

Another subject that deserves mention, although not meeting the definition of SUD, is subject 301-3110977, a 28 year old female with schizophrenia whose death occurred two days after discontinuing ziprasidone. Upon discharge from the study, this subject had ECG changes consistent with subendocardial ischemia with substernal pinching and was transferred to an internal medicine unit. Her death occurred two days later of unknown causes; her treatment regimen at the time of death included thioridazine and nitrazepam. The CRF did not provide more information than the patient summary and did not include any notes regarding this subjects' transfer to the medicine unit.

There were nine subjects whose death occurred within thirty days of discontinuing ziprasidone in which it appeared to be unlikely that their death was related to exposure to ziprasidone. Two subjects (116B-6590001 and 303-1970299) had been on another antipsychotic for more than three weeks after discontinuing ziprasidone. The remaining seven subjects (108-6090381, 116B-6940004, 117-6870317, 117-7060529, 302-2600156, 302E-1590029, JP-95-6011622) were victims of accidents or suicide.

In the ziprasidone treatment group there were a total of four probable suicides occurring within 30 days or less of discontinuing treatment. There was one subject (106-5520126) in the placebo group who committed suicide eight days after completing the study. There were two reports of suicide in the haloperidol group: 1) Subject 108-05820040 who committed suicide six days after discontinuing haloperidol, and 2) Subject 108-5940564 who overdosed while being treated with haloperidol. There were no subjects known to commit suicide during treatment with risperidone. The rate of suicide in 1000 subject-years for subjects in the ziprasidone group was 5.2. In the haloperidol group, the rate was 15 suicides per 1000 subject years; the rate of suicide for the placebo group was 19 suicides per 1000, and placebo group in this data base had a rate of zero. It is recognized that suicide may be a manifestation of the psychiatric disease under study, and this data does not suggest that ziprasidone increases the risk of suicide.

Appendix 8.1.1.2 gives the mortality rates for subjects in Phase II/III trials of the integrated safety data base who have died during the study or within thirty days of discontinuing the studies. In determining subject-years exposure, the sponsor used 5/15/97 as the cut-off date for deaths, while the cut-off date for the denominator determining the subjects years was sometime prior to 5/15/98 (despite requests, the sponsor did not provide the cut-off date for the denominator of the subject years calculation in the Safety Update of 8/29/97). In this data base, the placebo group demonstrates the highest mortality rate.

In Appendix 8.1.1.3, the rate of sudden unexpected death (SUD) is calculated for this NDA data base. The SUDs rate for the ziprasidone group (n=2565) is 9.1 SUD per 1000 subject years, while placebo (n=382) and haloperidol (n=585) groups had zero and the risperidone group (n=295) had a 9.5 SUD per 1000 rate. It would appear that ziprasidone and risperidone have a similar SUD rate within this data base; it is noted, however, that the risperidone rate is based on a sample size roughly one-tenth the size of the ziprasidone data base and that the SUD rate is based upon one death (due to acute aspiration).

Appendix 8.1.1.4 provides a comparison of the SUD rate of the most recent antipsychotic NDAs submitted to FDA; for ziprasidone, the information is based on the data base discussed in this review, while the other information has been obtained from the document: 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). From this table, it appears that both ziprasidone and sertindole surpass the SUD rate of olanzapine, risperidone, and quetiapine.

In his report Review of Data Quality, Coding, All Cause Mortality and Sudden Deaths (HFD-120: 2/3/98), Dr. Boehm concludes that the SUD rate found in the ziprasidone NDA data base is 6 times higher than the SUD rate from a pool of combined data of recently approved antipsychotic NDAs.

8.1.2 Other Serious Adverse Events

The sponsor did not define a serious adverse event in the Integrated Summary of Safety (ISS). A review of the pivotal study protocols revealed that Pfizer applied the same definition for a serious adverse event that is used by FDA (i.e. any drug experience that is fatal or life-threatening, is permanently disabling, requires hospitalization, or is a congenital anomaly, cancer, or overdose). These protocols included requests that any serious adverse event be immediately reported to Pfizer. Serious adverse events were submitted as listings itemized by subjects and COSTART body system/preferred term.

There were no serious adverse events reported in the Phase I ziprasidone studies. The original submission stated that within the primary safety data base, 261 subjects (12.2%) of the 2140 subjects treated with ziprasidone experienced serious adverse events in Phase II/III studies. Based on a count of the line listings submitted in the update (the sponsor did not provide a summary table of adverse events in the safety update), 115 additional subjects appeared to experience serious adverse events; therefore, 376 subjects (14.7%) of the total 2,565 subjects exposed to ziprasidone in Phase II/III studies of the integrated safety data base experienced a serious adverse event. The sponsor may have presented a single serious adverse event under two or three COSTART terms. It is noted that some individual subjects experienced more than one serious adverse event during these trials.

