BPRSd Total Score Study 115
(from Sponsor's Submission)

BPRSd Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 115

	Treatment Week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	86	53.8	84	-3.5	76	-5.0	61	-8.4	57	-9.3	51	-9.0	50	-11.0
60 mg BID	76	51.8	75	-4.1	68	-5.0	62	-6.5	56	-7.7	50	-7.8	39	-10.5
100 mg BID	82	51.8	82	-3.5	77	-5.9	69	-7.1	60	-7.8	57	-7.4	47	-8.3
Haloperidol	82	53.9	77	-5.3	72	-7.5	67	-8.2	58	-11.8	50	-11.3	47	-12.5
Placebo	80	54.3	77	-0.7	64	-2.7	48	-4.5	35	-8.7	32	-8.1	27	-9.6

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.749	0.015	0.111	0.057	0.598	0.824	0.717
Ziprasidone 60 mg BID vs placebo	0.096	0.004	0.096	0.241	0.758	0.929	0.757
Ziprasidone 100 mg BID vs placebo	0.095	0.011	0.024	0.187	0.987	0.907	0.741
Haloperidol vs placebo	0.754	0.000	0.004	0.228	0.275	0.254	0.363

Source Data: Appendix V Table 15. Date of Data Extraction: 20SEP96.
Date of Table Generation: 30SEP96.

BPRSd Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 115

	Treatment Week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	86	53.8	86	-3.3	86	-3.6	86	-5.5	86	-5.2	86	-4.2	86	-4.9
60 mg BID	76	51.8	76	-4.0	76	-4.4	76	-4.8	76	-4.8	76	-4.8	76	-5.2
100 mg BID	82	51.8	82	-3.5	82	-5.1	82	-5.4	82	-5.5	82	-5.0	82	-5.2
Haloperidol	82	53.9	82	-4.9	82	-6.7	82	-7.2	82	-8.9	82	-8.5	82	-8.8
Placebo	80	54.3	78	-0.9	80	-1.6	80	-1.6	80	-1.9	80	-1.4	80	-1.2

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.749	0.038	0.166	0.026	0.070	0.129	0.049
Ziprasidone 60 mg BID vs placebo	0.096	0.004	0.030	0.035	0.073	0.048	0.020
Ziprasidone 100 mg BID vs placebo	0.095	0.020	0.013	0.020	0.040	0.041	0.023
Haloperidol vs placebo	0.754	0.001	0.001	0.003	0.000	0.000	0.000

Source Data: Appendix V Table 15. Date of Data Extraction: 20SEP96.
Date of Table Generation: 27SEP96.

BPRSd Core Items Study 115
(from Sponsor's Submission)

BPRSd Core Items Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 115

Treatment Groups	Baseline n	Baseline Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
						Treatment Week								
Ziprasidone														
20 mg BID	86	16.1	84	-1.5	76	-2.0	61	-2.9	57	-3.1	51	-3.3	50	-3.9
60 mg BID	76	16.0	75	-1.5	68	-1.9	62	-2.7	56	-3.1	50	-2.8	39	-3.9
100 mg BID	82	15.9	82	-1.6	77	-2.5	69	-3.3	60	-3.5	57	-3.6	47	-4.1
Haloperidol	82	16.2	77	-2.3	72	-3.2	67	-3.7	58	-4.8	50	-4.6	47	-5.2
Placebo	80	16.6	77	-0.9	64	-1.9	48	-2.2	35	-3.7	32	-4.3	27	-3.9

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.326	0.133	0.767	0.389	0.534	0.269	0.985
Ziprasidone 60 mg BID vs placebo	0.225	0.130	0.848	0.447	0.512	0.127	0.819
Ziprasidone 100 mg BID vs placebo	0.146	0.069	0.208	0.132	0.990	0.594	0.578
Haloperidol vs placebo	0.459	0.002	0.017	0.078	0.227	0.595	0.119

Source Data: Appendix V Table 15. Date of Data Extraction: 20SEP96.
Date of Table Generation: 30SEP96.

BPRSd Core Items Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 115

Treatment Groups	Baseline n	Baseline Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean	Week 5 n	Week 5 Mean	Week 6 n	Week 6 Mean
						Treatment Week								
Ziprasidone														
20 mg BID	86	16.1	86	-1.4	86	-1.5	86	-2.2	86	-2.1	86	-2.1	86	-2.3
60 mg BID	76	16.0	76	-1.5	76	-1.8	76	-2.1	76	-2.2	76	-2.0	76	-2.2
100 mg BID	82	15.9	82	-1.6	82	-2.2	82	-2.5	82	-2.4	82	-2.3	82	-2.6
Haloperidol	82	16.2	82	-2.2	82	-3.0	82	-3.4	82	-4.0	82	-3.9	82	-4.1
Placebo	80	16.6	78	-0.9	80	-1.4	80	-1.0	80	-1.2	80	-1.3	80	-0.9

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.326	0.196	0.636	0.039	0.103	0.206	0.034
Ziprasidone 60 mg BID vs placebo	0.225	0.167	0.339	0.051	0.083	0.252	0.046
Ziprasidone 100 mg BID vs placebo	0.146	0.101	0.099	0.010	0.044	0.113	0.009
Haloperidol vs placebo	0.459	0.005	0.004	0.000	0.000	0.000	0.000

Source Data: Appendix V Table 15. Date of Data Extraction: 20SEP96.
Date of Table Generation: 30SEP96.

CGI Severity Score Study 115
(from Sponsor's Submission)

CGI Severity Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 115

	Treatment Week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	86	4.9	84	-0.1	77	-0.3	62	-0.5	57	-0.7	51	-0.8	50	-0.8
60 mg BID	76	4.9	75	-0.2	69	-0.4	62	-0.5	57	-0.6	50	-0.6	39	-0.8
100 mg BID	83	4.7	82	-0.1	77	-0.4	69	-0.5	60	-0.6	57	-0.6	47	-0.7
Haloperidol	83	5.0	77	-0.4	72	-0.7	67	-0.8	58	-0.9	50	-1.0	47	-1.1
Placebo	80	4.9	77	-0.1	65	-0.2	48	-0.4	35	-0.5	32	-0.5	27	-0.7

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.897	0.598	0.574	0.430	0.224	0.354	0.703
Ziprasidone 60 mg BID vs placebo	0.746	0.069	0.103	0.197	0.298	0.677	0.582
Ziprasidone 100 mg BID vs placebo	0.155	0.154	0.012	0.277	0.205	0.407	0.508
Haloperidol vs placebo	0.700	0.001	0.000	0.054	0.032	0.069	0.066

Source Data: Appendix V Table 16. Date of Data Extraction: 20SEP96.
Date of Table Generation: 30SEP96.

CGI Severity Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 115

	Treatment Week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	86	4.9	86	-0.1	86	-0.2	86	-0.3	86	-0.4	86	-0.4	86	-0.4
60 mg BID	76	4.9	76	-0.2	76	-0.3	76	-0.4	76	-0.4	76	-0.4	76	-0.4
100 mg BID	83	4.7	83	-0.1	83	-0.4	83	-0.3	83	-0.4	83	-0.4	83	-0.4
Haloperidol	83	5.0	83	-0.4	83	-0.6	83	-0.7	83	-0.8	83	-0.8	83	-0.8
Placebo	80	4.9	78	-0.1	80	-0.1	80	-0.1	80	-0.0	80	-0.1	80	-0.1

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.897	0.730	0.295	0.043	0.010	0.014	0.030
Ziprasidone 60 mg BID vs placebo	0.746	0.123	0.020	0.011	0.007	0.030	0.035
Ziprasidone 100 mg BID vs placebo	0.155	0.354	0.004	0.008	0.007	0.015	0.006
Haloperidol vs placebo	0.700	0.004	0.000	0.000	0.000	0.000	0.000

Source Data: Appendix V Table 16. Date of Data Extraction: 20SEP96.
Date of Table Generation: 30SEP96.

PANSS Total Score Study 115
(from Sponsor's Submission)

PANSS Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 115

	Treatment Week											
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	86	93.2	84	-5.1	76	-8.0	61	-13.3	57	-14.3	51	-14.2	50	-17.3
60 mg BID	76	90.4	75	-6.3	68	-8.5	62	-11.2	56	-13.4	50	-12.4	39	-18.0
100 mg BID	82	89.5	82	-5.3	77	-9.1	69	-11.4	60	-12.2	57	-11.6	47	-14.0
Haloperidol	82	94.1	77	-8.6	72	-12.4	67	-13.7	58	-20.4	50	-18.9	47	-21.0
Placebo	80	93.3	77	-0.3	64	-4.4	48	-6.1	35	-13.2	32	-12.8	27	-13.9

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.973	0.019	0.152	0.049	0.648	0.943	0.585
Ziprasidone 60 mg BID vs placebo	0.293	0.003	0.120	0.140	0.982	0.738	0.473
Ziprasidone 100 mg BID vs placebo	0.154	0.009	0.055	0.121	0.920	0.806	0.850
Haloperidol vs placebo	0.762	0.000	0.007	0.130	0.129	0.229	0.187

Source Data: Appendix V Table 15. Date of Data Extraction: 20SEP96.
Date of Table Generation: 30SEP96.

PANSS Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 115

	Treatment Week											
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	86	93.2	86	-4.8	86	-5.6	86	-8.6	86	-8.0	86	-6.6	86	-7.5
60 mg BID	76	90.4	76	-6.3	76	-7.5	76	-8.3	76	-8.3	76	-7.5	76	-8.6
100 mg BID	82	89.5	82	-5.3	82	-7.8	82	-8.5	82	-8.4	82	-7.8	82	-8.3
Haloperidol	82	94.1	82	-8.2	82	-10.9	82	-12.2	82	-15.6	82	-14.5	82	-15.2
Placebo	80	93.3	78	-0.4	80	-1.9	80	-1.1	80	-1.8	80	-1.2	80	-0.4

	2-Sided P-Values for Pairwise Comparisons					
Ziprasidone 20 mg BID vs placebo	0.973	0.041	0.156	0.013	0.051	0.107	0.031
Ziprasidone 60 mg BID vs placebo	0.293	0.004	0.022	0.012	0.032	0.051	0.011
Ziprasidone 100 mg BID vs placebo	0.154	0.017	0.021	0.012	0.032	0.041	0.012
Haloperidol vs placebo	0.762	0.001	0.001	0.001	0.000	0.000	0.000

Source Data: Appendix V Table 15. Date of Data Extraction: 20SEP96.
Date of Table Generation: 30SEP96.

PANSS Negative Score Study 115
(from Sponsor's Submission)

PANSS Negative Subscale Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 115

	Treatment Week											
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	86	22.9	84	-0.9	76	-1.6	61	-2.5	57	-2.6	51	-2.9	50	-3.7
60 mg BID	76	23.4	75	-1.2	68	-1.8	62	-2.4	56	-3.5	50	-2.6	39	-4.9
100 mg BID	82	22.5	82	-1.3	77	-1.7	69	-2.6	60	-2.5	57	-2.4	47	-3.3
Haloperidol	82	24.1	77	-1.5	72	-2.0	67	-2.6	58	-4.1	50	-3.7	47	-4.2
Placebo	80	22.4	77	0.9	64	-0.2	48	-0.4	35	-2.5	32	-2.0	27	-2.3

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.627	0.016	0.114	0.050	0.794	0.780	0.553
Ziprasidone 60 mg BID vs placebo	0.334	0.012	0.193	0.128	0.746	0.844	0.244
Ziprasidone 100 mg BID vs placebo	0.950	0.005	0.089	0.043	0.866	0.905	0.591
Haloperidol vs placebo	0.089	0.007	0.165	0.196	0.488	0.555	0.562

Source Data: Appendix V Table 15. Date of Data Extraction: 20SEP96.
Date of Table Generation: 30SEP96.

PANSS Negative Subscale Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 115

	Treatment Week											
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	86	22.9	86	-0.8	86	-1.1	86	-1.6	86	-1.3	86	-1.1	86	-1.5
60 mg BID	76	23.4	76	-1.2	76	-1.6	76	-1.8	76	-2.1	76	-1.5	76	-2.1
100 mg BID	82	22.5	82	-1.3	82	-1.7	82	-2.1	82	-2.0	82	-2.0	82	-2.2
Haloperidol	82	24.1	82	-1.5	82	-1.9	82	-2.5	82	-3.1	82	-2.8	82	-3.1
Placebo	80	22.4	78	0.8	80	0.3	80	0.5	80	0.0	80	0.2	80	0.2

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.627	0.032	0.168	0.026	0.206	0.261	0.121
Ziprasidone 60 mg BID vs placebo	0.334	0.016	0.077	0.025	0.064	0.204	0.069
Ziprasidone 100 mg BID vs placebo	0.950	0.006	0.039	0.005	0.041	0.039	0.020
Haloperidol vs placebo	0.089	0.008	0.050	0.006	0.010	0.017	0.008

Source Data: Appendix V Table 15. Date of Data Extraction: 20SEP96.
Date of Table Generation: 30SEP96.

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Appendix 7.2.4.2
(from Sponsor's Submission)

Subject Disposition
Ziprasidone Protocol 303

Treatment Group	Number of Subjects		Number of Subjects Completing Each Period of Study*					
	Randomized	Treated	Week 3	Week 6	Week 16	Week 28	Week 40	Week 52
Ziprasidone, 20 mg BID	76	76	67	61	48	40	38	35
Ziprasidone, 40 mg BID	72	72	66	58	47	36	33	33
Ziprasidone, 80 mg BID	71	71	68	66	50	42	36	34
Placebo	75	75	70	56	31	23	16	14
Total:	294	294	271	241	176	141	123	116

*Based on planned scheduled efficacy measurements of PANSS and CGI severity. Weeks are determined by visit designators.
Source Data: Appendix V Tables 6, 15, 16. Date of Data Extraction: 06JAN97. Date of Table Generation: 06JAN97.

Appendix 7.2.4.3
(from Sponsor's Submission)

Demographic Characteristics
Ziprasidone Protocol 303

	Ziprasidone 20 mg BID			Ziprasidone 40 mg BID			Ziprasidone 80 mg BID			Placebo		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number of Subjects Randomized	56	20	76	51	21	72	46	25	71	61	14	75
Age (years):												
18-44	23	6	29	29	3	32	20	7	27	27	3	30
45-64	24	8	32	20	10	30	21	14	35	29	8	37
>=65	9	6	15	2	8	10	5	4	9	5	3	8
Mean age (years)	49.1	55.5	50.8	45.4	59.4	49.5	48.4	52.0	49.6	47.7	53.7	48.8
Age range	18-75	31-82	18-82	24-75	36-78	24-78	22-72	23-73	22-73	20-76	29-70	20-76
Race:												
White	56	20	76	51	21	72	46	25	71	61	14	75
Mean weight (kg)	73.0	72.3		72.3	66.7		73.8	67.3		74.7	65.1	
Weight range	45-124	57-106		49-112	45- 95		51-155	44- 96		54-115	48- 90	

Source Data: APPENDIX V - TABLE 2 Date of Data Extraction: 03JAN97 Date of Table Generation: 06JAN97

Analysis of Time-to-Relapse - All Subjects
Ziprasidone Protocol 303

Treatment Group	N	Cumulative Incidence(%) of Relapse* <=28 weeks	Cumulative Incidence(%) of Relapse* <=52 weeks	Probability of Relapse** <=28 weeks	Probability of Relapse** <=52 weeks	Relative Risk	95% Confidence Limits Lower	95% Confidence Limits Upper	P-Value***
Ziprasidone									
20 mg BID	75	23 (30.7)	27 (36.0)	0.339	0.405	0.481	0.296	0.781	0.003
40 mg BID	72	21 (29.2)	22 (30.6)	0.326	0.346	0.414	0.247	0.693	0.001
80 mg BID	71	22 (31.0)	24 (33.8)	0.324	0.358	0.411	0.249	0.680	0.001
Placebo	75	35 (46.7)	43 (57.3)	0.545	0.708				
Overall									<0.001
Dose Response									0.002
Zip. vs Placebo									<0.001
Linear Among Zip.									0.595

* Percent to number of patients at baseline
** Estimates of probability of relapse at <=28 weeks or <=52 weeks are based on the Kaplan-Meier product-limit method.
***The p-values for comparing each treatment with placebo and for overall are derived from a Cox regression model that includes a contrast variable for each treatment group versus placebo. The p-value for dose response is based on Cox regression model using the actual dosage levels (0 mg for placebo). The dose response is further tested for Ziprasidone groups combined versus placebo using model contrasts (-3,1,1,1) and for linear effect among the Ziprasidone groups using contrasts (0,-1,0,1).

Source Data: Appendix III Table 27. Date of Data Extraction: 06JAN97. Date of Table Generation: 06FEB97.

