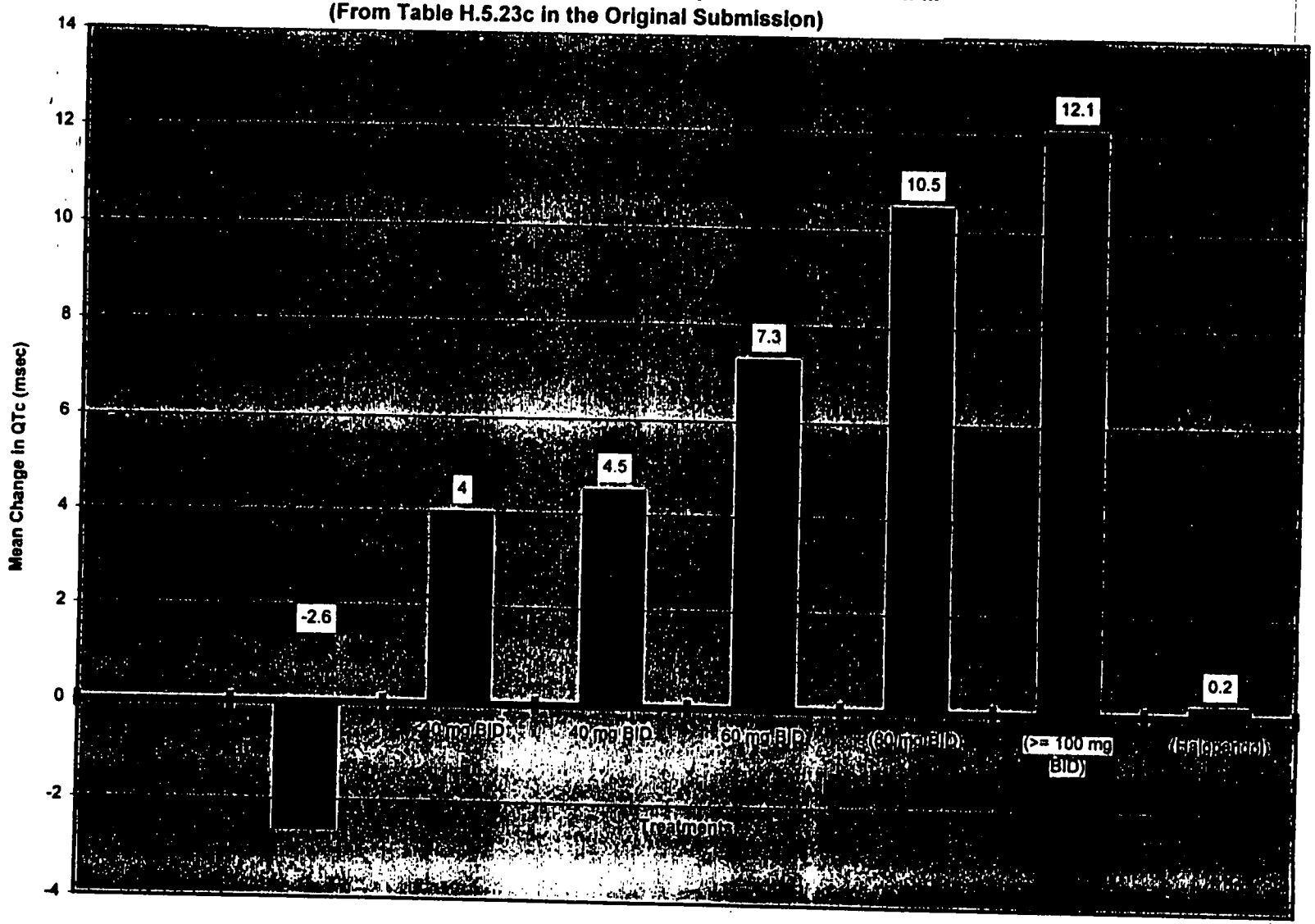


Table 11.5.23c
Change from Baseline to Last Observation in ECG Readings
Short-Term Fixed-Dose Placebo-Controlled Oral Dosing Phase II/III Studies
By BID Dose

Variable	Treatment Group	N	Base Mean	Base Median	Base Range	Final Mean	Final Median	Final Range	Mean Change
*QTc Int (msec)	Placebo	251	411.3	409.0		408.6	407.8		-2.6
	<40mg BID	232	409.9	406.9		413.9	412.6		4.0
	40mg BID	137	410.8	408.8		415.3	416.6		4.5
	60mg BID	111	410.9	409.4		418.2	416.6		7.3
	80mg BID	100	407.0	404.8		417.5	412.3		10.5
	>=100mg BID	77	413.0	410.3		425.1	422.2		12.1
	Haloperidol	76	409.7	411.6		409.9	409.0		0.2
QT Int (msec)	Placebo	251	361.5	360.0		360.2	360.0		-1.3
	<40mg BID	232	366.7	368.0		365.2	362.5		-1.5
	40mg BID	137	362.7	360.0		362.3	360.0		-0.4
	60mg BID	111	363.9	362.0		369.1	364.0		5.2
	80mg BID	100	363.3	364.0		370.8	369.0		7.6
	>=100mg BID	77	364.0	360.0		374.5	372.0		10.5
	Haloperidol	76	366.1	363.5		365.7	364.0		-0.5
Heart Rate (bpm)	Placebo	251	79.3	77.0		79.0	78.0		-0.3
	<40mg BID	232	76.4	75.0		78.6	79.0		2.2
	40mg BID	137	78.6	77.0		80.5	78.0		1.9
	60mg BID	111	78.4	78.0		78.9	78.0		0.5
	80mg BID	100	76.8	75.5		77.3	76.0		0.5
	>=100mg BID	77	78.7	77.0		78.9	79.0		0.2
	Haloperidol	76	76.8	75.0		77.0	75.5		0.2
PR Int (msec)	Placebo	251	150.6	151.0		151.7	152.0		1.1
	<40mg BID	231	150.9	150.0		150.5	150.0		-0.4
	40mg BID	136	150.2	150.5		149.3	148.0		-0.9
	60mg BID	111	153.4	150.0		151.2	150.0		-2.2

Protocols: 104,106,114,115
BID dose is modal dose
*QTc Int = QT Int/SQRT(60/(Heart Rate))
Baseline = last ECG taken before the first day of study treatment.
Final = last ECG taken while on study treatment or within six days after the last day of study treatment.
Date of table generation: 10FEB97.

dose dependent

The Original submission

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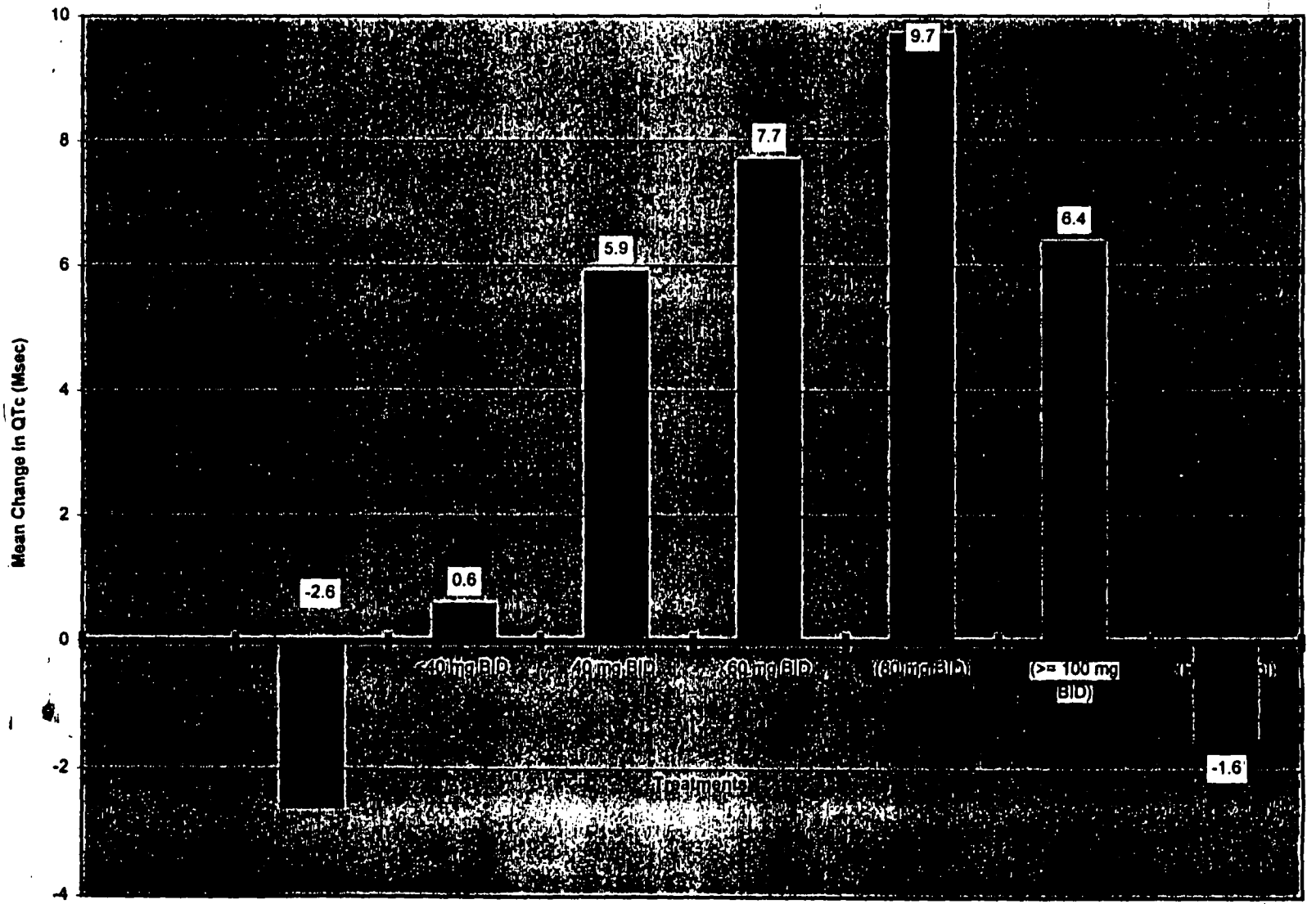
Mean Change in QTc After Administration of Ziprasidone in Phase II-III
(From Table H.5.23.2 in November 13, 1997 Submission)