Appendix 8.1.2 lists serious adverse events considered to be common events in the patient population studied or for which there is not sufficient evidence to state that they were drug related. Any event which occurred greater than 30 days after the study drug was discontinued will not be discussed in this review; in the NDA submission, the sponsor included these events which occurred greater than 30 days after the study drug was discontinued. There were several instances in the sponsor's tables in which individual events may have been listed under two or three COSTART terms; in most cases, this review will present them as a single event in only one body system below. Also, there were some instances in which this reviewer felt that alternative COSTART terms reflected the adverse event more accurately than the sponsor's choice of category; the cases which have been recategorized in this review are discussed in section 8.1.5.2. (Note: fatal cases will not be repeated in this section.)

8.1.2.1 Syncope/Hypotension

Because of ziprasidone's alpha adrenergic properties, it not unexpected that orthostatic hypotension and syncope would be present as an adverse event. There were 5 syncopal events and one hypotensive event that were considered to be serious adverse events. It is unclear what criteria the sponsor used to report a syncopal event as a serious event, as syncope was observed in 0.7 % (15/2140) of the subjects in the phase II/III safety data base (cutoff 10/31/96), while hypotension (combining postural hypotension and hypotension) occurred in 2.5 % (53/2140) of subjects in the phase II/III safety data base. For the sake of completeness, in the phase I studies, there were 14 subjects who experienced a syncopal episode of which four experienced a second episode upon rechallenge of ziprasidone. There were at least thirteen episodes of syncope [102-5130005, 102-5140005, , 114-6170217, 116B-5980001, 116B-6940002, 117-6870313, 303-0570124, 303-0710101, 303-2650321, 303-2120222 (source: line listing in Appendix VI table 1b of sponsor's submission) and 108-6050002, 108E-5550096, 108E-5780052 (source: safety narratives)] in the Phase II/III data base that were not reported by the sponsor as a serious adverse event. The following table summarizes the subjects who were determined to have syncope/hypotension as a serious adverse events:

Syncopal and Hypotension listed as a serious event in subjects taking ziprasidone

SUBJECT #	AGE/SEX	MODAL DOSE (MG/D)	DAYS OF TREATMENT	SERIOUS ADVERSE EVENT/ COMMENTS
102-5130005	62/M	40	20	Subject fell, breaking left lateral malleolus and ziprasidone was discontinued. 24 hours later, subject had two episodes (10 sec.) of loss of consciousness. Etiology was not determined.
116B-5900002	31/M	160	82	Subject was on ziprasidone when he fell backwards with loss of consciousness while smoking a cigarette. Subject reported headache the night before and dizziness prior to fall. Etiology of syncope was unclear
118-7090001	44/M	40	4	Subject fell backwards and was found to be hypotensive (70/50); incident attributed to orthostatic hypotension. One day after his last ziprasidone dose, subject was found on the floor unresponsive. He was found to have a sodium level of 120 (but his baseline was 127) and he was placed on fluid restriction. EEG and CAT scan were benign. No cardiac work up was done.
116B-5510003	32/M	80	43	On the same day that subject experienced syncopal episode, he developed a rash and edema in the regions of the lips, left hand and ankles. ECG showed sinus bradycardia of 52 bpm otherwise it was normal. Case also included in rashes.
116B-5230001	41/M	80		Case report form suggests that the syncopal event occurred because the subject had not eaten for a couple of days, but emergency work up was not located in the CRF.
SUBJECT #	AGE/SEX	MODAL DOSE (MG/D)	DAYS OF TREATMENT	SERIOUS ADVERSE EVENT/ COMMENTS
Hypotension				
303-0710098	59/M	40	4	Hypotension (95/70), vomiting, hypotension, sweating, pallor, dyspnea (h/o diabetes) ECG at baseline: QRS:80, PR:160, QT:346, QTc: 447, rate:100 bpm ECG at incident (according to CRF): QRS:90, QT:326, QTc:473, rate: 123 bpm. with flat t-wave and arrhythmia.

8.1.2.2 Rash

There were 21 subjects who discontinued for rashes in the originally submitted integrated safety data base; the haloperidol group only had 2 withdrawals, while the placebo group had 1 withdrawal. It was left to the investigator's discretion as to whether or not an event was reported as serious, and there did not appear to

be any consistent feature that merited reporting a rash as a serious event. The following table lists the subjects whose rashes were considered serious adverse events.