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BPRSd Total Score Study 303
(from Sponsor's Submission)

BPRSd Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 303

	Treatment Week													
	Baseline		Week 3		Week 6		Week 16		Week 28		Week 40		Week 52	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	75	46.1	67	-1.7	60	-4.3	48	-5.4	40	-5.8	38	-7.5	35	-9.3
40 mg BID	72	47.1	66	-2.1	58	-2.8	47	-5.4	36	-6.4	33	-7.1	33	-8.0
80 mg BID	71	45.9	68	-2.2	66	-3.6	50	-4.7	42	-7.7	36	-8.6	34	-9.2
Placebo	75	48.0	70	-0.2	56	-2.9	31	-5.5	23	-4.1	16	-3.0	14	-3.4

	2-Sided P-Values for Pairwise Comparisons					
Ziprasidone 20 mg BID vs placebo	0.302	0.120	0.068	0.265	0.056	0.127	0.543
Ziprasidone 40 mg BID vs placebo	0.615	0.073	0.869	0.261	0.053	0.444	0.768
Ziprasidone 80 mg BID vs placebo	0.272	0.053	0.425	0.723	0.002	0.034	0.487

Source Data: Appendix V Table 15, Date of Data Extraction: 06JAN97.
Date of Table Generation: 07JAN97.

BPRSd Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 303

	Treatment Week													
	Baseline		Week 3		Week 6		Week 16		Week 28		Week 40		Week 52	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	75	46.1	75	0.2	75	-0.1	75	1.6	75	3.1	75	2.6	75	2.5
40 mg BID	72	47.1	72	-0.1	72	0.2	72	0.7	72	2.2	72	2.3	72	1.9
80 mg BID	71	45.9	71	-1.5	71	-2.0	71	-0.1	71	0.0	71	0.7	71	0.5
Placebo	75	48.0	75	1.0	75	1.7	75	4.4	75	7.1	75	9.3	75	9.6

	2-Sided P-Values for Pairwise Comparisons					
Ziprasidone 20 mg BID vs placebo	0.302	0.546	0.265	0.158	0.041	0.001	0.001
Ziprasidone 40 mg BID vs placebo	0.615	0.544	0.556	0.139	0.035	0.004	0.002
Ziprasidone 80 mg BID vs placebo	0.272	0.083	0.042	0.043	0.001	<0.001	<0.001

Source Data: Appendix V Table 15, Date of Data Extraction: 06JAN97.
Date of Table Generation: 07JAN97.

BPRSd Core Items Study 303
(from Sponsor's Submission)

BPRSd Core Items Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 303

	Treatment Week											
	Baseline		Week 3		Week 6		Week 16		Week 28		Week 40		Week 52	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	75	11.2	67	-0.3	60	-1.0	48	-1.1	40	-1.3	38	-1.6	35	-2.3
40 mg BID	72	11.7	66	-0.6	58	-0.8	47	-1.3	36	-1.6	33	-2.0	33	-2.0
80 mg BID	71	11.2	68	-0.6	66	-0.6	50	-1.3	42	-1.8	36	-2.2	34	-2.1
Placebo	75	11.7	70	0.1	56	-0.6	31	-1.5	23	-0.7	16	-0.6	14	-0.2

	2-Sided P-Values for Pairwise Comparisons					
Ziprasidone 20 mg BID vs placebo	0.378	0.259	0.127	0.844	0.098	0.458	0.602
Ziprasidone 40 mg BID vs placebo	0.980	0.062	0.567	0.534	0.070	0.468	0.900
Ziprasidone 80 mg BID vs placebo	0.446	0.071	0.742	0.832	0.003	0.074	0.430

Source Data: Appendix V Table 15. Date of Data Extraction: 06JAN97.
Date of Table Generation: 07JAN97.

BPRSd Core Items Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 303

	Treatment Week											
	Baseline		Week 3		Week 6		Week 16		Week 28		Week 40		Week 52	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	75	11.2	75	0.3	75	0.3	75	0.8	75	1.2	75	1.3	75	1.3
40 mg BID	72	11.7	72	-0.1	72	-0.0	72	0.1	72	0.5	72	0.5	72	0.5
80 mg BID	71	11.2	71	-0.4	71	-0.3	71	0.2	71	0.3	71	0.4	71	0.5
Placebo	75	11.7	75	0.3	75	0.5	75	1.2	75	2.1	75	2.5	75	2.6

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.378	0.919	0.629	0.472	0.168	0.043	0.043
Ziprasidone 40 mg BID vs placebo	0.980	0.438	0.498	0.132	0.035	0.008	0.007
Ziprasidone 80 mg BID vs placebo	0.446	0.146	0.169	0.135	0.010	0.002	0.003

Source Data: Appendix V Table 15. Date of Data Extraction: 06JAN97.
Date of Table Generation: 07JAN97.

CGI Severity Score Study 303
(from Sponsor's Submission)

CGI Severity Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 303

	Treatment Week													
	Baseline		Week 3		Week 6		Week 16		Week 28		Week 40		Week 52	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	75	4.0	67	-0.1	60	-0.2	48	-0.4	40	-0.4	38	-0.5	35	-0.7
40 mg BID	72	4.0	66	-0.0	58	-0.2	47	-0.4	36	-0.6	33	-0.6	33	-0.8
80 mg BID	71	4.0	68	-0.1	66	-0.2	50	-0.4	42	-0.5	36	-0.6	34	-0.7
Placebo	75	4.1	70	0.1	56	-0.2	31	-0.4	23	-0.3	16	-0.3	14	-0.4

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.724	0.050	0.360	0.608	0.116	0.503	0.853
Ziprasidone 40 mg BID vs placebo	0.557	0.123	0.581	0.278	0.019	0.521	0.683
Ziprasidone 80 mg BID vs placebo	0.733	0.055	0.363	0.569	0.004	0.183	0.493

Source Data: Appendix V Table 16. Date of Data Extraction: 06JAN97.
Date of Table Generation: 07JAN97.

CGI Severity Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 303

	Treatment Week													
	Baseline		Week 3		Week 6		Week 16		Week 28		Week 40		Week 52	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	75	4.0	75	0.1	75	0.1	75	0.2	75	0.4	75	0.3	75	0.4
40 mg BID	72	4.0	72	0.1	72	0.1	72	0.1	72	0.2	72	0.2	72	0.2
80 mg BID	71	4.0	71	-0.0	71	-0.1	71	0.1	71	0.1	71	0.2	71	0.2
Placebo	75	4.1	75	0.2	75	0.3	75	0.5	75	0.8	75	0.9	75	0.9

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.724	0.226	0.165	0.041	0.013	0.001	0.001
Ziprasidone 40 mg BID vs placebo	0.557	0.389	0.282	0.011	0.002	<0.001	<0.001
Ziprasidone 80 mg BID vs placebo	0.733	0.049	0.008	0.006	<0.001	<0.001	<0.001

Source Data: Appendix V Table 16. Date of Data Extraction: 06JAN97.
Date of Table Generation: 07JAN97.

CGI Improvement Score Study 303
(from Sponsor's Submission)

CGI Improvement Score - Means and P-Values by Week
All Subjects, Observed Cases
Ziprasidone Protocol 303

	Treatment Week											
	Week 3		Week 6		Week 16		Week 28		Week 40		Week 52	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone												
20 mg BID	67	3.5	60	3.4	48	3.1	40	3.2	38	3.1	35	2.7
40 mg BID	66	3.6	58	3.6	47	3.2	36	3.0	33	2.8	33	2.7
80 mg BID	68	3.6	66	3.5	50	3.3	42	2.9	36	2.8	34	2.6
Placebo	70	3.9	56	3.5	31	3.3	23	3.3	16	3.3	14	3.1

	2-Sided P-Values for Pairwise Comparisons					
Ziprasidone 20 mg BID vs placebo	0.019	0.303	0.303	0.118	0.403	0.268
Ziprasidone 40 mg BID vs placebo	0.040	0.866	0.189	0.079	0.462	0.819
Ziprasidone 80 mg BID vs placebo	0.059	0.902	0.553	0.007	0.069	0.204

Source Data: Appendix V Table 16. Date of Data Extraction: 06JAN97.
Date of Table Generation: 07JAN97.

CGI Improvement Score - Means and P-Values by Week
All Subjects, LOCF
Ziprasidone Protocol 303

	Treatment Week											
	Week 3		Week 6		Week 16		Week 28		Week 40		Week 52	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone												
20 mg BID	75	3.7	75	3.8	75	4.0	75	4.2	75	4.3	75	4.2
40 mg BID	72	3.8	72	3.9	72	3.9	72	4.1	72	4.1	72	4.0
80 mg BID	71	3.7	71	3.7	71	3.9	71	3.9	71	4.0	71	3.9
Placebo	75	4.0	75	4.1	75	4.6	75	4.8	75	5.0	75	5.0

	2-Sided P-Values for Pairwise Comparisons					
Ziprasidone 20 mg BID vs placebo	0.097	0.182	0.015	0.025	0.004	0.001
Ziprasidone 40 mg BID vs placebo	0.231	0.488	0.014	0.009	0.001	0.001
Ziprasidone 80 mg BID vs placebo	0.109	0.089	0.012	0.001	<0.001	<0.001

Source Data: Appendix V Table 16. Date of Data Extraction: 06JAN97.
Date of Table Generation: 07JAN97.

PANSS Total Score Study 303
(from Sponsor's Submission)

PANSS Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 303

	Treatment Week													
	Baseline		Week 3		Week 6		Week 16		Week 28		Week 40		Week 52	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	75	85.1	67	-3.2	60	-7.7	48	-10.1	40	-11.1	38	-14.2	35	-17.8
40 mg BID	72	86.6	66	-4.0	58	-4.9	47	-9.1	36	-12.0	33	-13.7	33	-14.7
80 mg BID	71	85.2	68	-3.5	66	-5.7	50	-9.1	42	-14.2	36	-15.4	34	-17.0
Placebo	75	88.9	70	-1.2	56	-5.9	31	-10.3	23	-8.6	16	-6.5	14	-6.9

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.210	0.150	0.127	0.311	0.057	0.134	0.277
Ziprasidone 40 mg BID vs placebo	0.449	0.083	0.664	0.513	0.066	0.483	0.821
Ziprasidone 80 mg BID vs placebo	0.227	0.135	0.962	0.849	0.002	0.070	0.350

Source Data: Appendix V Table 15. Date of Data Extraction: 06JAN97.
Date of Table Generation: 07JAN97.

PANSS Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 303

	Treatment Week													
	Baseline		Week 3		Week 6		Week 16		Week 28		Week 40		Week 52	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	75	85.1	75	-0.2	75	-1.0	75	1.4	75	3.7	75	2.9	75	2.4
40 mg BID	72	86.6	72	-0.4	72	0.2	72	0.8	72	2.5	72	2.6	72	2.1
80 mg BID	71	85.2	71	-2.7	71	-3.6	71	-1.7	71	-1.5	71	-0.5	71	-1.1
Placebo	75	88.9	75	1.0	75	1.7	75	6.2	75	10.2	75	14.1	75	14.6

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.210	0.591	0.285	0.143	0.041	0.001	0.001
Ziprasidone 40 mg BID vs placebo	0.449	0.621	0.751	0.187	0.042	0.003	0.002
Ziprasidone 80 mg BID vs placebo	0.227	0.110	0.065	0.025	0.001	<0.001	<0.001

Source Data: Appendix V Table 15. Date of Data Extraction: 06JAN97.
Date of Table Generation: 07JAN97.

PANSS Negative Score Study 303
(from Sponsor's Submission)

PANSS Negative Subscale Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 303

	Treatment Week													
	Baseline		Week 3		Week 6		Week 16		Week 28		Week 40		Week 52	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	75	24.9	67	-1.4	60	-2.5	48	-3.4	40	-3.9	38	-4.8	35	-5.6
40 mg BID	72	24.7	66	-1.2	58	-1.4	47	-2.8	36	-3.7	33	-4.4	33	-4.2
80 mg BID	71	25.0	68	-1.3	66	-1.8	50	-3.1	42	-4.6	36	-5.1	34	-5.6
Placebo	75	25.7	70	-1.4	56	-2.3	31	-3.4	23	-3.7	16	-2.8	14	-3.0

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.326	0.715	0.429	0.457	0.249	0.277	0.455
Ziprasidone 40 mg BID vs placebo	0.253	0.928	0.162	0.857	0.479	0.817	0.433
Ziprasidone 80 mg BID vs placebo	0.401	0.920	0.469	0.974	0.063	0.290	0.487

Source Data: Appendix V Table 15. Date of Data Extraction: 06JAN97.
Date of Table Generation: 07JAN97.

PANSS Negative Subscale Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 303

	Treatment Week													
	Baseline		Week 3		Week 6		Week 16		Week 28		Week 40		Week 52	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
20 mg BID	75	24.9	75	-0.9	75	-1.3	75	-1.4	75	-1.4	75	-1.8	75	-2.0
40 mg BID	72	24.7	72	-0.4	72	-0.4	72	-0.8	72	-0.9	72	-1.1	72	-1.0
80 mg BID	71	25.0	71	-1.4	71	-1.7	71	-2.0	71	-2.3	71	-2.3	71	-2.6
Placebo	75	25.7	75	-0.7	75	-0.6	75	0.1	75	0.5	75	1.2	75	1.3

	2-Sided P-Values for Pairwise Comparisons						
Ziprasidone 20 mg BID vs placebo	0.326	0.673	0.272	0.039	0.012	<0.001	<0.001
Ziprasidone 40 mg BID vs placebo	0.253	0.750	0.767	0.246	0.082	0.009	0.012
Ziprasidone 80 mg BID vs placebo	0.401	0.203	0.118	0.007	0.001	<0.001	<0.001

Source Data: Appendix V Table 15. Date of Data Extraction: 06JAN97.
Date of Table Generation: 25FEB97.

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Appendix 7.2.5.2
(from Sponsor's Submission)

Subject Disposition
Ziprasidone Protocol 104

Treatment Group	Number of Subjects		Number of Subjects Completing Each Period of Study*			
	Randomized	Treated	Week 1	Week 2	Week 3	Week 4
Ziprasidone, 5 mg BID	47	47	45	37	33	30
Ziprasidone, 20 mg BID	55	55	54	46	38	27
Ziprasidone, 40 mg BID	48	48	42	32	24	20
Placebo	50	50	45	34	29	27
Total:	200	200	186	149	124	104

*Based on planned primary efficacy measurements. Weeks are determined by visit designators. Week 1 counts subjects who have at least one primary efficacy measurement at visit 7; Week 2 similarly counts those with visit 14; Week 3 similarly counts those with visit 21; Week 4 similarly counts those with visit 28.
Source Data: Appendix V Tables 6, 16, 17. Date of Data Extraction: 17JUL95. Date of Table Generation: 090CT96.

Appendix 7.2.5.3
(from Sponsor's Submission)

Demographic Characteristics
Ziprasidone Protocol 104

	Ziprasidone 5mg BID			Ziprasidone 20mg BID			Ziprasidone 40mg BID			Placebo		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number of Subjects Randomized	41	6	47	52	3	55	39	9	48	44	6	50
Age (years):												
18-44	31	2	33	39	1	40	32	3	35	33	1	34
45-64	10	4	14	13	2	15	7	6	13	11	5	16
Mean age (years)	38.4	44.7	39.2	40.4	51.7	41.1	37.5	49.0	39.7	38.5	47.8	39.6
Age range	22-60	24-57	22-60	25-64	44-56	25-64	20-61	39-63	20-63	22-64	37-56	22-64
Race:												
Caucasian	20	3	23	27	3	30	22	5	27	27	3	30
Black	17	3	20	18	0	19	12	4	16	15	2	17
Oriental	1	0	1	2	0	2	3	0	3	0	1	1
Other	3	0	3	4	0	4	2	0	2	2	0	2
Mean weight (kg)	77.5	71.3		76.8	65.8		76.9	69.4		79.5	67.8	
Weight range	52-120	56-100		55-115	63- 70		49-115	55- 93		58-113	57- 81	

Source Data: APPENDIX V - TABLE 2 Date of Data Extraction: 02AUG95 Date of Table Generation: 29AUG95

BPRS Total Score Study 104
(from Sponsor's Submission)

BPRS Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 104

Treatment Groups	Treatment Week: Baseline n	Baseline Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean
Ziprasidone										
5 mg BID	44	34.1	44	-2.3	37	-4.3	33	-7.5	30	-7.8
20 mg BID	55	34.5	54	-3.9	46	-4.9	38	-9.2	27	-13.0
40 mg BID	47	36.2	42	-3.4	32	-4.3	24	-8.9	20	-7.3
Placebo	47	33.4	45	-3.6	34	-4.4	29	-7.9	27	-7.3

	2-Sided P-Values for Pairwise Comparisons				
Ziprasidone 5 mg BID vs placebo	0.738	0.454	0.667	0.845	0.646
Ziprasidone 20 mg BID vs placebo	0.586	0.894	0.551	0.352	0.040
Ziprasidone 40 mg BID vs placebo	0.185	0.836	0.821	0.446	0.720

Source Data: Appendix V Table 16. Date of Data Extraction: 17JUL95.
Date of Table Generation: 11OCT96.