The information regarding the selection of the proposed dissolution method is provided below and has been excerpted from Section 3, Chemistry, Manufacturing and Controls (Section 3 III B.5).

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Conclusion

The studies described above demonstrate that the proposed two tiered dissolution test procedure, D 27.453, is a suitable procedure for ziprasidone hydrochloride monohydrate capsules of all strengths for the following reasons:

- The medium provides sink conditions for all capsule strengths of this low solubility drug substance.
- One procedure is applicable to all ziprasidone hydrochloride monohydrate capsule strengths.
- The test will not give misleading results for cross-linked gelatin capsules.
- The test allows setting a typical dissolution specification for an immediate release drug product with a low solubility drug substance,
- The test provides good accuracy, reproducibility and robustness (see validation data accompanying the test procedure).
- The test will discriminate against and allow rejection of aberrant capsule lots.

APPENDIX III

(Dissolution Methodology and Specifications)

based upon the degree of renal impairment is not required. In addition, ziprasidone was not removed by dialysis.

Hepatic Impairment - Although the presence of hepatic impairment may be expected to increase the AUC of ziprasidone, a multiple dose study of the effect of impaired liver function in subject (n=13) with clinically significant (Child-Pugh Class A and B) cirrhosis revealed little effect on the pharmacokinetics of ziprasidone (Protocol #030) indicating that no dose adjustment is required in subjects with mild-to-moderate hepatic impairment.

Age and Gender - In a multiple dose study involving 32 healthy subjects, there was little difference in the pharmacokinetics of ziprasidone between men and women and between elderly (≥ 65 years) and young (18 to 45 years) subjects (Protocol #028).

Smoking Status - In vitro studies utilizing human liver enzymes suggest that ziprasidone is not a substrate for CYP1A2 (Section 2.E) and thus, smoking should not have an effect on the pharmacokinetics of ziprasidone. Consistent with these *in vitro* results, pharmacokinetic screening of schizophrenic patients enrolled in Phase II-III clinical trials has not revealed any significant pharmacokinetic differences between smokers and non-smokers (Section 6.C.8).

Table 2.F.5.A *
Summary of Half-Life of Ziprasidone in Different Populations

	Terminal Half-Life (hr)**				
Subjects	Age (yrs)	N	Mean	5th to 95th Percentile	Full Range
Healthy Volunteers	18-45	59	6.6	2.9-18.0	
Healthy Volunteers	46-64	13	5.3	***	
Elderly Volunteers	≥ 65	19	6.1	3.7-8.9	
Schizophrenic Patients	23-39	6	9.8	***	
Cirrhotic Patients	35-66	13	7.7	***	
Renal Insufficiency Patients	26-73	28	5.9	3.2-9.0	

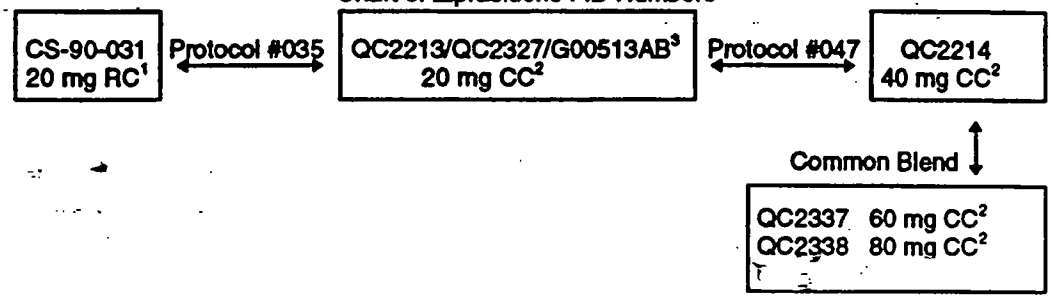
* Source Data: Protocols #013, #015, #026, #028, #030, #049
** Includes only multiple dose fed studies of 40 mg/day or higher
*** N not sufficient to define the 5th to 95th percentile range

2.F.5.B Bioequivalence

A [redacted] of the various ziprasidone FID numbers and the corresponding bioequivalence protocols is shown in Figure 2.F.5.A. On a mg basis, the 20 mg commercial capsules (FID #QC2327 and #QC2213 [only capsule color difference with #QC2327]) are bioequivalent to the 20 mg research capsules (FID #CS-90-031); the 40 mg commercial capsules (FID #QC2214) are bioequivalent to the 20 mg commercial capsules (FID #QC2327); and the 60 mg commercial capsules (FID #QC2337), 80 mg commercial capsules (FID #QC2338)

are prepared from the same common blend as the 40 mg commercial capsules.

Figure 2.F.5.A
Chart of Ziprasidone FID Numbers



[1]Research capsule
[2]Commercial capsule
[3]QC2327 and G00513AB differ from QC2213 only by capsule color

2.F.5.C Drug Interactions

Effect of other drugs on Ziprasidone - Agents that may induce CYP3A4 (e.g. carbamazepine) may increase ziprasidone metabolic clearance. Inhibitors of CYP3A4 (e.g. cimetidine, ketoconazole) could potentially inhibit ziprasidone elimination.

Carbamazepine - Carbamazepine therapy (200 mg bid) resulted in a small decrease (< 40%) in the AUC and Cmax of ziprasidone (Protocol #049).

Cimetidine - Multiple doses of cimetidine (800 mg) did not affect the oral bioavailability of ziprasidone (Protocol #039). This finding is expected as ziprasidone can be metabolized by an alternate pathway that is not mediated by CYP3A4.

Antacids - Multiple doses of aluminum- and magnesium-containing antacids did not affect the oral bioavailability of ziprasidone (Protocol #039).

Benztropine, Propranolol and Lorazepam - Pharmacokinetic screening of schizophrenic patients enrolled in Phase II-III clinical studies has not revealed evidence of clinically significant pharmacokinetic interaction of ziprasidone with these drugs.

2.F.6 Dissolution

Figure 1.6. Individual Saliva Ziprasidone Concentrations vs Serum Concentration Following Following an Approximately 0.5 Hour IV Infusion of Ziprasidone HCl at Various Infusion Rates to Subjects with Chronic or Subchronic Schizophrenia or Schizoaffective Disorder.