Subjects with rash as a serious adverse event

SUBJECT #	AGE/ SEX	MODAL DOSE (MG/D)	DAYS OF TREAT- MENT	SERIOUS ADVERSE EVENT/ COMMENTS
106-5520124	41/M	40	15	"Facial rash" developed 9 days after starting ziprasidone. Discontinued due to rash at day 15: diagnosis of sebaceous dermatitis on face arms, thighs, and legs. Subject also had hypertension with blood pressure of 148/112.
106-5520047	46/F	120	29	Raised rash on lips, arms, back and buttocks with pruritis. Biopsy showed superficial perivascularitis with extensive edema and eosinophilia. Treated with antihistamines.
115-6560036	48/M	200	40	Severe generalized rash with itching mostly on the chest and upper extremities. Hospitalized to rule-out Stevens-Johnson Syndrome. Treated with benedryl and calamine lotion. Improvement noted within 2 days of discontinuing ziprasidone.
115-6890088	55/M	120	37	Generalized urticaria. Resolution within 5 days. Treated with prednisone, hydroxyzine, and diphenhydramine.
301- 0720148*	54/F	200	33	Urticaria and itching
116B- 5510003	32/M	80	43	Syncope accompanied by a rash and edema in the regions of the lips, left hand and ankles. ECG showed sinus bradycardia of 52 bpm otherwise it was normal. Possible angioedema.

*Safety Update

As noted above, there were three subjects who discontinued from the study whose hospitalization was extended because of the symptoms of rash. Rash was the most common adverse event resulting in withdrawal from the ziprasidone treatment groups (see 8.1.3.2). A review of the NDA safety data base revealed that there were several subjects whose rash was accompanied by an elevated white blood count, and at least two subjects with rash whose eosinophil count was elevated. Most cases of rash resolved within one week of discontinuing ziprasidone; one subject (117-5130506) experienced "bullous drug eruptions/ pruritic blisters with post-excoriated papules" on the hands, wrist, scalp, and neck which resolved 24 days after discontinuing ziprasidone. Medications used to treat rashes included steroids (oral and topical) and antihistamines. Three subjects (115-6560036, 106-5520047, and 115-6890088) required hospitalization for observation of their rashes.

8.1.2.3 Elevated Transaminase

It is unclear how the sponsor determined whether or not a laboratory value was considered a serious adverse event; therefore, the reader is referred to section 8.1.6.3 for a listing of subjects who withdrew from studies because of an abnormal laboratory values.

Abnormal transaminase values listed as serious adverse events

SUBJECT #	AGE/SEX	MODAL DOSE (MG/D)	DAYS OF TREATMENT	SERIOUS ADVERSE EVENT/ COMMENTS
104-5310185	38/M	40	7	Increased ALT and AST at first lab test after starting ziprasidone with peak five weeks (normal at baseline.). This subject was diagnosed with Hepatitis C diagnosed six months after discontinuing ziprasidone. There was a temporal relationship of the elevated LFTs and the initiation of ziprasidone.
106-5390092	35/M	120	9	ALT:165, AST:89U/L. After stopping ziprasidone, ALT returned to normal in 5 days and AST returned to normal in 19 days.
104-5360293	56/F	80	28	Elevated LDH (peak 419)
117-6390290	21/M	80	72	ALT: 133 U/L; AST: 43 U/L LFTs returned to normalized after discontinuing ziprasidone.

8.1.2.4 Neuroleptic Malignant Syndrome

The sponsor did not identify any episodes of neuroleptic malignant syndrome (NMS) in this submission. However, upon review of the case histories, it appeared that there was one 51 year old male subject (109-5650041) who presented classic symptoms of NMS, and a 40 year old female who had symptoms which may have been also been a manifestation of NMS. The following table summarizes these two cases:

Serious events manifesting symptoms of NMS

SUBJECT #	AGE/SEX	MODAL DOSE (MG/D)	DAYS OF TREATMENT	SERIOUS ADVERSE EVENT/ COMMENTS
109-5650041	51/M	80	3	Became confused with temperature of 99.9 ° F, creatinine kinase of 955, and sinus tachycardia. Within two weeks of discontinuing ziprasidone, the CPK levels normalized and the tachycardia resolved within 3 days of ziprasidone discontinuation.
116B-5530001	40/F	120	830	Episode of odd and confused behavior, a temperature of 101° F, diaphoresis, bradycardia, urinary incontinence and CPK level of 944 U/L. Her husband reported that she had similar episodes in the past. Urine culture showed E. coli infection. The sponsor chose to categorize this serious episode as UTI.

8.1.2.5 Extrapyramidal Symptoms

The following table delineates episodes of extrapyramidal symptoms which were considered serious adverse events.