BPRS Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 104

Treatment Groups	Treatment Week: Baseline n	Baseline Mean	Week 1 n	Week 1 Mean	Week 2 n	Week 2 Mean	Week 3 n	Week 3 Mean	Week 4 n	Week 4 Mean
Ziprasidone										
5 mg BID	44	34.1	44	-2.3	44	-2.8	44	-4.3	44	-3.9
20 mg BID	55	34.5	55	-3.9	55	-3.6	55	-4.9	55	-5.4
40 mg BID	47	36.2	47	-3.0	47	-3.1	47	-3.7	47	-2.6
Placebo	47	33.4	46	-3.3	47	-2.4	47	-3.3	47	-3.5

	2-Sided P-Values for Pairwise Comparisons				
Ziprasidone 5 mg BID vs placebo	0.738	0.445	0.923	0.692	0.926
Ziprasidone 20 mg BID vs placebo	0.586	0.828	0.573	0.438	0.354
Ziprasidone 40 mg BID vs placebo	0.185	0.590	0.831	0.989	0.535

Source Data: Appendix V Table 16. Date of Data Extraction: 17JUL95.
Date of Table Generation: 11OCT96.

BPRS Core Items Study 104
(from Sponsor's Submission)

BPRS Core Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 104

	Treatment Week									
	Baseline		Week 1		Week 2		Week 3		Week 4	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone										
5 mg BID	44	12.8	44	-0.9	37	-1.6	33	-2.5	30	-2.9
20 mg BID	55	13.0	54	-1.6	46	-2.8	38	-4.1	27	-5.1
40 mg BID	47	12.8	42	-0.7	32	-0.8	24	-2.5	20	-2.9
Placebo	47	13.7	45	-2.2	34	-2.7	29	-3.8	27	-3.2

	2-Sided P-Values for Pairwise Comparisons				
Ziprasidone 5 mg BID vs placebo	0.201	0.062	0.313	0.556	0.491
Ziprasidone 20 mg BID vs placebo	0.299	0.398	0.761	0.341	0.022
Ziprasidone 40 mg BID vs placebo	0.201	0.042	0.090	0.978	0.292

Source Data: Appendix V Table 16. Date of Data Extraction: 17JUL95.
Date of Table Generation: 11OCT96.

BPRS Core Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 104

	Treatment Week									
	Baseline		Week 1		Week 2		Week 3		Week 4	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone										
5 mg BID	44	12.8	44	-0.9	44	-1.3	44	-1.6	44	-1.8
20 mg BID	55	13.0	55	-1.6	55	-2.0	55	-2.3	55	-2.3
40 mg BID	47	12.8	47	-0.7	47	-0.6	47	-1.2	47	-1.2
Placebo	47	13.7	46	-2.0	47	-2.1	47	-2.3	47	-2.2

	2-Sided P-Values for Pairwise Comparisons				
Ziprasidone 5 mg BID vs placebo	0.201	0.083	0.252	0.449	0.742
Ziprasidone 20 mg BID vs placebo	0.299	0.593	0.974	0.981	0.751
Ziprasidone 40 mg BID vs placebo	0.201	0.040	0.051	0.193	0.301

Source Data: Appendix V Table 16. Date of Data Extraction: 17JUL95.
Date of Table Generation: 11OCT96.

CGI Severity Score Study 104
(from Sponsor's Submission)

CGI Severity Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 104

	Treatment Week									
	Baseline		Week 1		Week 2		Week 3		Week 4	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone										
5 mg BID	46	4.9	45	-0.1	37	-0.1	33	-0.2	30	-0.3
20 mg BID	55	4.8	54	-0.2	46	-0.3	38	-0.6	27	-0.8
40 mg BID	47	4.9	42	-0.2	32	-0.2	24	-0.3	20	-0.4
Placebo	47	5.0	45	-0.3	33	-0.3	29	-0.7	27	-0.7

	2-Sided P-Values for Pairwise Comparisons				
Ziprasidone 5 mg BID vs placebo	0.492	0.143	0.444	0.055	0.333
Ziprasidone 20 mg BID vs placebo	0.241	0.604	0.985	0.802	0.293
Ziprasidone 40 mg BID vs placebo	0.788	0.313	0.453	0.232	0.595

Source Data: Appendix V Table 17. Date of Data Extraction: 17JUL95
Date of Table Generation: 11OCT96.

CGI Severity Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 104

	Treatment Week									
	Baseline		Week 1		Week 2		Week 3		Week 4	
Treatment Groups	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone										
5 mg BID	46	4.9	46	-0.1	46	-0.0	46	-0.0	46	-0.1
20 mg BID	55	4.8	55	-0.2	55	-0.2	55	-0.3	55	-0.3
40 mg BID	47	4.9	47	-0.1	47	-0.1	47	-0.1	47	-0.2
Placebo	47	5.0	46	-0.3	47	-0.2	47	-0.4	47	-0.4

	2-Sided P-Values for Pairwise Comparisons				
Ziprasidone 5 mg BID vs placebo	0.492	0.147	0.283	0.043	0.076
Ziprasidone 20 mg BID vs placebo	0.241	0.723	0.784	0.784	0.827
Ziprasidone 40 mg BID vs placebo	0.788	0.149	0.337	0.143	0.233

Source Data: Appendix V Table 17. Date of Data Extraction: 17JUL95.
Date of Table Generation: 11OCT96.

Appendix Table 8.1.1.1
Deaths occurring during or after trial treatment : Cut-off date: 5/15/97

Ziprasidone subjects who died ≤ 30 days after treatment

SUBJECT #	AGE / SEX	LAST DOSE (MG/D)	DAYS OF TREAT-MENT	CAUSE OF DEATH/COMMENTS
108-6070305*	46/M	80	61	Found dead (in heat of 100°F). Autopsy report stated cause of death as acute and chromic asthmatic bronchitis and granulomatous myocarditis. ECG: Screening: QTc =366 msec Baseline: QTc =393 Week 6: QTc=395 Was on ziprasidone at time of death.
108-5920750*	39/F	120	8	Found dead one day after her estimated date of death of unknown cause. Subject's face was burned and it was thought that she had fallen against a hot water pipe. The investigator's postmortem diagnosis was alcohol abuse/diabetic ketoacidosis, but there is no evidence for this. No coroner's report located in the CRF. Was on ziprasidone at time of death.
116B-5080001*	54/M	120	71	Found dead in his hospital bed. Autopsy showed generalized atherosclerosis, coronary artery disease, cerebral artery disease, visceral congestion (liver, spleen, and lung), COPD, and cardiac hypertrophy. ECGs during the study: Screening: QTc=391 msec baseline: QTc=383 week 2: QTc=367 week 6:QTc=391 Subject had complaint of chest pain once during the study, but ECG was normal and diagnosed as anxiety. Was on ziprasidone at time of death.
302E-3190375*	48/M	120	162	Found dead. CRF showed hypertension and tachycardia on last day of study with hypertension as adverse event during study. Narrative states that subject had history of polydipsia and seizure disorder. Details regarding the death are unclear. Died one day after discontinuing ziprasidone.

Appendix Table 8.1.1.1 (con't)

304E-1930379**	52/M	80	221	Found dead while taking a nap. No autopsy performed and exact cause of death is unknown. ECG during the study as shown in the safety update: QTc at: Screening=374.7 msec Week 12=415.69 Week 28=413.12 with flat T wave in lead AVL; no evidence of ischemic changes. The CRF had minimal information and the patient profile in the safety update had different ECG QTc values than the original submission. Was on ziprasidone at time of death.
105-5340021*	70/F	2	5	Subject had sudden onset of shallow respirations and diaphoresis. Death certificate stated acute cardiopulmonary arrest due to arteriosclerotic cardiovascular disease. Subject with history of right bundle branch block, otherwise ECG was normal. Was taking ziprasidone just prior to death.
308-0350003*	63/M	80	485	Sudden collapse and died. Coroner's report stated that cause was a ruptured abdominal aortic aneurysm and atherosclerosis. Was on ziprasidone at the time of death.
115-6940394	43/M	40	16	Found dead. Coroner's cause of death listed as asphyxiation due to aspiration of vomit . Was on risperidone, clonazepam and lorazepam at time of death. Subject had difficulty breathing three days before death, and complained of dyspnea on morning of death. Died 29 days after discontinuing ziprasidone.
301-3110977	28/F	120	62	Died suddenly of unknown causes. Upon discontinuing ziprasidone, this cachetic subject complained of substernal pinching and ECG changes showed an arrhythmia with probable subendocardial ischemia. She was treated with thioridazine and nitrazepam, and died two days later. Autopsy reportedly showed evidence of myocardosis. Coroner's report not found in CRF. **Death occurred two days after stopping ziprasidone.**

Appendix Table 8.1.1.1 (con't)				
116B-6590001	44/F	120	47	Subject had a UTI upon d/c and was diaghosed with gastritis with Helicobacter pylori 13 days later. She was seen in ER with diagnosis of panic attack 21 days after d/c (three days prior to death). Sponsor reports that the autopsy was not available due to legal issues in medical examiners, but Subject's attending physician reportedly got information from the medical examiners that subject had a benign cardiac neoplasm (myxoma).ECG: screening: QTc=444 msec baseline: QTc=443 week 1: QTc=433 week 2: QTc=440 week 6: QTc=407 Subject reported chest pain one day after starting ziprasidone: cardiology w/u was normal, but had elevated transaminases. Episodes of tachycardia and hypertension during the study: day 6:102 bpm day 20:120/100; 104 bpm day 27:140/100; 102 bpm day 42:164/98 It is unclear what medications she was on as the patient summary and the CRF do not list the same medications. **Subject stopped ziprasidone 24 days before her death.**
303-1970299	79/F	80	30	Cardiac arrest. No autopsy was performed. Subject had new diagnosis of atrial fibrillation and ischemic heart disease 27 days after d/c. At time of death was taking perphenazine, deparkin, digoxin, verapamil, and enalapril. **Death occurred 30 days after d/c from ziprasidone.**
Suicides and accidents				
108-6090381	21/F	160	54	Suicide by gunshot while on ziprasidone.
116B-6940004	24/M	160	146	Suicide by hanging while on ziprasidone. Subject had been complaining of increasing depressed mood; treatment included an increase in ziprasidone.
117-6870317	51/M	120	205	Death by defenestration. According to study profile, subject did not appear suicidal prior to death.
117-7060529	40/M	160	54	Subject stopped ziprasidone on his own and four days later he drove his car off a cliff. Subject was driving his car after a sleep deprived EEG against medical advice. Autopsy listed asphyxiation due to drowning and was classified as a probable traffic accident.
302-2600156	46/M	120	7	Subject's body found drowned in local river after being missing from the hospital for five days.
302E-1590029	22/M	120	179	Suicide by falling under a train. Was being treated with ziprasidone at time of suicide with plans to be admitted to the hospital that same day.
JP-95-6011622[1♦]	53/M	53	20	Suicide seventeen days after discontinuing ziprasidone (Japanese studies: not part of the integrated safety data base.)

*Included in Sudden Unexpected Death (SUD) rate calculation in Appendices 8.1.1.3 and 8.1.1.4

[1] Submitted in the safety update

♦Not included in integrated safety data base

Appendix Table 8.1.1.1 (con't)

Ziprasidone subjects who died ≥ 30 days after treatment

SUBJECT #	AGE/ SEX	DOSE (MG/D)	DURATION (DAYS)	CAUSE OF DEATH
104-5130213	40/M	40	28	Sudden death; cause unknown. Occurred 7½ months after discontinuation from ziprasidone .
106-05550117	35/M	40	27	Unknown cause of death but possible seizure and aspiration of vomit. Was taking risperidone at time of death. Death occurred 4½ months after stopping ziprasidone .
108-5780020	37/M	80	8	Accidental drowning. Died 1½ months after stopping ziprasidone .
117-6940542	38/M	160	15	Suicide by gun shot one year after d/c from ziprasidone .
301-1140331	30/M	200	26	Died of complication due to pancreatitis 9 months after stopping ziprasidone
301-1320771	34/M	120	53	Suicide by hanging approximately 3 months after stopping ziprasidone .
303-0640276	61/M	40	69	Died of bronchopneumonia with bronchial adenocarcinoma and metastasis. Death occurred 4 months after stopping ziprasidone.
303-1950250	68/M	40	350	Died of cranial trauma 2° to fall. Ziprasidone was stopped 45 days prior to death.
303-1950281	71/F	40	61	Sudden death due to acute purulent leptomeningitis. Death occurred 4 ½ months after stopping ziprasidone.
303-1970269	67/F	80	37	Bronchopneumonia. Stopped ziprasidone112 days before diagnosis.
303-1990089 no CRF available	55/M	80	27	Sudden death due to acute cerebral edema. death occurred 60 days after stopping ziprasidone.
303-2120222 [1]	58/M	160	349	Died of post operative cerebral edema after tumor removal. Occurred two months after stopping ziprasidone
304-2040222	55/F	160	29	Sudden death with proposed cause of acute heart failure due to pulmonary disease. Death occurred approximately 2 months after stopping ziprasidone.
307-2690047** [1]	49/F	100	196	Died of hepatic coma, cholestatic jaundice and malignant neoplasm 95 days after stopping ziprasidone. Discontinued ziprasidone because of jaundice and elevated AST (244 U/L) and ALT (375 U/L).

**Died after cutoff of 5/15/97

[1]Submitted in the safety update

Appendix Table 8.1.1.1 (con't)

From the sponsor's electronic submission:

Deaths in Risperidone group (table from sponsor's electronic submission)

Treatment Group: Risperidone

Subject I.D.	Preferred text /Investigator text	Age at onset	Sex	Race	Weight (KG)	Duration of Treatment (Days)	Dose at onset (mg)	Mode Dose (mg)	Maximum Dose (mg)	Onset (Day)	Treatment discontinued	Serious adverse event type
117 06879223	FOREIGN BODY IN LARYNX / ASPHYXIATION DUE TO ASPIRATION OF FOOD	65	Male	Caucasian	93.4	201	4	4	6	201	No	DEATH / AELIFETH

Deaths in Haloperidol group (table from sponsor's electronic submission) :

Subject I.D.	Preferred text /Investigator text	Age at onset	Sex	Race	Weight (KG)	Duration of Treatment (Days)	Dose at onset (mg)	Mode Dose (mg)	Maximum Dose (mg)	Onset (Day)	Treatment discontinued	Serious adverse event type
108 06820040	SUICIDE/SELF-INFLICTED INJURY BY OTH/UNSP FIREARM / SELF INFLICTED GUNSHOT WOUND	29	Male	Caucasian	64.9	84	N/A			102	No	DEATH
108 06940564	POISONING BY UNSPECIFIED DRUG/MEDICINAL SUBSTANCE / INTENTIONAL DRUG OVERDOSE	30		Other			N/A				No	DEATH
	SUICIDE/SELF-INJURY BY UNSPECIFIED MEANS / SUICIDE	30		Other			N/A				No	DEATH
	SUICIDE/SELF-POISONING BY CORROSIVE/CAUSTIC SUBST / INTENTIONAL INGESTION OF CORROSIVE SUBSTANCE	30		Other			N/A				No	DEATH
108E06840077	ACUTE MI, UNSPECIFIED SITE, UNSPECIF EPISODE CARE / ACUTE MYOCARDIAL INFARCTION	72		Other			N/A				Yes	DEATH / AEHOSP

Deaths in Placebo Group (Table from the sponsor's electronic submission):

Treatment Group: Placebo

Subject I.D.	Preferred text /Investigator text	Age at onset	Sex	Race	Weight (KG)	Duration of Treatment (Days)	Dose at onset (mg)	Mode Dose (mg)	Maximum Dose (mg)	Onset (Day)	Treatment discontinued	Serious adverse event type
106 05340018	CONGESTIVE HEART FAILURE / CONGESTIVE HEART FAILURE	82	Female	Caucasian	76.0	21	0	0	0	75	No	DEATH / AEHOSP
	RESPIRATORY FAILURE / RESPIRATORY FAILURE	82	Female	Caucasian	76.0	21	0	0	0	75	No	DEATH / AEHOSP
106 05340019	PNEUMONITIS DUE TO INHALATION OF FOOD OR VOMITUS / ASPIRATION PNEUMONIA	87	Female	Caucasian	46.8	13	0	0	0	17	Yes	DEATH / AELIFETH / AEHOSP
	RESPIRATORY FAILURE / RESPIRATORY FAILURE	87	Female	Caucasian	46.8	13	0	0	0	17	Yes	DEATH / AELIFETH / AEHOSP
106 05610063	PYREXIA OF UNKNOWN ORIGIN / COMPLICATIONS OF HYPERTHERMIA	34	Male	Caucasian	79.6	14	0	0	0	61	No	DEATH
106 05620126	POISONING BY ANTIALLERGIC AND ANTIEMETIC DRUGS / INTENTIONAL OVERDOSE - DIPHENHYDRAMINE	37	Female	Caucasian	79.4	32	0	0	0	39	No	DEATH
	SUICIDE/SELF-INJURY BY UNSPECIFIED MEANS / SUICIDE	37	Female	Caucasian	79.4	32	0	0	0	39	No	DEATH
303 01810067	MALIGNANT NEOPLASM OF PLEURA, UNSPECIFIED / LEFT SIDE PLEURAL MESOTHELIOMA	43	Male	Caucasian	86.0	232	0	0	0	286	Yes	DEATH / AELIFETH / AEHOSP
	SEC/UNSP MALIGN NEOPL LYMPH NODES/INTRATHORACIC / METASTASES TO MEDIASTINAL LYMPH NODES	43	Male	Caucasian	86.0	232	0	0	0	286	Yes	DEATH / AELIFETH / AEHOSP
	SECONDARY MALIGN NEOPL OF LIVER, SPEC AS SECONDARY / METASTASES TO LIVER	43	Male	Caucasian	86.0	232	0	0	0	286	Yes	DEATH / AELIFETH / AEHOSP
303 01970272	BRONCHOPNEUMONIA, ORGANISM UNSPECIFIED / BRONCHOPNEUMONIA	76	Male	Caucasian	66.0	16	0	0	0	19	No	DEATH
303 02120224	ACUTE PANCREATITIS / ACUTE HEMORRHAGIC PANCREATITIS	66	Female	Caucasian	70.0	10	0	0	0	49	No	DEATH
	PULMONARY EMBOLISM AND INFARCTION / PULMONARY EMBOLISM	66	Female	Caucasian	70.0	10	0	0	0	49	No	DEATH
	UNSPECIFIED CIRCULATORY SYSTEM DISORDER / CIRCULATORY INSUFFICIENCY	66	Female	Caucasian	70.0	10	0	0	0	49	No	DEATH
307 01780094	EXTRD HEMOR POST INJURY W/O OPEN IC WND, UNSP CONS / EXTRADURAL HEMATOMA	43					N/A				No	DEATH
307 02130122	HEART DISEASE, UNSPECIFIED / CARDIAC DECOMPENSATION	73					N/A				Yes	DEATH / AELIFETH / AEHOSP
	PNEUMONIA, ORGANISM UNSPECIFIED / LEFT SIDED PNEUMONIA	73					N/A				Yes	DEATH / AELIFETH / AEHOSP