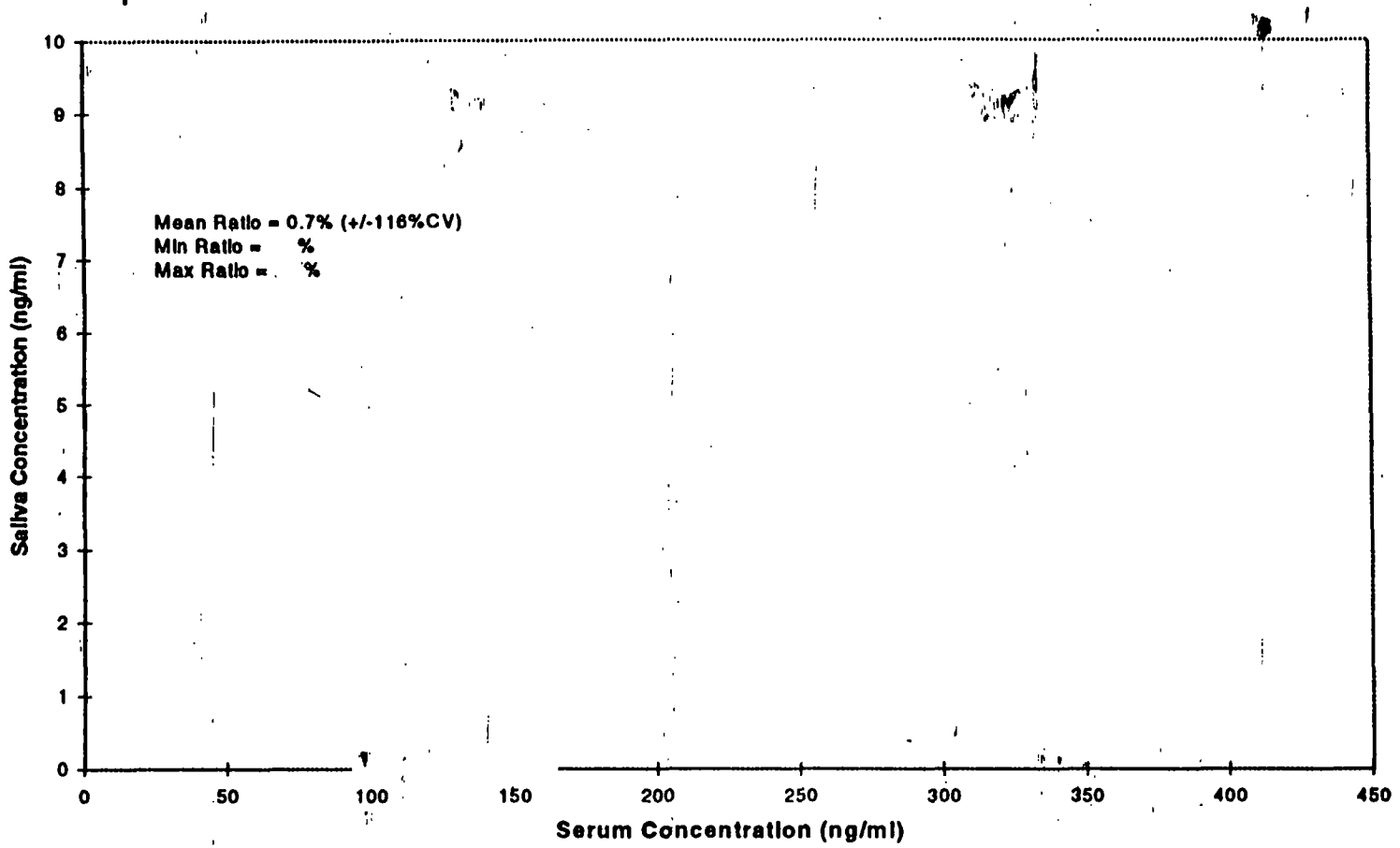


Figure 1.7. Comparison of Individual AUC(0-∞) Values versus Dose Following an Approximately 0.5 Hour IV Infusion of Ziprasidone HCl at Various Infusion Rates to Subjects with Chronic or Subchronic Schizophrenia or Schizoaffective Disorder.

Ziprasidone Protocol #128-032-572

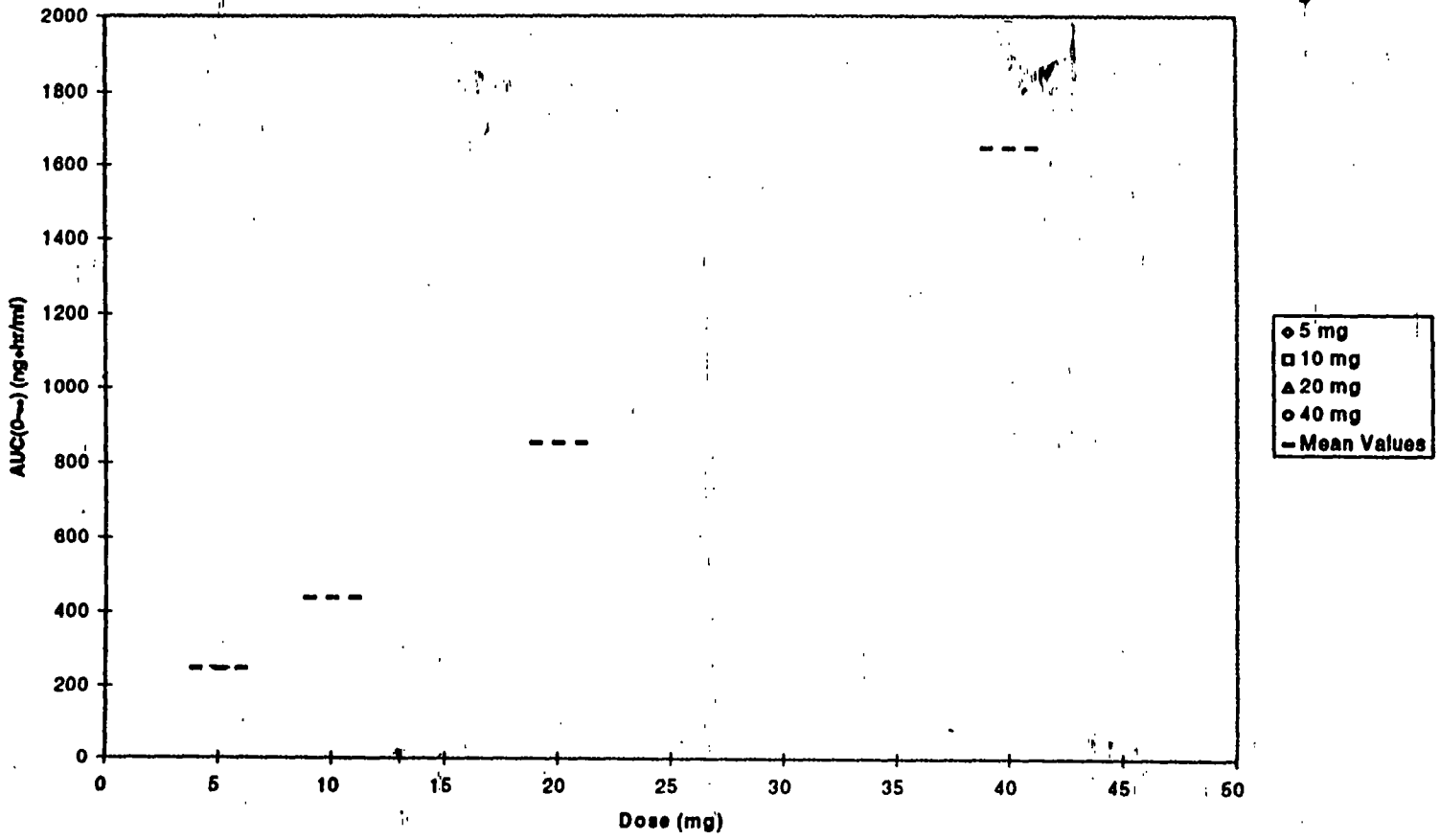


Figure 1.8. Comparison of Individual Cmax Values versus Dose Following an Approximately 0.5 Hour IV Infusion of Ziprasidone HCl at Various Infusion Rates to Subjects with Chronic or Subchronic Schizophrenia or Schizoaffective Disorder.

Ziprasidone Protocol #128-032-572

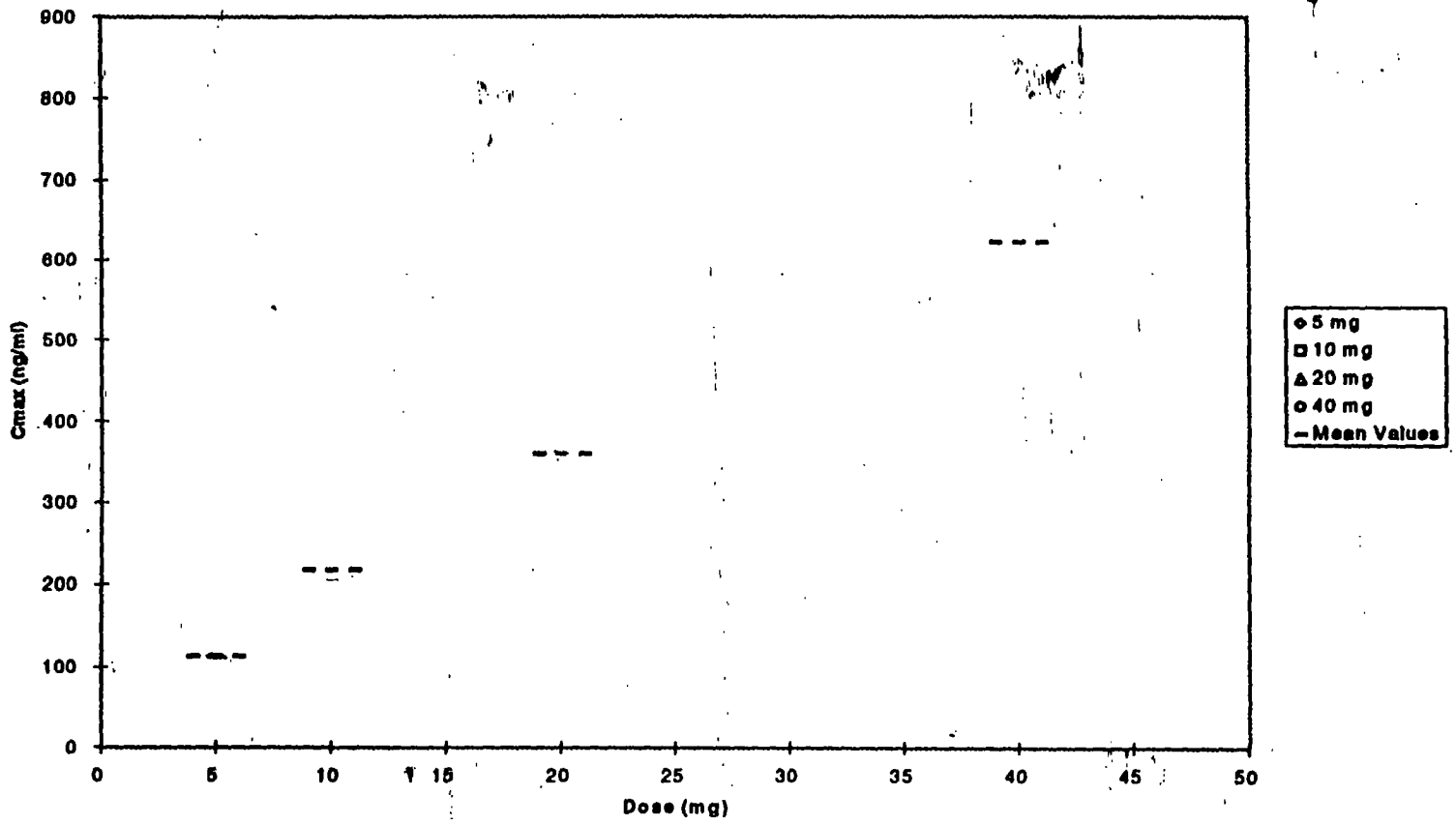


Figure 1.9. Comparison of Individual CL Values versus Dose by Subject Following Following an Approximately 0.5 Hour IV Infusion of Ziprasidone HCl at Various Infusion Rates to Subjects with Chronic or Subchronic Schizophrenia or Schizoaffective Disorder.

Ziprasidone Protocol #128-032-572

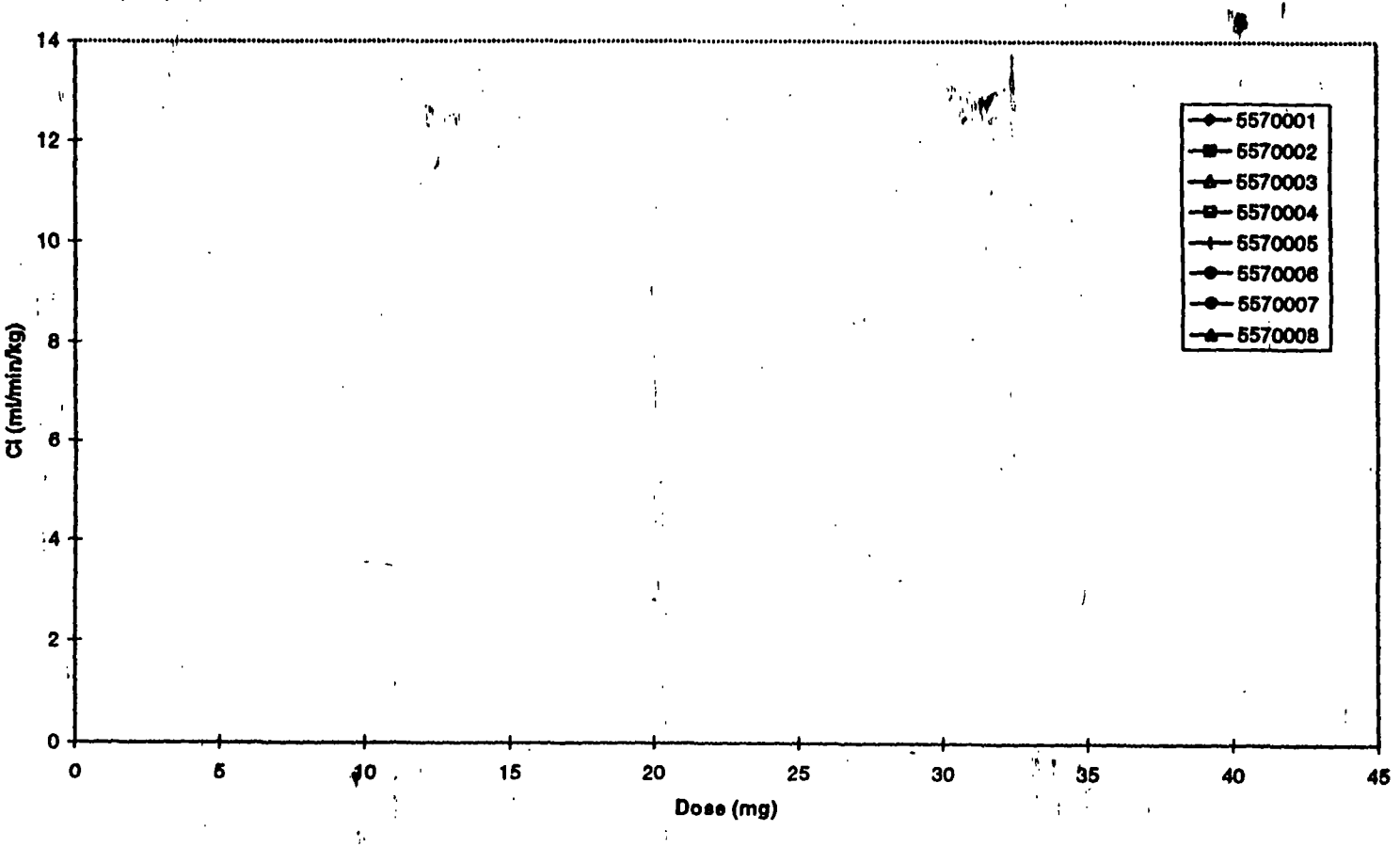


Figure 1.10. Comparison of Individual Vdss Values versus Dose by Subject Following Following an Approximately 0.5 Hour IV Infusion of Ziprasidone HCl at Various Infusion Rates to Subjects with Chronic or Subchronic Schizophrenia or Schizoaffective Disorder.

Ziprasidone Protocol #128-032-572

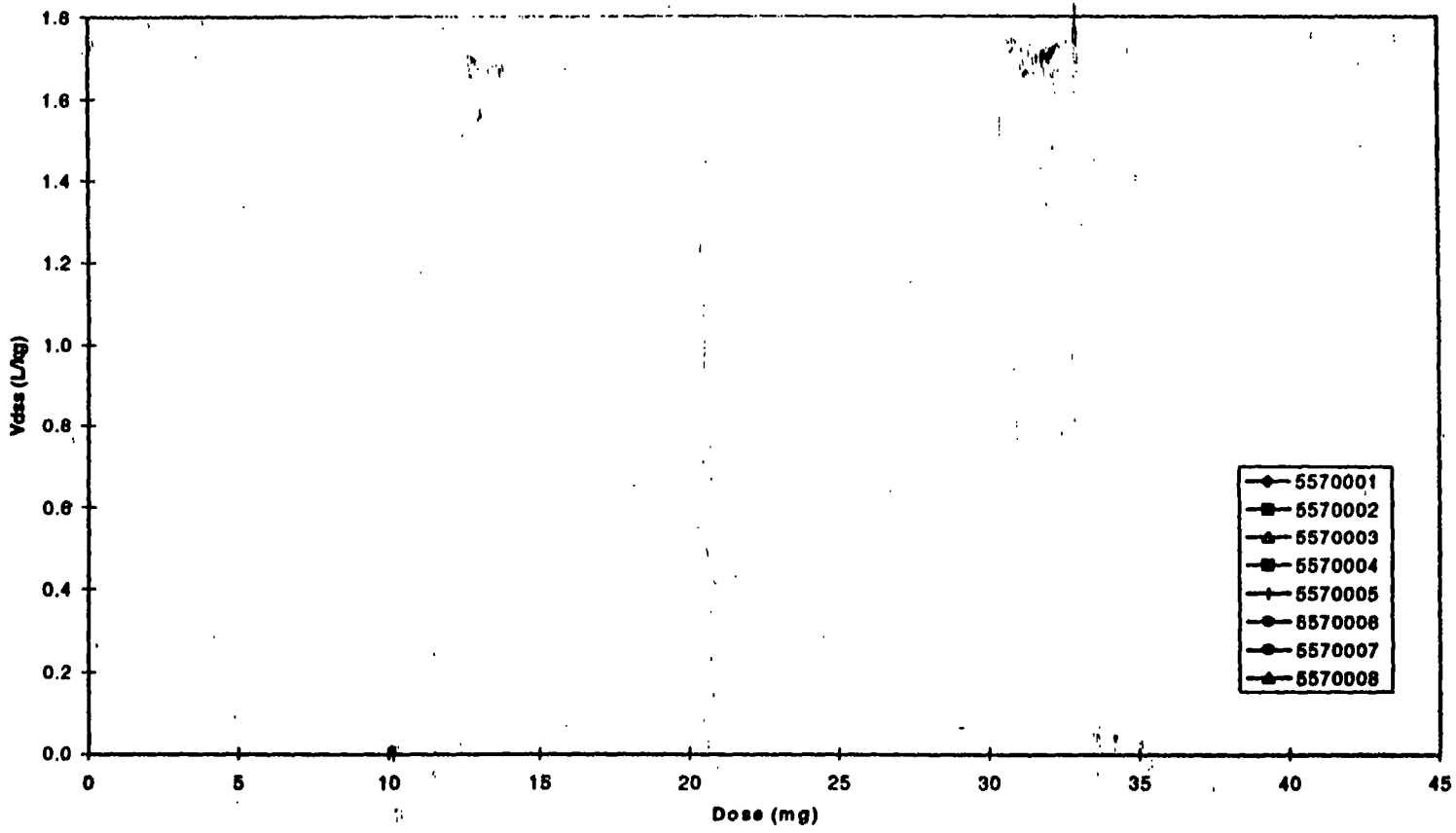


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Figure 1.11. Sedation Change from Baseline (SECB) versus Observed Ziprasidone Serum Concentration (ng/ml) by Dose (mg) for Subject 5570001.