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APPENDIX 8.1.1.2 Mortality rate for Phase II/III clinical programs in ziprasidone NDA 20-825

DRUGS	Number of Subjects [1]	Subject-years exposure [1]	Total # deaths	# deaths ≤ 30 days	Crude mortality rate [2]	Mortality per 100 subject- years [2]
Ziprasidone	2588	772	31 [3]	17	0.007	2.20
Placebo	382	52	9	5	0.013	9.62
Haloperidol	585	131	3	3	0.005	2.29
Risperidone	295	105	1	1	0.003	0.95

[1]Includes integrated safety data base, Study 105 (IM: ziprasidone n=11; placebo n=12) and Study 120 (dementia: ziprasidone n=12)
[2]Based on # of deaths ≤ 30 days
[3]Does not include subject 307-269-0047 (died after the cut-off date of 5/15/97) and subject JP-95-6011622

APPENDIX 8.1.1.3 Rate of Sudden Unexpected Death* (SUD) in ziprasidone NDA 20-825

DRUGS	Number of Subjects [1]	Subject-years exposure	# Sudden Deaths	SUD per 1000 subject years
Ziprasidone	2588	772	7#	9.1
Placebo	382	52	0	0
Haloperidol	585	131	0	0
Risperidone	295	105	1	9.5

*Sudden Unexpected Death (SUD) refers to subjects found dead or who died within 24 hours of symptoms
Refer to Appendix 8.1.1.1 for listing of deaths considered to be SUD.
#Does not include subject 115-6940394; please refer to the text of Section 8.1.1
[1]Includes integrated safety data base, Study 105 (IM: ziprasidone n=11; placebo n=12) and Study 120 (dementia: ziprasidone n=12)

APPENDIX 8.1.1.4 Rate of SUD in most recently submitted antipsychotic NDA data bases *

DRUGS	Subject-years exposure	# Sudden Deaths	SUD per 1000 subject years
Ziprasidone	772	7	9.1
Sertindole	476	5	10.5
Olanzapine	1122.2	4	3.5
Risperidone	508	2	3.9
Quetiapine	865.3	1	1.1

*Sources are the current NDA 20-852 and Review of Clinical Data: *General Characteristics of the Deaths in the NDAs for Olanzapine, Risperidone, Quetiapine and Sertindole* by Greg Burkhart, M.D. (HFD-120: 3/3/98)

APPENDIX 8.1.2

SUMMARY OF NONFATAL SERIOUS ADVERSE EVENTS OCCURING IN SUBJECTS TAKING ZIPRASIDONE AND CONSIDERED UNLIKELY TO BE DRUG RELATED

Subject #	Age/Sex	Modal Dose (mg/d)	Duration (days)	Adverse Event
Cardiac				
101-5050003	33/M	40	28	Syncopal event. Ziprasidone was d/ced 11 days prior to episode and subject was on multiple medications at time of incident.
104-5220146	45/F	80	12	Subject hospitalized with hypertensive episode with diastolic pressure up to 120 mm Hg, tremouslousness and weakness. Subject with history of hypertension which had been stable with nifedipine.
106-5520124	41/M	40	15	Hypertension with peak of 152/110. No h/o of hypertension also had facial rash (see dermatology)
116B-5510007	44/M	120	12	Chest pain, thought to be anxiety. Subject was hospitalized for observation and sponsor concluded this was a manifestation of anxiety.
116B-6590008	72/F	80	239	Hypertension of 200/90. Profile states that subject had a history of hypertension, but it was normal for the six months of the study prior to this onset.
118-7090004	40/M	40	4	Sinus bradycardia (48 bpm) at end of study. Elevated CPK, but this was not checked until the end of the study just as subject started risperidone.
303-2120105	56/M	160	280	Hypertensive episode (220/140) fell down steps resulting in subdural hematoma, skull fracture, pneumothorax
Gastrointestinal				
106-5550119	57/F	120	7	Incarcerated left inguinal hernia
109-5720027	49/F	80	3	Subject was hospitalized for chest pain; original work-up in CRF suggested ECG changes of QTc prolongation. Cardiology work up was negative and Dr. Charles Ganley, HFD-110 consultant, determined that ECGs did not reflect true QTc changes. Final diagnosis was exacerbation of gastroesophageal reflux.
116B-6590001	44/F	120	47	Gastritis with Helicobacter pylori diagnosed 13 days after discontinuing ziprasidone. Died of benign cardiac neoplasm (myxoma) 24 days after stopping ziprasidone.
303-2710228	54/M	160	87	Subject had heartburn, epigastric pain and weight loss and within three weeks of these symptoms discontinued ziprasidone and was hospitalized. Endoscopy showed chronic gastritis with Helicobacter pylori.

APPENDIX 8.1.2 (CON'T)				
Genitourinary				
116B-5870006	37/F	160	256	Hysterectomy and B/L oophorectomy
116B-5900005	33/F	160	440	Uterine Fibroids
117-6220029	53/M	40	4	benign prostatic hypertrophy
117-6380304	57/F	80	363	Total abdominal hysterectomy
117-6690008	39/F	160	315	Urinary bladder suspension surgery.
Pulmonary				
105-5340006	86/F	6	57	Tracheobronchitis 2½ months after d/c of ziprasidone
106-5550136	59/M	40	2	Asthma attack; subject with history of COPD.
106E-5550133	60/F	40	92	chest pain/exacerbation of COPD/bronchitis/adenovirus
110-5370007	33/M	60	4	Diagnosed with lung cancer five days after d/c of ziprasidone
116B-5680007	43/F	120	240	Test positive for HIV virus and had event of pneumocystis crainii
116B0-74004/ 108-5740080	33/M	80	301	Spontaneous pneumothorax
Metabolic				
117-5130512	35/M	120	194	Diabetic episode with 16 lb. wt loss and thirst and ketoacidosis
116B-6940003	26/M	200	164	Nausea, vomiting and loss of appetite. Weight loss of > 30 lb; was hospitalized for exacerbation of schizophrenia. . Also, loss of appetite, n/v.
117-5080350	75/M	80	52	Dehydration, erratic eating pattern associated with exacerbation of schizophrenia in this subject. Weight loss of 13.5 lb.
Miscellaneous				
101-05060084	52/M	4	20	Hyponatremia (Na=111), confusion. Hospitalized, resolved in 2 days with fluid restriction. Ziprasidone was discontinued.
104-05250132	64/M	40	28	Cellulitis, right lower leg occurring twenty-two days after d/c of ziprasidone.
104-5200275	63/F	80	28	Fall (unclear how subject fell) with fracture of left humeral head on day 15; on day 24, subject developed right lower leg cellulitis and lymphangitis and was treated with antibiotics, bedrest, and leg soaks.
116B-665008/ 117-6650101	23/M	160	365	Knee surgery.
118-709-0004	40/M	20	4	Pt had elevated CPK, but no CPK levels done until the subject was taking risperidone 1 day after taking ziprasidone. At that time the CPK levels were very high (702 U/L) and were eventually stabilized and decreased to 544 U/L before subject was discharged from the hospital.

APPENDIX 8.1.2 (CON'T)				
303-01980076	44/M	80	364	Subject was mugged and had brain concussion and facial contusions.
303-2640336	34/M	160	359	2nd degree burns of face, neck and shoulder from fire at psychiatry clinic.
303-2120222	58/M	160	349	Blood pressure was 180/90 after this loss of consciousness (2-3minutes). No ECG changes, but CT showed cerebral neoplasm.
* *From Japanese study which is not part of integrated safety data base	51/F	40,80 or 100 mg/d	24	Hyponatremia (Na=110 MEq/L), hypokalemia (K=3.2Meq/L),CPK=10,760 U/L, ↑ AST=91, ↑cortisol (32 ug/ml), LDH=796 U/L, 3+ blood in urine and **decreased level of consciousness** (unresponsive to verbal stimulation and abnormal reflexes). Hypertension (208/110) and tachycardia (110/min)Baseline values were normal for the above tests except for K=5.3 Meq/L. Within 8 days of hospitalization, this subjects level of consciousness improved and she was able to eat without assistance. This incident occurred 8 days after discontinuation of ziprasidone (she had akathisia and worsening depression) and subject was taking biperidene and sulpiride at time of the incident.
Overdose				
114-7150457	20/M	160	20	Overdose of metformin.
116B-5510005	38/M	80	72	Overdosed with acetylsalicylic acid.
116B-5950018	33/F	200	182	Overdosed on lorazepam and flurazepam in presence of hospital staff.
116B-6020005	27/M	160	159	Overdosed on lorazepam 10 days after d/c of ziprasidone.
117-05080352	54/M	80	308	Subject overdosed on chloral hydrate and lorazepam was treated with activated charcoal and developed rhabdomyolysis with nerve damage in leg. This occurred one day after d/c of ziprasidone.
117-06310477	35/F	80	92	Overdose on lithium eight days after d/c of ziprasidone.

Note: Psychiatric serious adverse events are not discussed in this review, as it is not always possible to distinguish between the effects of the study drug and the symptoms of the underlying illness.

Appendix 8.1.5.3 (From Sponsor's Electronic Submission)

Treatment-Emergent Adverse Events Reported in at Least 1% of Ziprasidone Subjects (All Causalities)
Incidence Rate for Ziprasidone Greater than Placebo
Short-Term Fixed-Dose Placebo-Controlled Oral Dosing Phase II/III Studies

	Ziprasidone	Haloperidol	Placebo
Number of Subjects: Evaluable for Adverse Events	702	85	273
% With Adverse Events			
BODY AS A WHOLE			
ACCIDENTAL INJURY	4.0	2.4	1.5
ASTHENIA	4.6	8.2	2.6
CHEST PAIN	3.3	2.4	2.9
INFECTION	1.3		0.7
CARDIOVASCULAR			
POSTURAL HYPOTENSION	1.3	2.4	0.4
TACHYCARDIA	1.6	2.4	1.1
DIGESTIVE			
ANOREXIA	1.9	4.7	1.1
CONSTIPATION	9.3	7.1	8.4
DIARRHEA	4.8	4.7	4.4
DRY MOUTH	4.1	11.8	2.2
DYSPEPSIA	8.1	15.3	7.0
INCREASED SALIVATION	1.3	1.2	0.7
NAUSEA	9.5	9.4	7.0
MUSCULOSKELETAL			
ARTHRALGIA	3.3	2.4	2.9
MYALGIA	1.1		0.4
NERVOUS			
AKATHISIA	8.4	28.2	7.0
ANXIETY	4.4	1.2	4.0
DIZZINESS	7.8	9.4	6.9
DYSTONIA	4.0	11.8	2.2
EXTRAPYRAMIDAL SYNDROME	4.7	14.1	1.1
HYPERTONIA	3.4	11.8	1.8
SOMNOLENCE	14.4	23.5	6.6
TREMOR	2.4	10.6	1.8
RESPIRATORY			
COUGH INCREASED	2.6	2.4	0.7
RESPIRATORY DISORDER	4.8		1.1
RESPIRATORY TRACT INFECTION	3.0	8.2	2.2
RHINITIS	3.7		2.2
SKIN AND APPENDAGES			
FUNGAL DERMATITIS	1.7		1.1
RASH	4.1	2.4	3.3
SPECIAL SENSES			
ABNORMAL VISION	2.7	4.7	1.5
CONJUNCTIVITIS	1.1	1.2	1.1
UROGENITAL			
URINARY INCONTINENCE	1.3	1.2	1.1

Subjects with multiple occurrences of the same adverse event are counted only once for that adverse event.
Only adverse events occurring while on study treatment or within the six days after the last day of study treatment were included in this table.
Protocols: 104,106,114,115

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Appendix 8.1.5.4
(Selected from Sponsor's Proposed Labeling)

Other Adverse Events Observed During the Premarketing Evaluation of Ziprasidone - Following is a list of COSTART terms that reflect treatment- emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with ziprasidone at multiple doses > 4 mg/ day within the database of 2163 patients. All reported treatment- related events are included except those already listed in Table 1 or elsewhere in labeling, those event terms which were so general as to be uninformative, and events reported only once and which did not have a substantial probability of being acutely life- threatening. It is important to emphasize that, although the events reported occurred during treatment with ziprasidone, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/ 100 patients (only those not already listed in the tabulated results from placebo- controlled trials appear in this listing); infrequent adverse events are those occurring in 1/ 100 to 1/ 1000 patients; rare events are those occurring in fewer than 1/ 1000 patients.

Body as a Whole *Frequent:* abdominal pain, back pain, fever, flu syndrome, headache, pain, suicidal ideation: *Infrequent:* , abscess, accidental fall, accidental overdose, allergic reaction, cellulitis, chills, bacterial infection, fungal infection, intentional overdose, lab test abnormal, malaise, photosensitivity reaction, suicide attempt: *Rare:* abdomen enlarged, hangover effect, neoplasm, pelvic pain.

Cardiovascular System *Frequent:* hypertension, hypotension: *Infrequent:* angina pectoris, arrhythmia, bradycardia, electrocardiogram abnormal, hemorrhage, migraine, palpitation, syncope, vasodilation. *Rare:* peripheral vascular disorder, QT interval prolonged, retinal vascular disorder.

Digestive System *Frequent:* vomiting: *Infrequent:* cheilitis, duodenal ulcer, dysphagia, flatulence, gastritis, gastroenteritis, gingivitis, increased appetite, liver function tests abnormal,

oral moniliasis, rectal hemorrhage, tongue edema, tooth caries: *Rare:* eructation, fecal incontinence, gum hemorrhage, stomach ulcer.

Hemic and Lymphatic System *Infrequent:* anemia, ecchymosis, eosinophilia, leukocytosis, leukopenia: *Rare:* iron deficiency anemia, thrombocytopenia.

Metabolic and Nutritional Disorders *Frequent:* weight gain, weight loss: *Infrequent:* albuminuria, dehydration, edema, hyperglycemia, peripheral edema, SGOT increased, SGPT increased, thirst: *Rare:* bilirubinemia, hypercholesteremia.

Musculoskeletal System *Infrequent:* arthrosis, bone pain, leg cramps, myasthenia, tenosynovitis.

Nervous System *Frequent:* agitation, delusions, depression, dyskinesia, hallucinations, hostility, insomnia, manic reaction, myoclonus, nervousness, paranoid reaction, paresthesia, personality disorder, psychosis, schizophrenic reaction, speech disorder, tardive dyskinesia, thinking abnormal, twitching: *Infrequent:* abnormal dreams, abnormal gait, akinesia, amnesia, apathy, ataxia, catatonic reaction, choreoathetosis, cogwheel rigidity, confusion, convulsion, delirium, dementia, depersonalization, drug dependence, dysarthria, emotional lability, euphoria, grand mal convulsion, hyperkinesia, hypesthesia, hypokinesia, libido decreased, libido increased, neurosis, oculogyric crisis, paralysis, sleep disorder, stupor, vertigo,

withdrawal syndrome: *Rare:* diplopia, incoordination, neuropathy, nystagmus.

Respiratory System *Frequent:* bronchitis, dyspnea, pharyngitis: *Infrequent:* asthma, epistaxis, pneumonia, respiratory distress syndrome, sinusitis: *Rare:* pneumothorax, voice alteration.

Skin and Appendages *Frequent:* pruritus: *Infrequent:* acne, alopecia, contact dermatitis, dry skin, eczema, exfoliative dermatitis, herpes simplex, maculopapular rash, psoriasis, seborrhea, skin hypertrophy, skin ulcer, sweating, urticaria, vesiculobullous rash: *Rare:* furunculosis, lichenoid dermatitis, pustular rash.