Ziprasidone Protocol #128-032-572

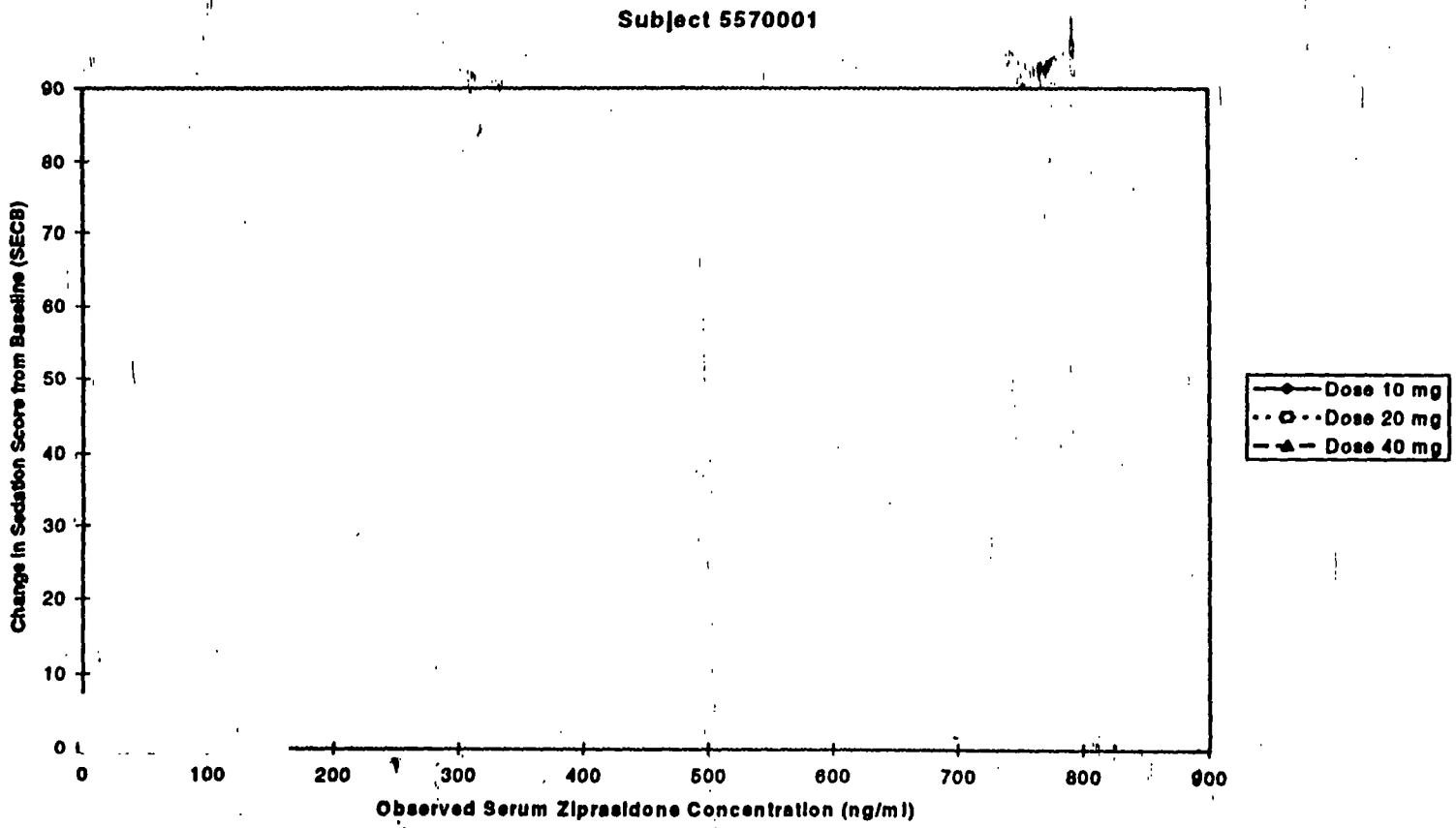

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Figure 1.12. Sedation Change from Baseline (SECB) versus Observed Ziprasidone Serum Concentration (ng/ml) by Dose (mg) for Subject 5570002.

Ziprasidone Protocol #128-032-572

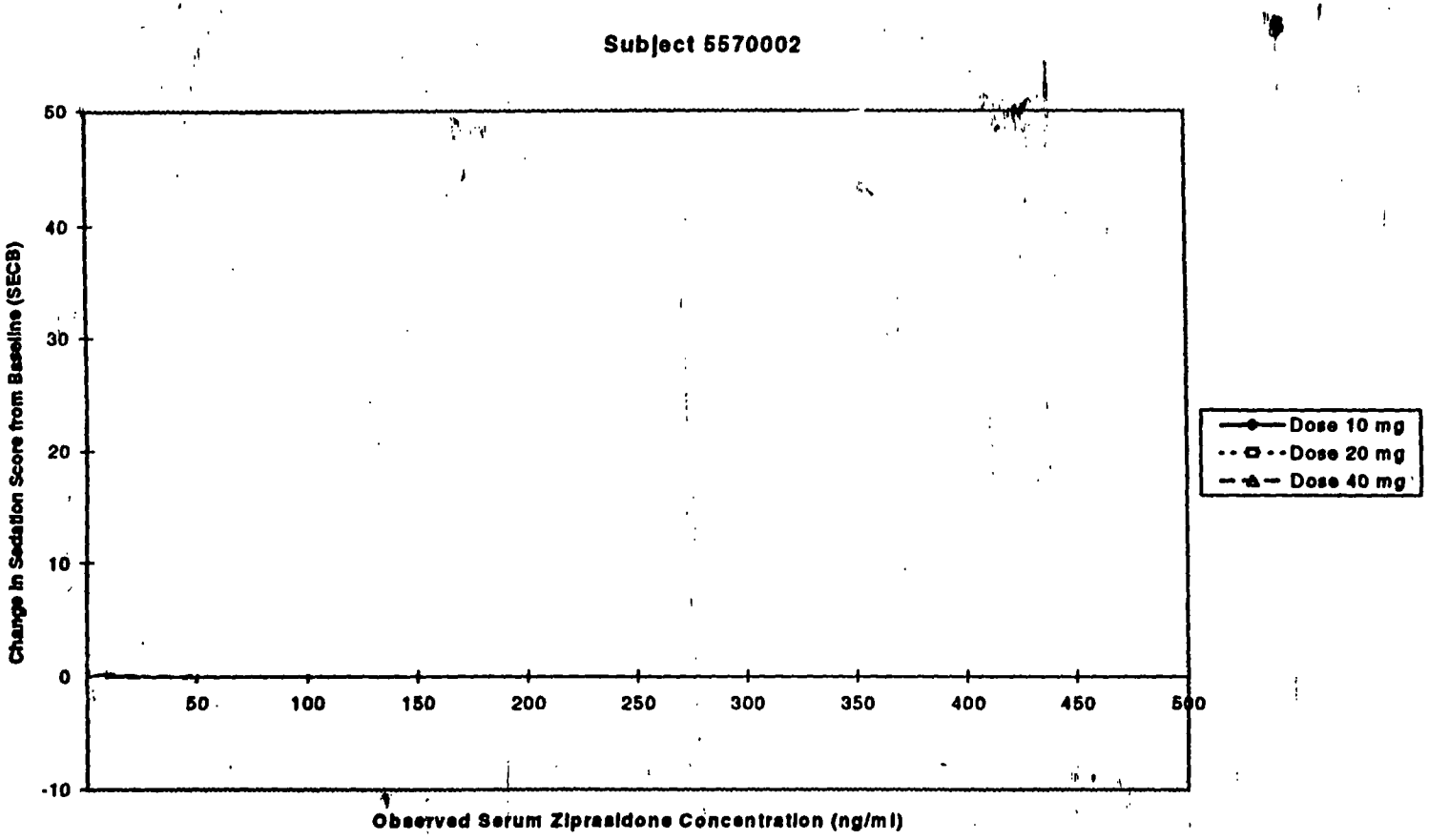

Figure 1.19. Observed and Predicted Standing Sedation Score Change from Baseline (SECB) versus Predicted Ziprasidone Effect Compartment Concentration (Ce) (ng/ml) by Dose (mg) for Subject 5570001.