Special Senses *Infrequent:* blepharitis, deafness, dry eyes, ear pain, eye pain, otitis externa, otitis media, retinal disorder, taste perversion, tinnitus: *Rare:* abnormality of accommodation, mydriasis.

Urogenital System *Infrequent:* abnormal ejaculation, amenorrhea, cystitis, dysmenorrhea, dysuria, gynecomastia, hematuria, impotence, leukorrhea, menorrhagia, metrorrhagia, polyuria, urinary frequency, urinary retention, vaginitis: *Rare:* anorgasmia, breast pain, kidney pain, nephritis, pyelonephritis, uterine fibroids enlarged.

APPEARS THIS WAY
ON ORIGINAL

Appendix 8.1.6.3.1 Mean Change from Baseline to Last Observation for Laboratory Test Data Short-term Fixed-Dose Placebo Controlled from Phase II/III* (adapted from sponsor's electronic submission)

			Ziprasidone			Placebo		
GROUP	PARAMETER	UNITS@	N	BASELINE MEDIAN	CHANGE FROM BASELINE	N	BASELINE MEDIAN	CHANGE FROM BASELINE
HEMATOLOGY	Hemoglobin (HGB)	G/DL	680	15.3	-0.1	261	15.1	0.1
	Hematocrit (HCT)	%	679	45	-1	261	45	0
	RBC Count	MILL/CMM	680	4.9	0	261	4.9	0
	Platelets	THOU/CMM	678	266	0	260	266	-1
	WBC Count	THOU/CMM	680	7.4	0.1	261	7.5	0
	Eosinophils (%)	%	679	3	0	261	3	0
	Neutrophils (abs)	THOU/CMM	679	4.41	0.13	261	4.34	-0.06
LIVER FUNCTION	Total Bilirubin	MG/DL	681	0.5	0	261	0.5	0.1
	Total Protein	G/DL	682	7.1	0	261	7.2	0
	Serum Albumin	G/DL	681	4.3	0	261	4.3	0
	Serum Globulin	G/DL	680	2.9	0	260	3	0
	SGOT(AST)	IU/L	682	18	0	261	18	0
	SGPT(ALT)	IU/L	681	20	0	261	19	-1
	LDH	IU/L	682	140	4	261	142	1
	Alk. Phosphatase	IU/L	682	79	-1	261	76	-1
RENAL FUNCTION	Blood Urea Nitrogen	MG/DL	682	13	-1	261	12	0
	Serum Creatinine	MG/DL	682	1	0	261	1	0
ELECTROLYTES	Uric Acid	MG/DL	682	5.2	0.2	261	5.2	0.2
	Sodium	MEQ/L	682	140	0	261	140	0
	Potassium	MEQ/L	682	4.4	0	261	4.4	0
	Chloride	MEQ/L	682	103	0	261	103	1
	Bicarbonate	MEQ/L	2	22	1	.	.	.
	Calcium	MG/DL	682	9.6	0	261	9.6	0
	Phosphorus	MG/DL	681	3.8	0	261	3.8	-0.1
	Glucose, Fasting	MG/DL	3	86	2	1	190	-41
	Glucose, Random	MG/DL	678	93	0	259	93	3
	Magnesium	MG/DL	1	2	0	.	.	.
LIPIDS	Cholesterol	MG/DL	682	185	-3	261	186	-2
	Triglycerides	MG/DL	681	126	-6	260	130	-13
URINE	Specific Gravity		679	1.02	0	258	1.02	0
	Urine pH		678	5.5	0	258	5.5	0
	Protein (qual)		588	0	0	214	0	0
	Urine Glucose		588	0	0	214	0	0
	Ketones (qual)		588	0	0	214	0	0
	Bilirubin (qual)		588	0	0	214	0	0

Based on Laboratory Test Results.
1. Converted to Standard Reporting Units
2. Adjusted to a Common Set Upper and Lower Reference Limits
@ Kruskal-Wallis test yielded a significant association at the .05 level of alpha by using the RANK and ANOVA procedures

*The sponsor clarified that these were studies 104, 106, 114, 115

Appendix 8.1.6.3.2a Sponsor's Laboratory Reference Ranges to Determine Baseline Abnormality (11/7/97 submission from sponsor)

Ziprasidone Project Laboratory Reference Ranges

TEST	REF_MIN	REF_MAX	STDUNIT
Hemoglobin			G/DL
Hematocrit			%
Red Blood Cells			MILL/CMM
Platelets			THOU/CMM
White Blood Cells			THOU/CMM
Eosinophils (%)			%
Erythrocyte Sedimentation Rate			MM/H
Prothrombin Time Quick			SEC
Total Bilirubin			MG/DL
Direct Bilirubin			MG/DL
Protein (total)			G/DL
Albumin			G/DL
Globulin			G/DL
Aspartate Aminotransferase (GOT)			IU/L
Alanine Aminotransferase (GPT)			IU/L
Lactate Dehydrogenase			IU/L
Alkaline Phosphatase			IU/L
Blood Urea Nitrogen			MG/DL
Creatinine			MG/DL
Urate			MG/DL
Sodium			MEQ/L
Potassium			MEQ/L
Chloride			MEQ/L
Bicarbonate			MEQ/L
Calcium			MG/DL
Phosphate			MG/DL
Cholesterol			MG/DL
Triglycerides			MG/DL
Glucose (fasting)			MG/DL
Glucose (random)			MG/DL
Urine Specific Gravity			
Urine pH			
Urine Protein			
Urine Glucose			
Urine WBC			/HPF
Urine RBC			/HPF
Urine Ketones			
Urine Granular Casts			/LPF
Urine Hyaline Casts			/LPF
Urine Bilirubin			

Appendix 8.1.6.3.2a (con't) Sponsor's Laboratory Reference Ranges to Determine Baseline Abnormality (11/7/97 submission from sponsor)

Cholesterol (LDL)	MG/DL
Cholesterol (HDL)	MG/DL
Thyroxine (T4)	MCG/DL
Magnesium	MG/DL
Prolactin	NG/ML
Urine Calcium	MG/DAY
Urine Glucose (24 Hr) Quantitative	MG/DAY
Urine (24hr) Protein	MG/DAY
TSH	MCIU/ML
Urine WBC Cast	/LPF
Urine (24hr) Creatinine	MG/DAY
Urine RBC Casts	/LPF
Neutrophils (Abs)	THOU/CMM

APPEARS THIS WAY
ON ORIGINAL

Appendix 8.1.6.3.2b Sponsor's criterion for determining post baseline clinical significance of laboratory values (adapted from sponsor's submission of 11/7/97)

					Column "A"	Column "B"
Test Code	Lab Test	Standard Unit	Test Type	Baseline Abnormality Criterion	Post-baseline Clin Sig Criterion for BL normal/abnormal (Tier 1)	Post-baseline Clin Sig Criterion for BL abnormal (Tier 2)
1	Hemoglobin (HGB)	G/DL	HEMATOLOGY	> 1.0 x ULN	>20% Decrease from baseline	< 75% of baseline
				< 1.0 x LLN	>20% Decrease from baseline	< 90% of baseline
2	Hematocrit (HCT)	%	HEMATOLOGY	> 1.0 x ULN	>20% Decrease from baseline	< 75% of baseline
				< 1.0 x LLN	>20% Decrease from baseline	< 90% of baseline
3	RBC Count	MILL/CMM	HEMATOLOGY	> 1.0 x ULN	>25% Decrease from baseline	< 75% of baseline
				< 1.0 x LLN	>25% Decrease from baseline	< 90% of baseline
5	Platelets	THOU/CMM	HEMATOLOGY	> 1.0 x ULN	> 700	> 120% of baseline
				< 1.0 x LLN	< 75	< 80% of baseline
7	WBC Count	THOU/CMM	HEMATOLOGY	> 1.0 x ULN	> 17.5	> 125% of baseline
				< 1.0 x LLN	< 2.5	< 75% of baseline
14	ESR	MM/H	HEMATOLOGY	> 1.0 x ULN (x)	> 1.2 x ULN	> 120% of baseline
19	Prothrombin Time	SEC	HEMATOLOGY	> 1.0 x ULN	> 1.2 x ULN	> 120% of baseline
608	Neutrophils (abs)	THOU/CMM	HEMATOLOGY	< 1.0 x ULN	<1.0	< 75% of baseline
9	Eosinophils (%)	%	HEMATOLOGY	> 1.0 x ULN	>= 10%	> 150% of baseline
21	Total Bilirubin	MG/DL	LIVER FUNCTION	> 1.0 x ULN (x)	> 1.5 x ULN	> 150% of baseline
22	Direct Bilirubin	MG/DL	LIVER FUNCTION	> 1.0 x ULN (x)	> 1.5 x ULN	> 150% of baseline
24	Total Protein	G/DL	LIVER FUNCTION	> 1.0 x ULN	> 1.1 x ULN	> 110% of baseline
				< 1.0 x LLN	0.9 < x LLN	< 90% of baseline
25	Serum Albumin	G/DL	LIVER FUNCTION	> 1.0 x ULN	> 1.1 x ULN	> 120% of baseline
				< 1.0 x LLN	< 0.9 x LLN	< 80% of baseline
26	Serum Globulin	G/DL	LIVER FUNCTION	> 1.0 x ULN	> 1.2 x ULN	> 150% of baseline
				< 1.0 x LLN	< 0.8 x LLN	< 50% of baseline

Appendix 8.1.6.3.2b (con't) Sponsor's criterion for determining post baseline clinical significance of laboratory values (adapted from sponsor's submission of 11/7/97)

Test Code	Lab Test	Standard Unit	Test Type	Baseline Abnormality Criterion	Column "A" Post-baseline Clin Sig Criterion for BL normal/abnormal (Tier 1)	Column "B" Post-baseline Clin Sig Criterion for BL abnorma (Tier 2)
28	SGOT(AST)	IU/L	LIVER FUNCTION	>1.0 x ULN (x)	> 3 x ULN	> 200% of baseline
30	SGPT(ALT)	IU/L	LIVER FUNCTION	> 1.0 x ULN (x)	> 3 x ULN	> 200% of baseline
32	LDH	IU/L	LIVER FUNCTION	> 1.0 x ULN (x)	> 3 x ULN	> 200% of baseline
35	Alkaline Phosphatase	IU/L	LIVER FUNCTION	> 1.0 x ULN (x)	> 3 x ULN	> 150% of baseline
47	BUN	MG/DL	RENAL FUNCTION	> 1.0 x ULN (x)	> 1.3 x ULN	> 130% of baseline
48	Creatinine	MG/DL	RENAL FUNCTION	> 1.0 x ULN (x)	> 1.3 x ULN	> 130% of baseline
54	Sodium	MEQ/L	ELECTROLYTES	> 1.0 x ULN	> 1.05 x ULN	> 105% of baseline
				< 1.0 x LLN	< 0.95 x LLN	< 95% of baseline
55	Potassium	MEQ/L	ELECTROLYTES	> 1.0 x ULN	> 1.1 x ULN	> 110% of baseline
				< 1.0 x LLN	< 0.9 x LLN	< 90% of baseline
56	Chloride	MEQ/L	ELECTROLYTES	> 1.0 x ULN	> 1.1 x ULN	> 110% of baseline
				< 1.0 x LLN	< 0.9 x LLN	< 90% of baseline
57	Bicarbonate	MEQ/L	ELECTROLYTES	> 1.0 x ULN	> 1.1 x ULN	> 110% of baseline
				< 1.0 x LLN	< 0.9 x LLN	< 90% of baseline
58	Calcium	MG/DL	ELECTROLYTES	> 1.0 x ULN	> 1.1 x ULN	> 110% of baseline
				< 1.0 x LLN	< 0.9 x LLN	< 90% of baseline
59	Phosphorus	MG/DL	ELECTROLYTES	> 1.0 x ULN	> 1.2 x ULN	> 120% of baseline
				< 1.0 x LLN	< 0.8 x LLN	< 80% of baseline
50	Uric Acid	MG/DL	ELECTROLYTES	> 1.0 x ULN	> 1.2 x ULN	> 120% of baseline
199	Magnesium	MEQ/L	ELECTROLYTES	> 1.0 x ULN	> 1.1 x ULN	> 110% of baseline
				< 1.0 x LLN	< 0.9 x LLN	< 90% of baseline
63	Cholesterol	MG/DL	LIPIDS	> 1.0 x ULN (x)	> 1.2 x ULN	> 150% of baseline
173	HDL Cholesterol	MG/DL	LIPIDS	< 1.0 x LLN (?)	< 0.8 x LLN	< 80% of baseline
172	LDL Cholesterol	MG/DL	LIPIDS	> 1.0 x ULN (x)	> 1.2 x ULN	> 120% of baseline
64	Triglycerides	MG/DL	LIPIDS	> 1.0 x ULN (x)	> 1.2 x ULN	> 150% of baseline
67	Glucose, Fasting	MG/DL		> 1.0 x ULN	> 1.2 x ULN	> 150% of baseline
				< 1.0 x LLN	< 0.6 x LLN	< 50% of baseline
223	Prolactin	NG/ML		> 1.0 x ULN (x)	> 1.1 x ULN	> 150% of baseline

Appendix 8.1.6.3.2b (con't) Sponsor's criterion for determining post baseline clinical significance of laboratory values (adapted from sponsor's submission of 11/7/97)

					Column "A"	Column "B"
Test Code	Lab Test	Standard Unit	Test Type	Baseline Abnormality Criterion	Post-baseline Clin Sig Criterion for BL normal/abnormal (Tier 1)	Post-baseline Clin Sig Criterion for BL abnormal (Tier 2)
78	Protein (qual)		URINE	> 1.0 x ULN	>= 2+	> baseline + 2
79	Urine Glucose		URINE	> 1.0 x ULN	>= 2+	> baseline + 2
80	Urine WBC	/HPF	URINE	> 1.0 x ULN	>= 6	> baseline + 6
81	Urine RBC	/HPF	URINE	> 1.0 x ULN	>= 6	> baseline + 6
86	Ketones (qual)		URINE	> 1.0 x ULN	>= 1+	> baseline + 1
88	Granular Casts	/LPF	URINE	> 1.0 x ULN	> 1	> baseline + 1
90	Hyaline Casts	/LPF	URINE	> 1.0 x ULN	> 1	> baseline + 1
115	Bilirubin (qual)		URINE	> 1.0 x ULN	>= 1+	> baseline + 1
600	Red Cell Cast	/LPF	URINE	> 1.0 x ULN	>= 1	> baseline + 1
442	White Cell Cast	/LPF	URINE	> 1.0 x ULN	>= 1	> baseline + 1
76	Specific Gravity		URINE	> 1.0 x ULN	> 1.035	> 1.035
				< 1.0 x LLN	< 1.000	< 1.000
77	Urine pH		URINE	> 1.0 x ULN	> 1.1 x ULN	> 1.1 x ULN
				< 1.0 x LLN	< 0.9 x LLN	< 0.9 x LLN
495	Creatinine	MG/DAY	URINE	> 1.0 x ULN (x)	> 1.1 x ULN	> 110% of baseline
302	Calcium (quant)	MG/DAY	URINE	> 1.0 x ULN (x)	> 1.1 x ULN	> 110% of baseline
308	Protein (quant)	MG/DAY	URINE	> 1.0 x ULN (x)	> 1.1 x ULN	> 110% of baseline
307	Glucose (quant)	MG/DAY	URINE	> 1.0 x ULN (x)	> 1.1 x ULN	> 110% of baseline

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Appendix 8.1.6.3.2c Incidence of Clinically Significant Laboratory Abnormalities for Short term Fixed-dose placebo controlled studies 104, 106, 114, 115. (adapted from sponsor's electronic submission)

Number of Subjects:	Ziprasidone	Placebo
Evaluable for laboratory abnormalities	688	261
With Clinically significant laboratory abnormalities	255 (37%)	86 (33%)