Ziprasidone Protocol #128-032-572

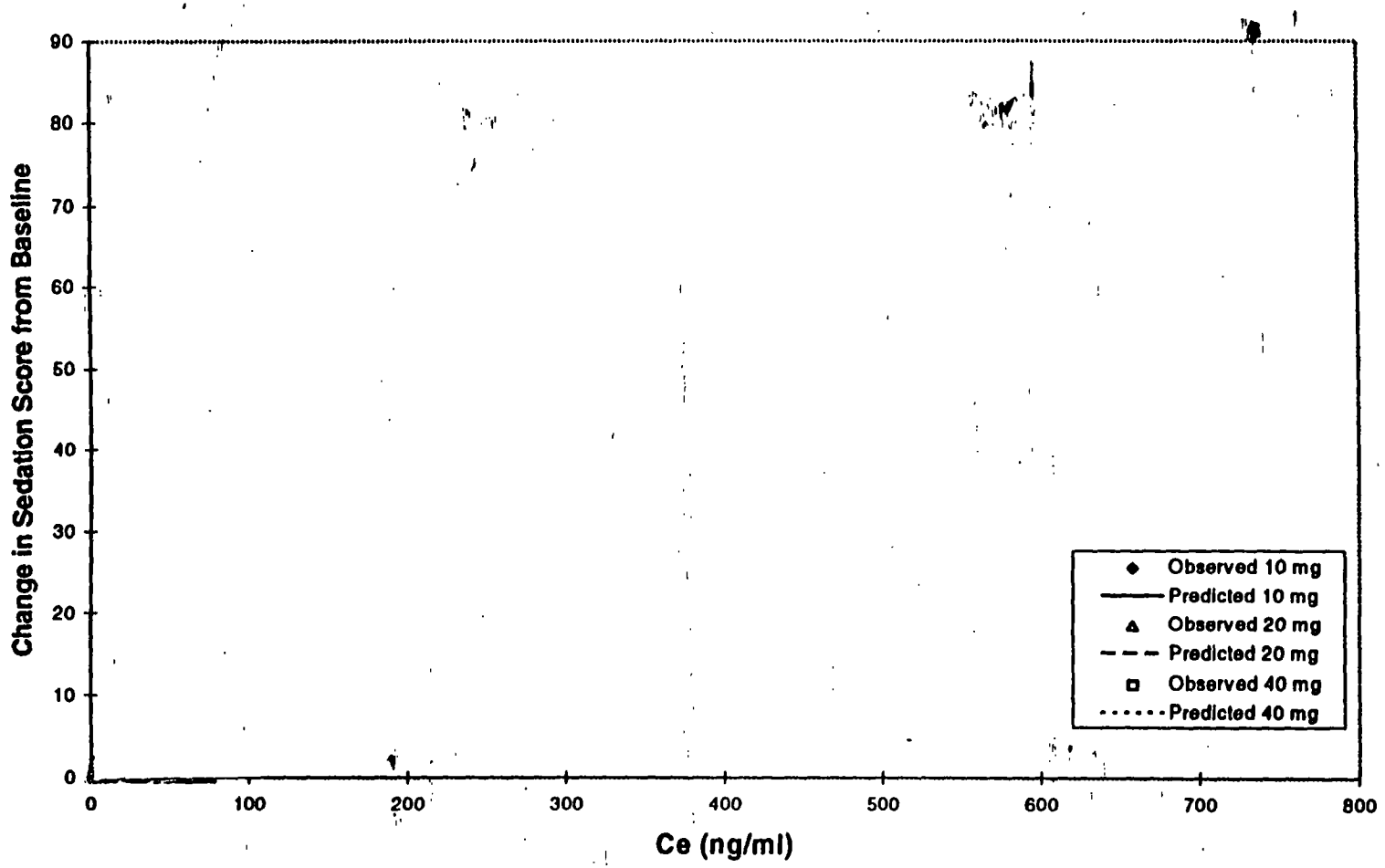

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Figure 1.20. Observed and Predicted Standing Sedation Score Change from Baseline (SECB) versus Predicted Ziprasidone Effect Compartment Concentration (Ce) (ng/ml) by Dose (mg) for Subject 5570002.

Ziprasidone Protocol #128-032-572

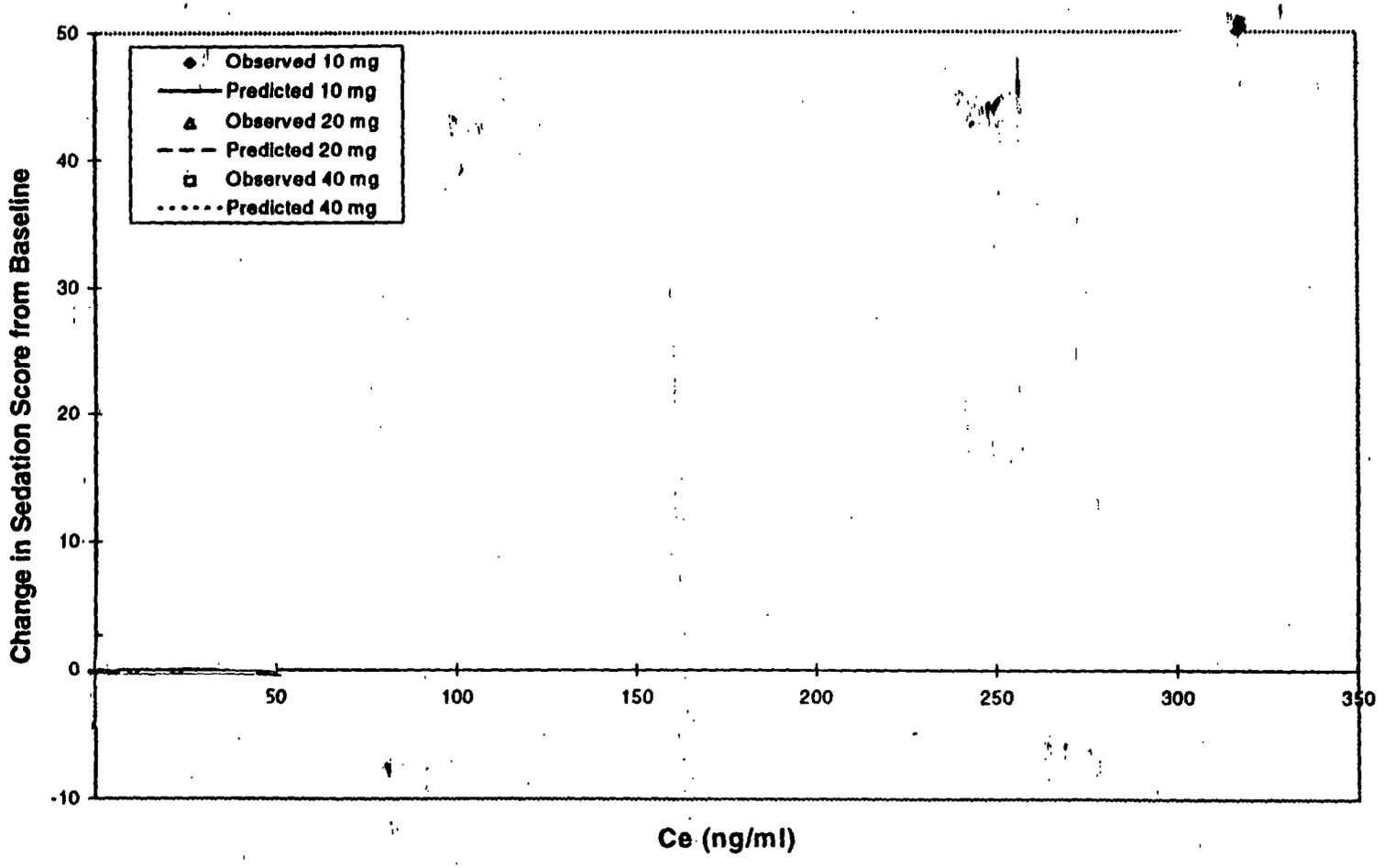

Figure 1.21. Observed and Predicted Standing Sedation Score Change from Baseline (SECB) versus Predicted Ziprasidone Effect Compartment Concentration (Ce) (ng/ml) by Dose (mg) for Subject 5570004.

Ziprasidone Protocol #128-032-572

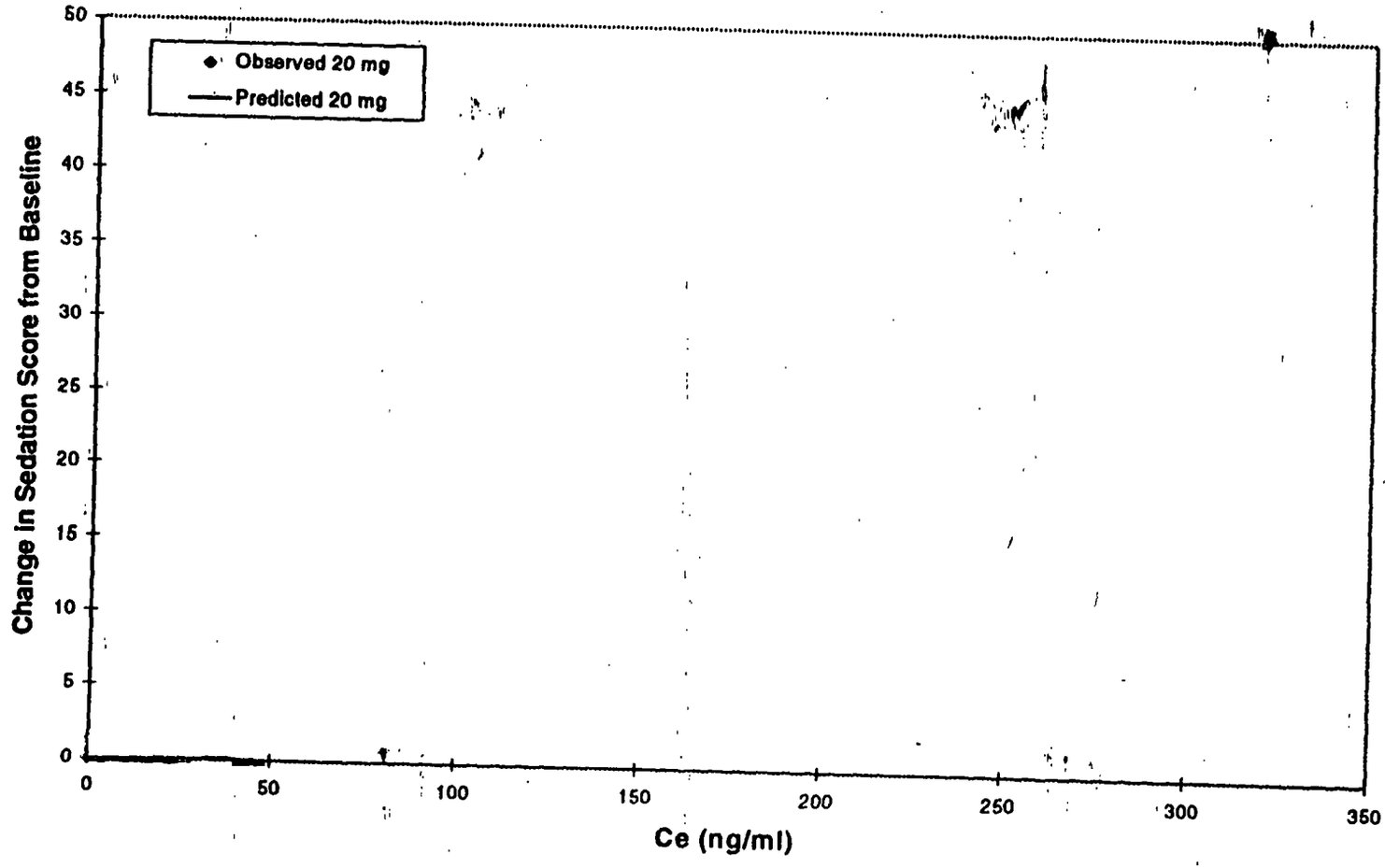

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Figure 1.22. Observed and Predicted Standing Sedation Score Change from Baseline (SECB) versus Predicted Ziprasidone Effect Compartment Concentration (Ce) (ng/ml) by Dose (mg) for Subject 5570007.

Ziprasidone Protocol #128-032-572

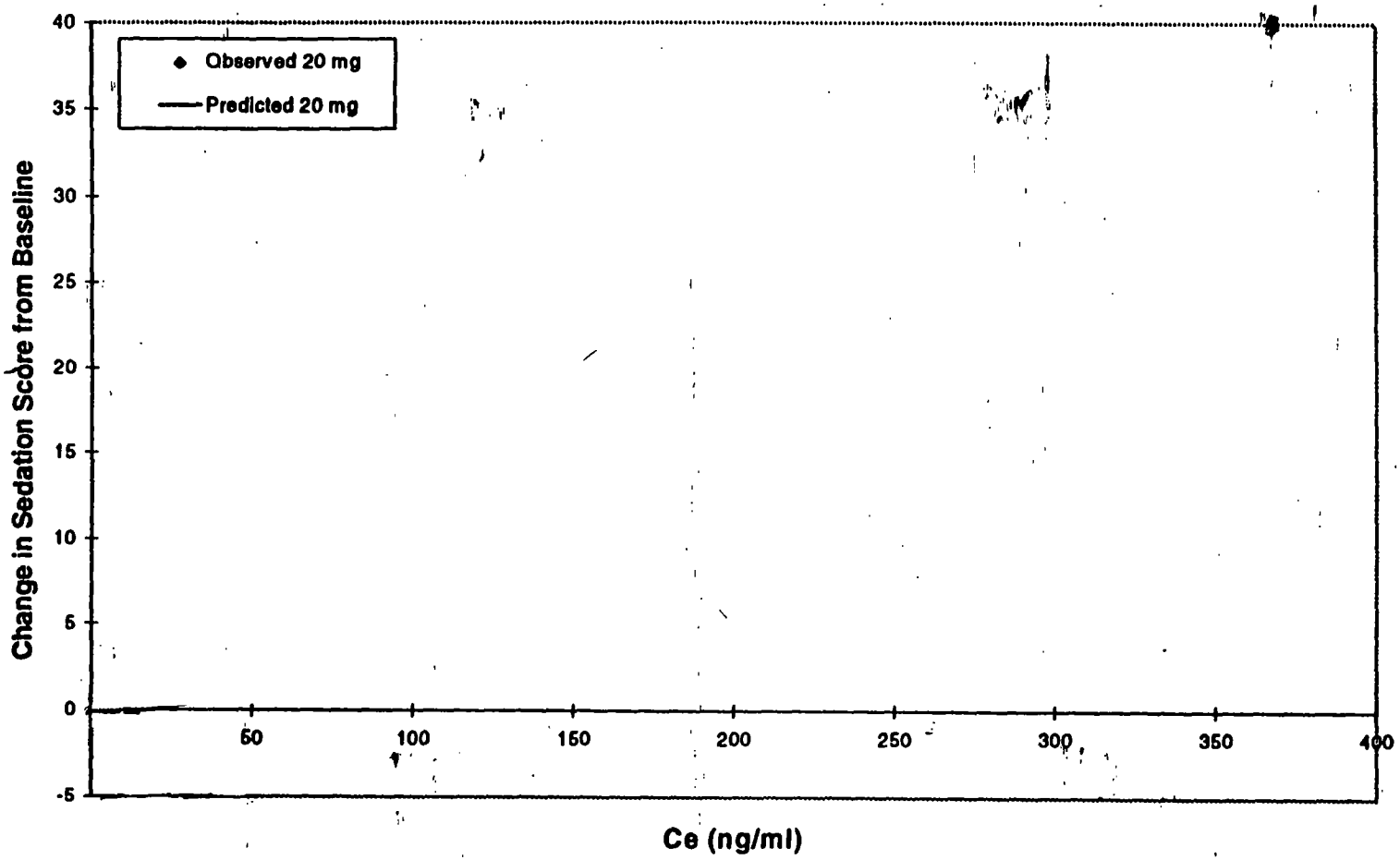
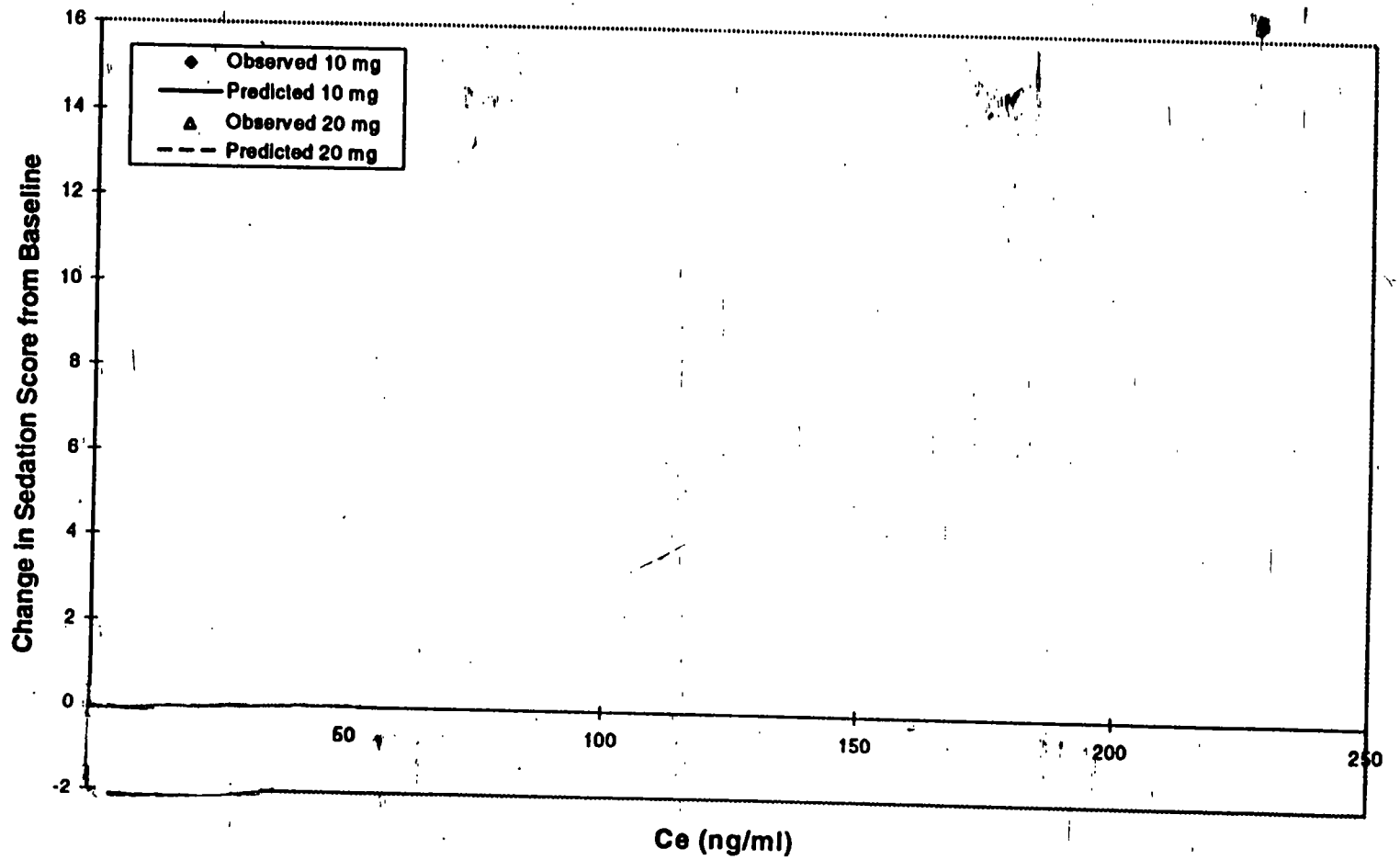