Group	Parameter	Units	Criteria* @	Ziprasidone Subjects with Abnormalities N	n	%	Placebo Subjects with Abnormalities N	n	%
HEMATOLOGY	Hemoglobin (HGB)	G/DL	> 20% decrease*	684	3	0	261	0	0
	Hematocrit (HCT)	%	> 20% decrease*	684	1	0	261	0	0
	RBC Count	MILL/CMM	> 25% decrease*	684	2	0	261	0	0
	Platelets	THOU/CMM	< 75	683	2	0	261	2	1
			> 700	683	0	0	261	0	0
	WBC Count	THOU/CMM	< 2.5	684	0	0	261	0	0
			> 17.5	684	4	1	261	1	0
	Eosinophils (%)	%	>= 10%	683	21	3	261	3	1
	Prothrombin Time	SEC	> 1.2 x ULN	2	0	0	1	0	0
	Neutrophils (abs)	THOU/CMM	< 1.0	683	3	0	261	1	0
	ESR	MM/H	> 1.2 x ULN				1	0	0
LIVER FUNCTION	Total Bilirubin	MG/DL	> 1.5 x ULN	685	2	0	261	0	0
	Direct Bilirubin	MG/DL	> 1.5 x ULN	9	1	11	4	0	0
	Total Protein	G/DL	< 0.9 x LLN	685	0	0	261	0	0
			> 1.1 x ULN	685	1	0	261	0	0
	Serum Albumin	G/DL	< 0.9 x LLN	685	0	0	261	0	0
			> 1.1 x ULN	685	0	0	261	0	0
	Serum Globulin	G/DL	> 1.2 x ULN	684	0	0	261	0	0
			< 0.8 x LLN	684	2	0	261	0	0
	SGOT(AST)	IU/L	> 3.0 x ULN	685	2	0	261	0	0
	SGPT(ALT)	IU/L	> 3.0 x ULN	684	8	1	261	1	0
	LDH	IU/L	> 3.0 x ULN	685	1	0	261	0	0
	Alk. Phosphatase	IU/L	> 3.0 x ULN	685	0	0	261	0	0
RENAL FUNCTION	Blood Urea Nitrogen	MG/DL	> 1.3 x ULN	685	1	0	261	0	0
	Serum Creatinine	MG/DL	> 1.3 x ULN	685	1	0	261	0	0
ELECTROLYTES	Uric Acid	MG/DL	> 1.2 x ULN	685	3	0	261	1	0
	Sodium	MEQ/L	< 0.95 x LLN	685	4	1	261	0	0
			> 1.05 x ULN	685	0	0	261	0	0
	Potassium	MEQ/L	< 0.9 x LLN	685	0	0	261	0	0
			> 1.1 x ULN	685	10	1	261	5	2
	Chloride	MEQ/L	< 0.9 x LLN	685	2	0	261	0	0
			> 1.1 x ULN	685	1	0	261	0	0
	Bicarbonate	MEQ/L	< 0.9 x LLN	21	0	0	6	0	0
			> 1.1 x ULN	21	0	0	6	0	0
	Calcium	MG/DL	< 0.9 x LLN	685	1	0	261	0	0
			> 1.1 x ULN	685	0	0	261	2	1
	Phosphorus	MG/DL	> 1.2 x ULN	685	7	1	261	6	2
			< 0.8 x LLN	685	2	0	261	0	0
ELECTROLYTES	Glucose, Fasting	MG/DL	> 1.2 x ULN	14	0	0	3	0	0
			< 0.6 x LLN	14	0	0	3	0	0
	Glucose, Random	MG/DL	> 1.2 x ULN	684	67	8	261	20	8
			< 0.6 x LLN	684	3	0	261	0	0
	Magnesium	MG/DL	< 0.9 x LLN	4	0	0	1	0	0
			> 1.1 x ULN	4	0	0	1	1	100
LIPIDS	Cholesterol	MG/DL	> 1.2 x ULN @	685	16	2	261	0	0
	Triglycerides	MG/DL	> 1.2 x ULN @	684	85	12	261	17	7
URINE	Specific Gravity		< 1.000	685	0	0	259	0	0
			> 1.035 @	685	0	0	259	4	2
	Urine pH		< 0.9 x LLN	685	0	0	259	0	0
			> 1.1 x ULN	685	3	0	259	3	1
	Protein (qual)		>= 2+	685	3	0	259	1	0
	Urine Glucose		>= 2+	685	2	0	259	0	0
	Urine WBC	/HPF	>= 6	566	63	11	228	21	9
	Urine RBC	/HPF	>= 6	561	32	6	223	21	9
	Ketones (qual)		>= 1+	685	11	2	259	4	2
	Granular Casts	/LPF	> 1	2	0	0	3	0	0
	Hyaline Casts	/LPF	> 1	5	3	60	4	1	25
	Bilirubin (qual)		>= 1+	684	1	0	259	0	0
	LDL Cholesterol	MG/DL	> 1.2 x ULN	1	0	0			
	HDL Cholesterol	MG/DL	< 0.8 x LLN	2	0	0			
	Protein (quant)	MG/DAY	> 1.1 x ULN	1	0	0	1	0	0
	White Cell Cast	/LPF	>= 1	1	1	100			
	Red Cell Cast	/LPF	>= 1	1	1	100			
HORMONES	Prolactin	NG/ML	> 1.1 x ULN	2	1	50			

Includes protocols 104, 106, 114, 115

N = Total number of subjects with at least one observation of the given lab parameter while on study treatment or during lag time.
n = Number of subjects with a clinically significant abnormality
* Change from baseline
@ Fisher Exact 2-tailed test yielded a significant association at the .05 level of alpha

Note: The criteria in this table lists only Column "A" from Appendix 8.1.6.3.2a when in fact both Column "A" and Column "B" were used to establish criteria for abnormal values in this table.

Appendix 8.1.6.4 Incident of Clinically Significant Laboratory Test in all oral Phase II/II Studie (adapted from sponsor's electronic submission)

Number of Subjects:	Ziprasidone	Placebo
Evaluable for laboratory abnormalities	1794	835
With clinically significant laboratory abn	916 (51%)	157 (47%)

Group	Parameter	Units		Subjects with Abnormalities N	n	%	Subjects with Abnormalities N	n	%
HEMATOLOGY	Hemoglobin (HGB)	G/DL		1778	6	0	833	1	0
	Hematocrit (HCT)	%		1778	2	0	833	1	0
	RBC Count	MILL/CMM		1778	4	0	833	0	0
	Platelets	THOU/CMM		1777	6	0	833	8	1
				1777	2	0	833	0	0
	WBC Count	THOU/CMM		1777	5	0	833	0	0
				1777	16	1	833	1	0
	Eosinophils (%)	%		1775	65	4	833	8	2
	ESR	MM/H		8	0	0	1	0	0
	Prothrombin Time	SEC		6	0	0	1	0	0
	Neutrophils (abs)	THOU/CMM		1771	9	1	833	1	0
LIVER FUNCTION	Total Bilirubin	MG/DL		1780	9	1	836	3	1
	Direct Bilirubin	MG/DL		19	1	5	5	0	0
	Total Protein	G/DL		1778	3	0	834	1	0
				1778	6	0	834	0	0
	Serum Albumin	G/DL		1780	3	0	836	1	0
				1780	1	0	836	0	0
	Serum Globulin	G/DL		1352	2	0	264	0	0
				1352	6	0	264	0	0
	SGOT (AST)	IU/L		1780	6	0	836	2	1
	SGPT (ALT)	IU/L		1776	17	1	836	2	1
	LDH	IU/L		1361	1	0	264	0	0
	Alk. Phosphatase	IU/L		1781	0	0	836	0	0
RENAL FUNCTION	Blood Urea Nitrogen	MG/DL		1363	3	0	264	1	0
	Serum Creatinine	MG/DL		1783	4	0	836	1	0
ELECTROLYTES	Uric Acid	MG/DL		1359	9	1	264	3	1
	Sodium	MEQ/L		1782	26	1	836	2	1
				1782	3	0	836	0	0
	Potassium	MEQ/L		1779	0	0	836	0	0
				1779	17	1	836	7	2
	Chloride	MEQ/L		1363	4	0	264	0	0
				1363	1	0	264	0	0
	Bicarbonate	MEQ/L		41	0	0	6	0	0
				41	0	0	6	0	0
	Calcium	MG/DL		1362	2	0	264	1	0
				1362	1	0	264	2	1
	Phosphorus	MG/DL		1361	16	1	264	7	3
ELECTROLYTES	Phosphorus	MG/DL		1361	8	1	264	1	0
	Glucose, Fasting	MG/DL		70	5	7	3	1	33
				70	0	0	3	0	0
	Glucose, Random	MG/DL		1344	178	13	264	32	12
				1344	7	1	264	0	0
	Magnesium	MG/DL		10	0	0	1	0	0
				10	0	0	1	1	100
LIPIDS	Cholesterol	MG/DL		1363	227	17	264	40	15
	Triglycerides	MG/DL		1359	322	24	264	48	18
URINE	Specific Gravity			1359	0	0	262	0	0
			#	1359	4	0	262	4	2
	Urine pH			1359	0	0	262	0	0
				1359	7	1	262	3	1
	Protein (qual)			1761	29	2	332	5	2
	Urine Glucose			1760	13	1	832	0	0
	Urine WBC	/HPF		1201	147	12	231	24	10
	Urine RBC	/HPF		1199	91	8	226	25	11
	Ketones (qual)			1760	41	2	332	11	3
	Granular Casts	/LPF		5	1	20	3	0	0
	Hyaline Casts	/LPF		17	9	53	4	1	25
	Bilirubin (qual)			1259	2	0	262	0	0
	LDL Cholesterol	MG/DL		4	0	0			
	HDL Cholesterol	MG/DL		6	0	0			
	Protein (quant)	MG/DAY		2	0	0	1	0	0
	White Cell Cast	/LPF		1	1	100			
	Urine Creatinine	MG/DAY		1	1	100			
	Red Cell Cast	/LPF		1	1	100			
HORMONES	Thyroxine (T4)	MCG/DL		218	4	2	57	1	2
				218	0	0	57	0	0
	Prolactin	NG/ML	#	741	148	20	75	3	4
	TSH	MCIU/ML		224	4	2	56	0	0
				224	8	4	56	1	2

Includes protocols 016, 101, 102, 104, 104e, 106, 106e, 108, 108e, 109, 109e, 110, 111, 114, 115, 116B, 117, 118, 122, 901, 902, 903, 904, 905

N = Total number of subjects with at least one observation of the given lab parameter while on study treatment or during lag time.
n = Number of subjects with a clinically significant abnormality
° Change from baseline
Fisher Exact 2-tailed test yielded a significant association at the .05 level of alpha
Criteria for clinically significant laboratory abnormalities not adjusted for abnormal baseline laboratory values

Appendix 8.1.7.3.1 Median changes from baseline for short term placebo controlled Phase II/III trials (from sponsor's electronic submission)

	Ziprasidone			Haloperidol			Placebo		
	N	Median Baseline	Median Change From Baseline To Last Obs	N	Median Baseline	Median Change From Baseline To Last Obs	N	Median Baseline	Median Change From Baseline To Last Obs
Standing									
Systolic BP (mmHg)	674	114.5	0.0	83	120.0	1.0	260	118.0	0.0
Diastolic BP (mmHg)	674	78.0	0.0	83	80.0	0.0	260	80.0	0.0
Heart Rate (bpm)	669	88.0	0.0	83	86.0	0.0	256	88.0	0.0
Sitting									
Systolic BP (mmHg)	690	118.0	0.0	84	120.0	2.0	265	118.0	0.0
Diastolic BP (mmHg)	690	76.0	0.0	84	78.0	0.0	265	76.0	0.0
Heart Rate (bpm)	690	84.0	0.0	84	80.0	1.5	265	80.0	0.0
Supine									
Systolic BP (mmHg)	1	120.0	-8.0						
Diastolic BP (mmHg)	1	78.0	-10.0						
Heart Rate (bpm)	1	76.0	2.0						
Temperature (C)	243	36.6	0.0				99	36.6	0.1
Weight (kg)*	622	75.0	0.5	74	79.4	0.0	227	75.5	0.0

N is the total number of subjects with a baseline observation and at least one observation while on study treatment or within six days after the last day of study treatment for the given vital sign parameter.
* Kruskal-Wallis test yielded a significant association at the .05 level of alpha by using the RANK and ANOVA procedures.
Protocols: 104,106,114,115

Appendix 8.1.7.3.2 Incidence of Clinically Significant Changes in Vital Signs in Short-term Placebo Controlled Studies:

	Ziprasidone			Haloperidol			Placebo		
	N	Total Changed	Percent Changed	N	Total Changed	Percent Changed	N	Total Changed	Percent Changed
Standing Systolic BP (mmHg)									
Increase (BP>180, CHG>=20)	674	1	0.1	83	0	0.0	260	1	0.4
Decrease (BP<90, CHG<=-20)	674	22	3.3	83	3	3.6	260	9	3.5
Standing Diastolic BP (mmHg)									
Increase (BP>105, CHG>=15)	674	14	2.1	83	1	1.2	260	4	1.5
Decrease (BP<50, CHG<=-15)	674	3	0.4	83	3	3.6	260	3	1.2
Standing Heart Rate (bpm)									
Increase (BP>120, CHG>=15)	669	21	3.1	83	2	2.4	256	9	3.5
Decrease (BP<50, CHG<=-15)	669	3	0.4	83	1	1.2	256	0	0.0
Sitting Systolic BP (mmHg)									
Increase (BP>180, CHG>=20)	690	1	0.1	84	0	0.0	265	1	0.4
Decrease (BP<90, CHG<=-20)	690	11	1.6	84	3	3.6	265	6	2.3
Sitting Diastolic BP (mmHg)									
Increase (BP>105, CHG>=15)	690	12	1.7	84	1	1.2	265	7	2.6
Decrease (BP<50, CHG<=-15)	690	5	0.7	84	0	0.0	265	2	0.8
Sitting Heart Rate (bpm)									
Increase (BP>120, CHG>=15)	690	1	0.1	84	0	0.0	265	2	0.8
Decrease (BP<50, CHG<=-15)	690	2	0.3	84	3	3.6	265	2	0.8
Supine Systolic BP (mmHg)									
Increase (BP>180, CHG>=20)	1	0	0.0	0	0		0	0	
Decrease (BP<90, CHG<=-20)	1	0	0.0	0	0		0	0	
Supine Diastolic BP (mmHg)									
Increase (BP>105, CHG>=15)	1	0	0.0	0	0		0	0	
Decrease (BP<50, CHG<=-15)	1	0	0.0	0	0		0	0	
Supine Heart Rate (bpm)									
Increase (BP>120, CHG>=15)	1	0	0.0	0	0		0	0	
Decrease (BP<50, CHG<=-15)	1	0	0.0	0	0		0	0	
Weight (kg)									
Increase (CHG>=7%)*	622	61	9.8	74	4	5.4	227	9	4.0
Decrease (CHG<=-7%)	622	16	2.6	74	1	1.4	227	7	3.1

N is the total number of subjects with a baseline observation and at least one observation while on study treatment or within six days after the last day of study treatment for the given vital sign parameter.
To be a clinically significant change, a value has to both meet the criterion value and represent a change from baseline of at least the magnitude noted at any time during the study treatment or within the six days after the study treatment.
* Fisher exact two-tailed test yielded a significant association at the .05 level of alpha.
Protocols: 104,106,114,115

Appendix 8.1.8.3.1 Mean and Mean Change values of electrocardiogram variables comparing baseline and end of treatment with ziprasidone and placebo in short term placebo controlled Phase II/III trials (from sponsor's submission dated 11/13/97).

Table N.5.23.1 (Short Term) - Centrally Read 104,106,114, & 115 Page 1 of 2
Change from Baseline to Maximum Reading Value in ECG Readings
Short-Term Fixed-Dose Placebo-Controlled Oral Dosing Phase II/III Studies
By BID Dose - Centrally Read Date

	Placebo			<40mg BID			40mg BID			60mg BID			80mg BID		
	N	Base Mean	Max Mean**	N	Base Mean	Max Mean**	N	Base Mean	Max Mean**	N	Base Mean	Max Mean**	N	Base Mean	Max Mean**
*QTc int	250	399.0	4.3	230	396.9	8.6	138	397.6	12.6	111	398.0	15.2	100	394.6	19.8
QT int	250	348.6	7.6	230	354.6	5.0	138	351.2	7.5	111	352.6	15.1	100	352.4	14.4
Heart Rate	250	80.4	4.6	230	76.6	7.8	138	78.6	6.6	111	78.5	5.4	100	76.7	6.7
PR int	250	149.2	3.4	230	148.8	4.3	138	148.4	1.9	111	149.2	2.6	100	150.0	2.5
QRS int	250	86.1	1.6	230	86.6	1.5	138	86.3	1.3	111	86.8	1.2	100	85.5	1.8

(CONTINUED)
Protocols: 104,106,114,115
*QTc int = QT int/SQRT(60/(Heart Rate))
** Maximum change from baseline for each subject where baseline is the last ECG taken before the first day of study treatment.
Total Changed = number of subjects with both a baseline ECG value and post-baseline value within six days after the last day of study treatment.
Date of table generation: 12NOV97.

Table N.5.23.1 (Short Term) - Centrally Read 104,106,114, & 115 Page 2 of 2
Change from Baseline to Maximum Reading Value in ECG Readings
Short-Term Fixed-Dose Placebo-Controlled Oral Dosing Phase II/III Studies
By BID Dose - Centrally Read Date

	>=100mg BID			Haloperidol		
	N	Base Mean	Max Mean**	N	Base Mean	Max Mean**
*QTc int	77	402.7	15.0	76	400.2	4.1
QT int	77	354.9	17.1	76	357.3	7.1
Heart Rate	77	78.8	4.6	76	76.8	4.4
PR int	77	148.3	1.6	76	150.9	3.1
QRS int	77	87.3	1.2	76	87.1	0.9

Protocols: 104,106,114,115
*QTc int = QT int/SQRT(60/(Heart Rate))
** Maximum change from baseline for each subject where baseline is the last ECG taken before the first day of study treatment.
Total Changed = number of subjects with both a baseline ECG value and post-baseline value within six days after the last day of study treatment.
Date of table generation: 12NOV97.

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Appendix 8.1.8.3.2 ECG: percent of subjects who met sponsors criteria for clinically significant changes in short term placebo controlled studies. (from sponsor's submission dated 11/13/97)

Table N.5.22 [Short Term] - Centrally Read 104.106.114. & 115 — Page 1 of 2
Incidence of Clinically Significant Changes in ECG Readings
Short-Term Fixed-Dose Placebo-Controlled Oral Dosing Phase II/III Studies
By BID Dose - Central Reader Data

		Placebo			<40mg BID			40mg BID			60mg BID			80mg BID		
		N	Total Changed	%	N	Total Changed	%	N	Total Changed	%	N	Total Changed	%	N	Total Changed	%
*QTc int	>=480 msec	251	0	0	233	0	0	138	0	0	112	1	0.9	100	0	0
	>=500 msec	251	0	0	233	0	0	138	0	0	112	0	0	100	0	0
	>=75 msec increase **	250	0	0	230	0	0	138	0	0	111	0	0	100	0	0
	>=10% increase **	250	11	4.4	230	12	5.2	138	11	8.0	111	12	10.8	100	16	16.0
	>=15% increase **	250	2	0.8	230	1	0.4	138	1	0.7	111	1	0.9	100	3	3.0
	>=20% increase **	250	0	0	230	0	0	138	0	0	111	0	0	100	0	0

(CONTINUED)
Protocols: 104,106,114,115
*QTc int = QT int/SQRT(60/(Heart Rate))
** From baseline where baseline is the last ECG taken before the first day of study treatment.
Total Changed = number of subjects with an ECG reading meeting criteria while on study treatment or within six days after the last day of study treatment.
Date of table generation: 21OCT97.

Table N.5.22 [Short Term] - Centrally Read 104.106.114. & 115 — Page 2 of 2
Incidence of Clinically Significant Changes in ECG Readings
Short-Term Fixed-Dose Placebo-Controlled Oral Dosing Phase II/III Studies
By BID Dose - Central Reader Data

		>=100mg BID			Haloperidol		
		N	Total Changed	%	N	Total Changed	%
*QTc int	>=480 msec	77	0	0	76	0	0
	>=500 msec	77	0	0	76	0	0
	>=75 msec increase **	77	0	0	76	0	0
	>=10% increase **	77	11	14.3	76	4	5.3
	>=15% increase **	77	1	1.3	76	0	0
	>=20% increase **	77	0	0	76	0	0

Protocols: 104,106,114,115
*QTc int = QT int/SQRT(60/(Heart Rate))
** From baseline where baseline is the last ECG taken before the first day of study treatment.
Total Changed = number of subjects with an ECG reading meeting criteria while on study treatment or within six days after the last day of study treatment.
Date of table generation: 21OCT97.

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...idix 8.1.9.2a Extrapyramidal Symptoms Assessment for Studies 114 and ...15 using the Simpson-Angus Rating Score (adapted from sponsor's submission)

Simpson-Angus Rating Scale Score** - Percent of Subjects with a Postbaseline Change by Visit -
All Subjects Not Taking Benztropine, Observed Cases
Ziprasidone Protocol 114

		Day 7*	Day 21	Day 42	Last
Ziprasidone, 40 mg BID	Increase	19.8	30	16.3	15.7
	Decrease	34.6	36.7	48.8	42.2
	No Change	45.7	33.3	34.9	42.2
	N	81	60	43	83
Ziprasidone, 80 mg BID	Increase	19.7	27.9	39.1	32.5
	Decrease	18.4	20.6	23.9	23.4
	No Change	61.8	51.5	37	44.2
	N	76	68	46	77
Placebo	Increase	21.1	16.4	16.7	21.5
	Decrease	23.7	24.6	40.5	25.3
	No Change	55.3	59	42.9	53.2
	N	76	61	42	79

**Simpson-Angus Rating Scale Score equals the sum of SARS items 1 through 10.
*Day 7 = visit 7; Day 21 = visit 21; Day 42 = visit 42; Last = last visit, planned or unplanned.

Simpson-Angus Rating Scale Score** - Percent of Subjects with a Postbaseline Change by Visit -
All Subjects Not Taking Benztropine, Observed Cases
Ziprasidone Protocol 115

		Day 7*	Day 21	Day 42	Last
Ziprasidone, 20 mg BID	Increase	23.3	20.9	30.3	27
	Decrease	26.7	23.3	30.3	28.6
	No Change	50	55.8	39.4	44.4
	N	60	43	33	63
Ziprasidone, 60 mg BID	Increase	15.3	16.3	12.5	20
	Decrease	28.8	40.8	37.5	33.3
	No Change	55.9	42.9	50	46.7
	N	59	49	32	60
Ziprasidone, 100 mg BID	Increase	17	20.5	20	21.3
	Decrease	25.5	41	36.7	38.3
	No Change	57.4	38.5	43.3	40.4
	N	47	39	30	47
Haloperidol	Increase	27.8	33.3	35	45
	Decrease	8.3	10	15	15
	No Change	63.9	56.7	50	40
	N	36	30	20	40
Placebo	Increase	15.4	20	4.8	13
	Decrease	21.2	22.9	23.8	25.9
	No Change	63.5	57.1	71.4	61.1
	N	52	35	21	54

**Simpson-Angus Rating Scale Score equals the sum of SARS items 1 through 10.
*Day 7 = visit 7; Day 21 = visit 21; Day 42 = visit 42; Last = last visit, planned or unplanned.

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Appendix 8.1.9.2b Akathisia Assessment for Studies 114 and 115 using the Barnes Akathisia Scale (adapted from sponsor's submission)

rnes Akathisia Scale Global Score - Percent of Subjects with a Postbaseline Change by Visit -
l Subjects Not Taking Beta-Blockers, Observed Cases
prasidone Protocol 114

		Day 7*	Day 21	Day 42	Last
iprasidone, 0 mg BID	Increase	20.6	12.5	15.7	16.3
	Decrease	12.4	16.7	17.6	18.4
	No Change	67	70.8	66.7	65.3
	N	97	72	51	98
iprasidone, 0 mg BID	Increase	13	19.5	13.8	12.9
	Decrease	18.5	17.1	22.4	18.3
	No Change	68.5	63.4	63.8	68.8
	N	92	82	58	93
lacebo	Increase	11.1	12.7	9.3	8.2
	Decrease	23.5	27	25.6	27.1
	No Change	65.4	60.3	65.1	64.7
	N	81	63	43	85

y 7 = v... 7; Day 21 = visit 21; Day 42 = visit 42; Last = last visit, planned or unplanned.

Barnes Akathisia Scale Global Score - Percent of Subjects with a Postbaseline Change by Visit -
All Subjects Not Taking Beta-Blockers, Observed Cases
Ziprasidone Protocol 115

		Day 7*	Day 21	Day 42	Last
Ziprasidone, 20 mg BID	Increase	17.9	10.5	11.1	13.8
	Decrease	14.1	21.1	20	21.3
	No Change	67.9	68.4	68.9	65
	N	78	57	45	80
Ziprasidone, 60 mg BID	Increase	14.7	16.4	8.3	14.5
	Decrease	14.7	10.9	13.9	10.1
	No Change	70.6	72.7	77.8	75.4
	N	68	55	36	69
Ziprasidone, 100 mg BID	Increase	18.4	9.5	9.3	14.5
	Decrease	6.6	17.5	18.6	14.5
	No Change	75	73	72.1	71.1
	N	76	63	43	76
Haloperidol	Increase	29	29.1	23.1	29.9
	Decrease	12.9	21.8	20.5	19.4
	No Change	58.1	49.1	56.4	50.7
	N	62	55	39	67
Placebo	Increase	14.3	18.6	8.3	16.4
	Decrease	21.4	20.9	29.2	27.4
	No Change	64.3	60.5	62.5	56.2
	N	70	43	24	73

*Day 7 = visit 7; Day 21 = visit 21; Day 42 = visit 42; Last = last visit, planned or unplanned

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Review of Clinical Data

Review of Data Quality, Coding, All Cause Mortality and Sudden Deaths

NDA:	**NDA 20-825**
Sponsor:	**Pfizer**
Drug:	**Ziprasidone**
Route of Administration:	**Oral**
Reviewers:	**Gerard Boehm, M.D., M.P.H.** **James F. Knudsen, M.D., Ph.D.**
Author:	**Gerard Boehm, M.D., M.P.H.**
Review Completion Date:	**2/3/98**

The objectives of this review are to evaluate the methods of coding and overall quality of the data and to review all cause and cause specific mortality with emphasis on sudden deaths in ziprasidone trials. This review covers information presented in the NDA and the 4 month safety update. I used the results from Dr. Knudsen's evaluation of the data quality and coding for this report.

Methods

Accuracy of the database
To verify accuracy of the data submitted with the NDA, we cross checked the data for deaths and cardiac adverse events presented in line listings/tabulations, narrative summaries, and CRF's. Specifically, the sources were examined for inconsistencies and omissions.

To evaluate the coding process, subsumed investigator verbatim terms for adverse events were compared with the preferred terms included in appendix VI. In addition, the events that were coded with selected preferred terms were reviewed in more detail. Using narrative summaries and CRF's, the adverse events coded with the preferred terms arrhythmia, tachycardia, bradycardia, syncope, hypotension, postural hypotension, heart arrest and circulation failure were compared across sources to determine if the coding process resulted in appropriate groupings.

Deaths
The overall mortality rates were compared between ziprasidone group and the comparator groups using the number of deaths that occurred within 30 days of the last

exposure to drug for deaths presented in the NDA and safety update. The ziprasidone mortality rate was also compared to the mortality rates of other recently approved antipsychotic medications.

I reviewed and summarized the narrative summaries and the CRF data for ziprasidone patient deaths. I then classified the deaths into 4 categories. Those deaths for which there was a definite external cause (ex. suicide jumped in front of a train) were placed in the first category. Those deaths with a probable external cause, but where there remains some question about the possibility of a sudden death (ex. a car accident where the driver could have experienced sudden death) were placed in the second category. The third category contains deaths that appear to be related to an underlying process (ex. cancer or pneumonia). The last category contains the deaths that occurred suddenly, noting which deaths were explained by an underlying process (example sudden death with ruptured aneurysm discovered on autopsy). Using this scheme, I calculated an external cause (definite + probable) and sudden death rate for the NDA data alone, and for the combined NDA and safety update information. The calculated sudden death rate for ziprasidone was compared to the sudden death rate for recently approved antipsychotic medications.

Results

Approach to Safety, Data Accuracy and Specificity of the AE Coding

The sponsor defined treatment emergent adverse events as 1) events not present at baseline or during the baseline period and that occurred after treatment began 2) events that were present at baseline but increased in severity after beginning treatment. AE surveillance occurred at each study visit. Investigators recorded observed or volunteered AE's that occurred during the treatment period or within 6 days after the last day of treatment. The sponsor translated investigator verbatim terms to preferred terms using the COSTART dictionary. The AE's were presented in tabular form with information about treatment emergence, body system classification, investigator assessment of severity (mild, moderate or severe) and causality. When an event for a patient was reported with more than one severity, the summary tables reported the greatest severity recorded by the investigator. Events without investigator assessments of severity were classified as severe.

The investigator verbatim terms listed in the CRF's of the patients who died, had serious cardiovascular adverse events, or dropped out due to cardiac related events, were congruent with those listed in the tabulations/data listings and included in the narrative summaries. The narrative summaries often provided more clinical detail, particularly about past medical history. Additionally, the narrative summaries often cited autopsy data that were not included in the CRF. The CRF's were limited for clinical information with the exception that they contained vital sign, ECG, and laboratory data which was less complete in the narrative summaries.

In general, the COSTART coding of the investigator verbatim terms was appropriate. The sponsor provided a comprehensive line listing of adverse events aggregated across all Phase II/III studies which included the investigator verbatim and coded preferred term for each report. With few exceptions, the sponsor's coding practices were neither excessively narrow nor broad. The sponsor may have been too overly inclusive in deciding what to subsume under the preferred term postural hypotension. The verbatim terms orthostatic hypotension, dizziness on standing, and lightheadedness with standing were subsumed under the preferred term postural hypotension. This approach increases the sensitivity of the coding for detecting patients with orthostatic changes in blood pressure but probably lessens the specificity.

Orthostatic change in pulse, irregular pulse, and arrhythmia were subsumed under the preferred term arrhythmia, whereas orthostatic tachycardia and elevated pulse were subsumed under the preferred term tachycardia. This grouping probably decreased the ability to detect orthostatic changes by report of change in pulse. Since there are other parameters for detecting orthostatic changes (blood pressure change, symptoms) these coding practices probably had minimal impact on the ability to identify this event. Loss of consciousness and fainting were appropriately subsumed under the preferred term syncope and not under hypotension.

The data quality for death and cardiovascular adverse events was adequate. With few exceptions, the sponsor's coded terms accurately reflected the investigator verbatim terms. These data allow an accurate assessment of the events occurring during the ziprasidone development program.

Deaths

There were 32 deaths reported with the NDA and safety update. Eighteen deaths occurred within 30 days of the last exposure to ziprasidone. One of these deaths (suicide from the safety update) was from the Japanese database which was maintained separately and did not contribute to the person time used to calculate rates (p.5 Safety Update). That death is not included in the following discussions or the mortality rate calculations.

In the original NDA submission, there were 14 deaths that occurred within 30 days of the discontinuation of ziprasidone. The all cause mortality rate for this population was 2.2/100PY (14/626PY). The safety update included 3 additional deaths within 30 days of last exposure and almost 150 additional patient years of exposure. The all cause mortality rate including the safety update data was 2.2/100PY (17/772PY). This mortality rate is higher than the rates observed for other recently reviewed antipsychotic medications.

The sponsor also provides a calculation of crude mortality for the comparator groups through the safety update. The cumulative crude mortality rate for the placebo exposed group is 9.6/100 patient years exposure (5 deaths in 52 patient years). The crude mortality rate observed in patients exposed to haloperidol was 2.3 per 100 patient years (3 deaths in

131 patient years) and for risperidone 0.95 per 100 patient years (1 death in 105 patient years).

Cause Specific Mortality

Cardiovascular related deaths were more commonly observed in ziprasidone treated individuals compared to patients receiving placebo or active comparator medications. Ten of the 17 deaths that occurred within 30 days of the last dose of ziprasidone (including the safety update) are possibly cardiovascular related. These deaths included diagnoses such as cardiac arrest, ruptured abdominal aortic aneurysm and several unwitnessed, and sudden deaths without clear diagnoses that are suspicious for cardiovascular events. The other causes of death reported in ziprasidone trials were suicide (3), drowning (2), aspiration (1), and accident(1). The deaths in the placebo patients were from pneumonia (3), extradural hematoma, and suicide. In the haloperidol group there were 2 suicides and a post operative MI leading to death. The death in the risperidone group was due to aspiration of food.

Ziprasidone and Sudden Deaths

In the sponsor's review, a death was "sudden" if it occurred within 24 hours of the onset of symptoms directly associated with the death. Including safety update data, the sponsor classified 7 deaths as sudden, giving a sudden death rate of 0.9 per 100 PY exposure (7 sudden deaths in 772 patient years exposure). In my opinion, 6 deaths (35%) had an external cause (definite + probable) and 11 deaths (65%) were sudden. One of the sudden deaths included with the safety update was explained at autopsy (ruptured abdominal aortic aneurysm).

Considering only the NDA death information (not including the safety update), I felt that 6 deaths (43%) had an external cause (definite + probable), and 8 deaths (57%) were sudden (see appendix). The death rate due to external cause was 0.9 per 100PY (6/626) and the sudden death rate was 1.3/100PY (8/626).

A combined sudden death rate was calculated from the NDA data for several recently approved antipsychotic medications. For these 3 drugs, there were 6 sudden deaths in 2496 patient years exposure giving a sudden death rate of 2 per 1000PY. The population in the phase II/III ziprasidone trials was similar to the populations studied in other recently reviewed antipsychotic medications with respect to mean age (39.6), age range (7-82), percent males (72%) and percent caucasians (76%).

Discussion

Because the placebo and active comparator experience within the NDA was limited, the death rate information for ziprasidone was compared with the rates observed for other recently reviewed antipsychotic medications. The all cause mortality rate for ziprasidone was higher than the rate observed with the other medications. After applying the

classification scheme described above, the causes of death appeared to differ from the causes observed with the other medications. Sudden deaths were 6 times more common for the ziprasidone group compared to the rates for the other medications. The rate of deaths with external, explained causes in the ziprasidone development program was similar to the rates estimated for other recently reviewed drugs.

The classification of sudden deaths in these analyses is a function of the quality of available data and reviewer opinion. The quality of information is dependent, in large part, on the data collection methods employed by the sponsor and the investigators. One must consider that variability in the quality of data across NDA's could lead to a classification bias resulting in the observed differences in mortality rates.

Development programs are usually separated by place and time and differ with respect to populations studied, inclusion/exclusion criteria, and concomitant medications allowed. Any or all of these factors could have an influence on the observed sudden death rate. Therefore, comparisons across NDA's should be interpreted cautiously and in the context of all available safety data.