Figure 1.23. Observed and Predicted Standing Sedation Score Change from Baseline (SECB) versus Predicted Ziprasidone Effect Compartment Concentration (Ce) (ng/ml) by Dose (mg) for Subject 5570008.

Ziprasidone Protocol #128-032-572



APPENDIX IV

(Analytical Methodology)

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information

RECEIVED MAR 1 8 1998
MAR 16 1998

Office of Clinical Pharmacology and Biopharmaceutics (OCPB) Review

NDA: 20-825 Submission Date: February 27, 1998

Compound: Ziprasidone Capsules

Sponsor: Pfizer, Inc.

Type of Submission: Supplemental Data on *In-Vitro* Dissolution

Reviewer: Sayed Al-Habet, Ph.D.

Date of Review: March 11, 1998

Background:

Pfizer, Inc. has submitted for review data related to *in-vitro* dissolution of ziprasidone capsules. The supplement includes the individual data on all to-be marketed capsule strengths and a justification for the dissolution media (attachment 1).

It should also be noted that the sponsor had faxed these information to OCPB which were presented at ziprasidone briefing. In addition, the dissolution specification was based on the attached data for the individual capsules.

Recommendation:

The data and the justifications included in this supplement were found acceptable. No further action is necessary.

Reviewer

/S/ March 11, 98

Sayed Al-Habet, Ph.D.
Division of Pharmaceutical Evaluation I

RD/FT Initialed by R. Baweja, Ph.D. /S/ 3/16/98.

cc: NDA # 20-825, HFD-120, HFD-860 (Al-Habet, Baweja, Malinowski), Drug file (Barbara Murphy, Central Document Room)

Attachment 1

ATTACHMENT 1

Information requested by Dr. Al-Habet of FDA in a teleconference with C. Ritrovato of Pfizer 1/27/98.

Information includes: 1) Correlation of Lot Numbers to Formulation Identification Numbers and 2) Dissolution Data for lots of Zeldox research capsules manufactured by FID # CS-90-031

APPEARS THIS WAY
ON ORIGINAL

Pharmacokinetic Reviewer's Comment #1: (Communicated during a telephone conversation with C. Ritrovato of Pfizer)

The reviewer would like to receive something in writing showing the correlation between lot numbers and QC numbers (i.e. N5246 = QC2327). A few sentences explaining how these codes correlate would be helpful as well: For example, is it always a 1:1 correlation or can one N equate to multiply QCs etc.

Pfizer Response:

As requested the following is a brief summary of the lot number / Formulation Identification system employed at Pfizer. Also provided is a table linking the assigned material lot number to the respective Formulation Identification Number (FID#) and Code Number for the Dissolution data presented in the response to the Pharmacokinetic Reviewer, dated January 20, 1998.

Every batch of formulated product manufactured at Pfizer is assigned a discreet lot number. The terminology used in assigning lot numbers varies from Pfizer site to site. Specifically, the Groton site will utilize to assign lot numbers. The Pfizer Brooklyn site will utilize prefix to assign lot numbers.

Each lot will be manufactured according to a specific manufacturing process which is identified according to a specific FID Number or QC Code Number. As with differences in lot number terminology from site to site, there are also differences in terminology used to identify manufacturing processes. Specifically, the Groton site will identify a given manufacturing process according to a FID Number. The Brooklyn site will identify a manufacturing process according to a QC Code Number.

In cases where manufacturing process technology is transferred from one site to another, a unique Brooklyn QC Code Number would be assigned and considered equivalent to a Groton FID Number. (Note that these capsules are designated with an prefix which indicates that they were all manufactured at our Brooklyn manufacturing site).

The following is a table linking the Lot Number to the respective QC Code Number and equivalent FID Number.

Formulation Description	Lot #	QC Code #	FID#
20 mg Capsules	N5246	QC2327	G00513AA
40 mg Capsules	N5086	QC2214	G00514AA
80 mg Capsules	N5235	QC2337	G00714AA
80 mg Capsules	N5248	QC2338	G00356AB

Pharmacokinetic Reviewer's Comment #2: (Communicated during a telephone conversation with C. Ritrovato of Pfizer)

The second request was in regard to lots of Research Capsules manufactured according to Formulation Identification Number CS-90-031. The reviewer would like to receive dissolution data for lots manufactured according to this manufacturing process. He noted that research capsules manufactured by this FID Number were used rather frequently in our B/E studies.

Pfizer Response:

Research Capsules manufactured according to Formulation Identification Number CS-90-031 contain the same excipients as those contained in the proposed commercial formulation. However, research capsules manufactured according to Formulation Identification Number CS-90-031 were manufactured by [redacted] employed in the manufacture of the proposed commercial supplies.

The following is the dissolution data for two lots of research capsules manufactured according to Formulation Identification Number CS-90-031. This data was provided in Attachment E of the Human Pharmacokinetic and Bioavailability Section in the initial NDA Filing (as a mean value with a range).

20 mg Capsules; Lot ED-G-124-593 / FID# CS-90-031
Percent of Labeled Potency Dissolved
(Q @ min: Avg = % / Range ( )

Capsule #	15 min	30 min	45 min	60 min
1				
2				
3				
4				
5				
6				

Pfizer Response: (Continued)

20 mg Capsules; Lot ED-G-086-295 / FID# CS-90-031
Percent of Labeled Potency Dissolved
(Q @ min: Avg = % / Range ( ))

Capsule #	15 min	30 min	45 min	60 min
1				
2				
3				
4				
5				
6				

APPEARS THIS WAY
ON ORIGINAL

Attachment #2

Information requested by Raman Baewja of FDA in a teleconference with D. Casey of Pfizer during a teleconference on 2/3/98.

Information includes: Mean and Individual dissolution data points for stressed vs. Non-stressed capsules

Pharmacokinetic Reviewer's Comment #3: (Communicated during a telephone conversation with Dennis Casey of Pfizer

The reviewer requested dissolution data for the Dissolution Rate Profiles provided in Attachment E, page 61, of the Human Pharmacokinetic and Bioavailability Section in the initial NDA Filing (pg. 61; Dissolution Rate Profiles provided to aide in review).

Pfizer Response:

The following Is the requested dissolution data for the Dissolution Profile Plots provided in Attachment E, page 61, of the Human Pharmacokinetic and Bioavailability Section in the initial NDA Filing.

40 mg Capsules; Lot N6092/ QC Code # QC2414
Percent of Labeled Potency Dissolved
Non-stressed
(Q @ min: Avg = % / Range ( )

Capsule #	15 min	30 min	45 min	60 min
1				
2				
3				
4				
5				
6				

40 mg Capsules; Lot N6092/ QC Code # QC 2414
Percent of Labeled Potency Dissolved
Stressed
(Q @ min: Avg = % / Range ( )

Capsule #	15 min	30 min	45 min	60 min
1				
2				
3				
4				
5				
6				

Pfizer Response: (Continued)

40 mg Capsules; Lot N6092/ QC Code # 2414
Percent of Labeled Potency Dissolved
Stressed
(Q @ min: Avg = % / Range (

Capsule #	30 min	45 min	60 min	75 min
1				
2				
3				
4				
5				
6				

APPEARS THIS WAY
ON ORIGINAL

Attachment #3

Information requested by Dr. Raman Baewja of FDA in a teleconference with D. Casey of Pfizer on 2/3/98.

Information includes: Request from FDA District Inspector as a result of a facilities inspection at the Pfizer Brooklyn site.

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