Conclusions

1. The data quality and approach to coding were adequate for the purpose of this review.
2. The all cause mortality rate was higher for ziprasidone compared to rates for other recently reviewed antipsychotic medications.
3. The sudden death rate for ziprasidone is 6 times higher than that for combined data from recently reviewed NDA's.

Because of potential differences in available data and in the drug development programs, these mortality rate comparisons are not conclusive evidence for determining if there is increased risk associated with exposure to ziprasidone. The signal of increased sudden deaths may become an important complementary piece of evidence in the presence of other safety data. One concern that has potential relevance to this finding is an apparent dose dependent QTc prolonging effect associated with ziprasidone in the STFDPC study population.

AM /S/

Gerard Boehm M.D., M.P.H.

2-3-98
Agree
/S/

cc:HFD-120\Boehm\Burkhart\Laughren\Leber \Glass

Appendix
Summaries for the 17 deaths that occurred within 30 days of last exposure to drug from the ziprasidone NDA and the safety update.

Category 1 (Definite external cause)
128-302E-159-0029 Suicide, falling under a train.
128-116B- 694-0004 Suicide, hanging.
128-108-609-0381 Suicide, gunshot.

Category 2 (Probable external cause)
128-117-706-0529 This 40 YO male with a past medical history significant for bronchitis, took ziprasidone for 54 days and the last recorded dose was 160mg per day. Four days after self-discontinuing ziprasidone, he underwent a sleep deprived EEG to evaluate complaints of amnesia that began following an assault. He left the testing site after 30 hours of sleep deprivation and drove himself home. Two hours after leaving the site, he drove his car off a cliff and died. The autopsy listed asphyxiation due to salt water drowning as the cause of death. Concomitant medications at the time of death included propranolol, antacids, and clonazepam. The investigator felt that this was an accidental death caused by sleep deprivation. There sponsor noted that the patient had plans for the future and there was no suicide note.

128-117-687-0317 This 51 YO male took ziprasidone for 205 days at a dose of 120mg daily. He died from injuries sustained from a fall from his 10th floor balcony. The patient was taking no other medications at the time of death. His last study visit was 9 days prior to his death and he appeared to be doing well and had plans for the future. The sponsor notes that on the day of his death he went to a church crisis center and appeared intense. The sponsor states that the coroner initially felt this was a suicide but was reconsidering that initial conclusion. The investigator felt that this was an accident.

128-303-260-0156 This 46 YO male took ziprasidone for 7 days and the last recorded dose was 120mg daily. His body was found in a river 5 days after leaving a hospital where he was an inpatient. He was taking no other medications at the time of his death. The autopsy listed drowning as the cause of death. He had no prior history of suicidal ideation or suicide attempts. The investigator felt that this was possibly a suicide.

Category 3 (Underlying disease)

Category 4 (Sudden deaths)

128-308-035-0003 *This 63 YO male was treated with ziprasidone for 75 days and the last recorded dose was 80mg daily. While at a lunch club, he collapsed and died suddenly. He was taking no other medications at the time of his death. The coroners report listed ruptured abdominal aortic aneurysm as the cause of death.

128-115-694-0394 This 43 YO male took ziprasidone for 16 days and the last recorded dose was 40mg daily. He withdrew consent and left the study. Subsequently, he had 2 psychiatric hospitalizations for severe generalized anxiety and tardive dyskinesia. He also had been seen in an ER for breathing difficulties and was discharged without prescribed treatment. Thirty days after stopping ziprasidone, he awoke with difficulty breathing and while getting ready to go to the hospital, he vomited. He was found unconscious by his sister, and did not respond to resuscitative measures. The coroner listed asphyxia due to aspiration of vomit as the cause of death. He was taking risperidone, lorazepam, and clonazepam at the time of death.

128-116B-659-0001 This 44 YO female took ziprasidone for 40 days and the last recorded dose was 80mg daily. The study drug was discontinued due to lack of efficacy. While still taking drug, she experienced chest pain. Cardiac work-up (including stress echo) was normal. A GI work-up revealed mildly elevated LFT's and non specific gastritis. Thirteen days after stopping ziprasidone she was admitted to a hospital for hematemesis and endoscopy revealed gastritis with H. pylori. She was treated with clarithromycin, omeprazole, and cisapride. Five days later she was treated in an ER for panic attack. Three days after the ER visit (24 days after stopping ziprasidone) she was found dead in bed. Medications at the time of death included buspirone, sucralfate, acetaminophen, lorazepam, omeprazole, clarithromycin, and cisapride. An autopsy report was not available, but the subject's attending physician learned of a possible atrial myxoma from the ME's office.

128-304E-0193-0379 This 52 YO male took ziprasidone for 221 days and the last recorded dose was 80mg daily. The patient was found dead in bed. At the time of death, the patient was taking acetaminophen as needed for headaches. The physician who attempted resuscitation felt that death was due to cardiac arrest with possible myocardial infarction. Multiple ECG's recorded for the study did not show ischemic changes. The patient had 3 cardiovascular disease risk factors (male, tobacco use and sedentary lifestyle). There was no autopsy.

128-301-311-0977 This 28 YO female received ziprasidone for 62 days and the last recorded dose was 120mg daily. The drug was stopped for insufficient response. On the day that ziprasidone was stopped, the patient had an end study ECG suggesting subendocardial ischemia. Because of this finding, she was transferred to an internal medicine service in another hospital. She complained of a substernal pinching sensation. The physician did not think this symptom was due to a cardiac disorder. The admitting diagnoses were schizophrenic psychosis, somatic asthenia, chronic disturbance of food intake, and arrhythmia without clear cause. The patient was started on thioridazine, nitrazepam, and a liquid diet supplement. The next day she was noted to have orthostatic symptoms and an ECG reportedly showed sinus arrhythmia at a rate of 58 beats per minute. She died the next day (2 days after stopping ziprasidone). Concomitant medications were biperiden, temazepam, thioridazine, fresubin liquide, nitrazepam, duovit, and vitamin B complex. At the time of death, she was described as cachetic and malnourished (height 5'6" and weight 42kg). An autopsy revealed atrophic and

dystrophic heart muscle fibers which could be associated with toxins, infection, or metabolic abnormalities. A consultant pathologist was unable to determine the cause of death and did not find any changes in the myocardium suggesting a specific disease or drug reaction. A consultant cardiologist reviewed the ECG tracings and felt the bradycardia and T-wave abnormalities were consistent with abnormalities seen with malnutrition.

128-108-607-0305 This 46 YO male took ziprasidone for 61 days at a dose of 80mg daily. He had a past medical history significant for asthma, COPD, PUD, gastroenteritis, microhematuria, and gallstones. During the study, he had a hospitalization for pneumonia and gastroenteritis. Approximately 1 month later, he was found dead in a chair on his front porch presumably after mowing his lawn on a hot day. Concomitant medications at the time of death were beclamethasone, metaproterenol, and Maalox. Autopsy revealed acute and chronic asthmatic bronchitis and granulomatous myocarditis. The liver and brain each had a granulomma-like lesion. The conclusion of the autopsy was that the patient died from asthmatic bronchitis possibly exacerbated by lawn mowing. An independent pathology consultant interpreted the histologic slides as focal myocarditis of unknown etiology. The sponsor admitted that the exact cause of death in this case was uncertain and offered several possible explanations(asthmatic bronchitis, possible heat related illness, myocardial inflammation).

128-116B-508-0001 This 54 YO male took ziprasidone for 72 days, and his last recorded dose was 120mg daily. His past medical history was significant for hypertension, COPD, GERD, constipation, and peripheral vascular disease. He was found dead in his hospital bed. Concomitant medication at the time of death included Procardia XL, ipratropium, triamcinolone, albuterol, docusate lorazepam, aspirin, disulfiram, propranolol, and ranitidine. The sponsor noted that the patient had an episode of chest pain approximately 1 month prior to death. ECG done at that time was reportedly normal. An autopsy revealed severe generalized atherosclerosis, cerebral artery disease, visceral congestion, COPD, cardiac hypertrophy, and vocal cord congestion. The investigator felt that the death was due to atherosclerosis.

128-108-592-0750 *This 39 YO female received ziprasidone for a total of 7 days and the last recorded dose of the drug was 120mg daily. She had a past medical history significant for diabetes mellitus type II, tobacco abuse and alcohol abuse. She was found dead in her apartment. The diagnosis, according to the ME, was chronic alcoholism with hepatic steatosis, supported by a clinical history of alcohol abuse. The sponsor noted that decomposition of the body made a final post-mortem diagnosis difficult. The investigator attributed the death to alcohol abuse and DKA (no supporting blood glucose or pH data provided).

128-302E-319-0375* This 48 YO male took ziprasidone for 162 days and the last recorded dose was 120mg. He had a past medical history significant for hypertension. The investigator discontinued ziprasidone because of increasing psychopathology and started the patient on haloperidol. The following day he was found dead in his apartment.

He had a prior history of water intoxication and associated hyponatremia. The sponsor stated that the autopsy report was not available. A preliminary opinion from the ME attributed the death to cardiac arrest secondary to sodium depletion associated with water intoxication. Supporting data (serum sodium concentration) was not provided.

128-303-197-0299 This 79 YO female took ziprasidone for 30 days and the last recorded dose was 80mg daily. She had a past medical history significant for ischemic heart disease and atrial fibrillation. Thirty days after discontinuing ziprasidone, she experienced a presumed cardiac arrest. An autopsy was not performed.

128-105-534-0021 This 70 YO female took ziprasidone for 5 days and the last recorded dose was 2mg daily. She was treated with ziprasidone for behavioral disturbances associated with dementia. She had a past medical history significant for COPD, right bundle branch block, tobacco abuse, hypothyroidism, and hip fracture. On the 5th day of treatment, she developed shallow respirations and diaphoresis. She was taken to the hospital, arrested and died. The death certificate listed acute cardiopulmonary arrest due to arteriosclerotic cardiovascular disease as the cause of death. Concomitant medications at the time of death included atenolol, ranitidine, levothyroxine, potassium chloride, theophylline, heparin, albuterol, ipratropium bromide, diltiazem, furosemide, docusate, mycolog, and glypizide.

*Indicates death was identified in the safety update.

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JAN 11 2000

Review of Clinical Data

Preliminary Review of Study 054

IND: [ ]

Sponsor: **Pfizer**

Drug: **Ziprasidone**

Route of Administration: **PO**

S 1-11-00

Reviewer: **Greg Burkhart, M.D., M.S.**

Review Completion Date: **January 11, 2000**

Study 054 was an open-label study comparing QT interval duration between patients randomly assigned to ziprasidone, risperidone, quetiapine, olanzapine, thioridazine, or haloperidol. Pfizer initiated the study to address concerns raised in the June 17, 1998 not-approvable letter about ziprasidone's capacity to increase cardiac repolarization.

We received a summary of the findings from study 054 on December 6, 1999 and the full study report on January 3, 2000. My review is preliminary because the study report was incomplete. It relied upon the square root method of correcting the QT interval for heart rate. Dr. Laughren, prior to completion of study 054, had informed Pfizer that the square method causes a bias particularly for drugs that increase the heart rate. This bias was discovered after study 054 was in progress but is a significant concern since many antipsychotics increase the heart rate. While Pfizer provided summary data for analyses that used other more appropriate methods of correcting the QT in a separate submission, they will not provide a full presentation and discussion of these findings until they submit their response to the not-approvable letter.

Study 054 began with a 7-day out-patient period during which pre-existing antipsychotic medication was tapered. Patients then entered the treatment facility for a 7-day washout/ baseline period. Following baseline data collection, patients were titrated to the maximum marketed dose for their assigned drug (80 mg BID for ziprasidone) and observed at steady state. (Drop-outs were replaced.) Because of different kinetic properties, the duration of the dose escalation period varied by drug group with ziprasidone and thioridazine having the shortest (10 days) and risperidone having the longest (18 days). Once patients had achieved steady state and ECGs were collected, a protocol-specified metabolic inhibitor was added to each drug group and observation continued. After ECGs were collected in the presence of the metabolic inhibitor, treatment was tapered and terminated for all patients.

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HFD-120 Burkhart, Katz, Laughren, Glass, Anderson

Daily ECGs were taken for the last 3 days of baseline. A single ECG was taken at day 2 of the dose escalation period and daily ECGs were taken for 3 days at steady state. Pfizer timed the 4 ECGs taken during exposure to the estimated c max for each drug. Daily ECGs were also collected for 3 days in the presence of the metabolic inhibitor. A blinded reviewer read all ECGs to manually measure the QT interval. The analysis focused on the change from baseline that occurred at steady state and any change occurring in the presence of the metabolic inhibitor.

I have attached some of the tables and figures from the study report and those provided in a separate fax. Figure 2.1 shows that at steady state (period 3) all drugs but haloperidol caused an increase in the heart rate. This certainly raises the possibility that the square root correction method would not standardize the QT, and could more importantly, cause a biased comparison with haloperidol. (I am showing the data for completers, but the findings are the same when using all randomized patients.)

As a reminder, the haloperidol group was added to the study at the insistence of the FDA because we were aware of a large amount of data across several NDAs showing that oral haloperidol had no effect on the QT when compared to placebo. (One study was a 7-arm study that evaluated three doses of haloperidol.) Thus, it was our view at the start of study 54 that haloperidol would serve as the control arm providing a formal basis for comparison. We also recommended that thioridazine be added as a treatment group since there was some data suggesting that it prolonged the QT and there were also cases of TDP reported in the post-marketing literature.

Figure 3.1 shows the change from baseline in the uncorrected QT. For drugs that cause an increase in heart rate, one would expect the QT to decrease, as occurred with risperidone, olanzapine, and quetiapine. However, for thioridazine and ziprasidone, both of which caused an increase in heart rate, the QT increased. (Haloperidol also had an increase in QT, but the heart rate decreased from baseline in this group so that the increase in QT would be expected.)

Figure 1.1.1 shows the square root corrected QTCs by treatment group whereas tables 6b and 6c show QTCs using other methods of correction that do a better job of standardizing the QT for heart rate. Focusing on tables 6b and 6c, it seems fairly clear that there are only two between group differences in study 054 when using haloperidol as the basis for comparison. Both ziprasidone and thioridazine clearly caused a prolongation in the QT with the size of the effect much more impressive for thioridazine. The effect for ziprasidone appears to be about 10 msec, which was similar to that observed in the NDA. (Pfizer did not provide any statistical testing of these findings, but by examining the 95% CIs, one can reasonably conclude that there is significant statistical evidence of a difference when comparing either ziprasidone or thioridazine with haloperidol; the evidence for thioridazine being much stronger since there is no overlap in CIs.)

After seeing the findings from study 054, I believe there are three significant conclusions. First, ziprasidone affects cardiac repolarization within its proposed dose range whereas

risperidone, quetiapine, and olanzapine do not have such an effect, at least within their marketed dose range. Second, the size the effect attributable to ziprasidone is about 10 msec, which is similar to that observed in the ziprasidone NDA. Finally, thioridazine clearly has a large effect upon cardiac repolarization that is almost certainly clinically significant and life threatening. Several cases of TDP have been documented with thioridazine use in the literature and significantly lower doses of thioridazine than that studied in 054 have also been shown to prolong the QT.

I should also point out that patients in all dose groups seemed to tolerate the study fairly well. There were no deaths or serious events on drug, and no reported cases of TDP or syncope. One patient on thioridazine had an adverse event reported as "QT prolonged". The groups were also fairly comparable in the rate of discontinuation. For ziprasidone, 35 patients were randomized with 31 completing the study.

Pfizer appears to have concluded that study 054 shows that all drugs in the study prolonged the QTC. This conclusion is apparently based upon the fact that there was a positive change from baseline in QTC observed in each drug group. However, in my view, the empirical evidence does not support this conclusion. An additional control group such as placebo or even a lower dose of haloperidol that experienced significantly less change in QTC during study would be necessary to justify such a conclusion.

The sponsor also argues that the size of the effect attributable to ziprasidone is not clinically significant because of the absence of any clinical evidence of a risk and because of the terfenadine experience. In the ziprasidone NDA, there was no compelling evidence that sudden death was increased above background, no patients had QT prolongation at levels considered clinically significant and there were no cases of TDP. It is true that the experience with ziprasidone is in direct contrast to that with sertindole. With sertindole the effect on the QT was larger, patients had clinically significant prolongation, and the rate of sudden death appeared to be increased in both the NDA (compared to other NDAs) and in the European post-marketing experience. Pfizer also points out that terfenadine at its c max had a similar effect size and that no cases of TDP or QT prolongation have ever been found with terfenadine in the absence of a metabolic inhibitor.

I think there are at least 2 problems with this line of reasoning. First, while the facts with terfenadine are generally correct, patient exposure to parent terfenadine is fleeting - in the order of a few minutes. So patients do not remain at risk, if there was any, for very long until terfenadine is co-administered with a metabolic inhibitor. Second, the capacity of any development program to detect an increased rate of sudden death is limited. It would have to be a large increase compared to the rates observed in other NDAs for one to reasonably conclude there was a signal of concern. Likewise, the timing of ECGs to c max may have not been sufficient to detect prolongation. TDP can be difficult to capture clinically unless investigators are looking for such events. Thus, the absence of any clinical signal in the NDA development program is not a compelling argument that they won't necessarily occur.