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Serious adverse events of extrapyramidal symptoms

SUBJECT #	AGE/ SEX	MODAL DOSE (MG/D)	DAYS OF TREAT- MENT	SERIOUS ADVERSE EVENT/ COMMENTS
109-5670019	39/M	160	23	Discontinued with ziprasidone due to severe akathisia.
115-6940394	43/M	40	16	Developed tardive dyskinesia 3 days after stopping ziprasidone and was on risperidone at the time of the incident.
116B-06820005	52/M	120	81	Parkinsonism, restlessness and insomnia Subject took 200 mg qd x 2 weeks and was considered as an overdose.
303-1970265	68/M	40	7	Case report form listed him as having "worsening of vital functions" and was later clarified to be severe extrapyramidal symptoms (asthenia), general weakness, dehydration, hypotension, hypersalivation. This subject was categorized by the sponsor as having hypotension as a serious adverse event when in fact his blood pressure was consistently low (approximately 90/50) for the duration of the study as well as at baseline.
303-2000113	35/F	40	13	Acute dystonia.
In combination with haloperidol				
116B-05530002	62/F	200	137	Severe akathisia in combination with haloperidol .
301E-12106661	35/M	80	43	Severe generalized dystonia 1 day after stopping ziprasidone. Subject was given one dose of haloperidol prior to episode

8.1.2.6 Aspiration Pneumonia

Because aspiration pneumonia has been associated with neuroleptic use, the following cases are listed as possibly related to ziprasidone use:

Cases of pneumonia

SUBJECT #	AGE/ SEX	MODAL DOSE (MG/D)	LENGTH OF TREAT- MENT (DAYS)	SERIOUS ADVERSE EVENT/ COMMENTS
105-5340003	98/F	6	59	Subject had cough, rales, episode of vomiting and temperature of 100.8 ° F and was admitted to the hospital for aspiration pneumonia
116B-7010012	47/M	160	321	Hospitalized x 2 days for pneumonia.

8.1.2.7 Seizures

In the safety update (submitted 8/29/97), the sponsor reported the seizure rate to be 1.8 subjects per 100 subject years (12/772) or 0.54 % (12/2588) of the subjects in the NDA data base experienced a seizure while taking ziprasidone. The original NDA submission (3/18/97) includes six subjects who discontinued as a result of their seizure or possible seizure activity. The safety update did not include specific subject information.

The occurrences of seizure reported in the original submission is summarized in the tables below; seizures occurring beyond 6 days of treatment were not included. The first table is a summary of the subjects who experienced seizures within the original NDA submission of 3/18/97. The second table summarizes only subjects who discontinued because of an episode of seizure activity as of the safety update of 8/29/97. Information was obtained from the sponsor's ISS, patient narratives in the original NDA submission and the safety update of 8/29/97.

Summary of seizures with ziprasidone treatment in the original NDA data base (cut-off 10/31/96)

SUBJECT #	AGE/ SEX	MODAL DOSE (MG/D)	LENGTH OF TREAT- MENT (DAYS)	ADVERSE EVENT/ COMMENTS
108-5880461	45/M	80-120	22	Complex partial seizure. Treated with phenytoin and lorazepam. No h/o seizure.
108E-6060082/ 108-6060053	44/M	Unclear	9 months	Listed as possible seizure. Unresponsive when brought to the hospital. MRI was normal except for sinusitis; blood gas was pH 7.35, pCO ₂ =59, pO ₂ =50, HCO ₃ =33, Na=133, and WBC=20D/micro. Subject became alert within first hour and according to the patient summary was discharged with phenytoin and abuterol nebulizer. He was hospitalized two days later for further evaluation as he was febrile and had labored breathing requiring intensive care unit and corticosteroids.
116B-5900002 (also listed as syncope)	31/M	160	82	Listed as possible seizure. Subject was on ziprasidone when he fell backwards with loss of consciousness while smoking a cigarette. Subject reported headache the night before and dizziness prior to fall. Some limb movement occurred during episode.
301-2170651	31/M	120	45	Convulsive crisis on day 3.
303-0570124	35/M	40	364	Listed as possible seizure. Subject was found unconscious in the hospital ward; no abnormalities found in EEG and ECG showed "some tachycardia" up to nine days following the episode. (Note: there was no CRF available and no specific information regarding the work up of this episode). Subject completed the study for about two more weeks with metoprolol added to his medication regimen. One month after stopping ziprasidone, subject had a seizure. No prior h/o seizure.
303-1780041	45/M	40	2	Grand mal seizure. Treated with lorazepam.

Summary of seizures with ziprasidone (con't)				
SUBJECT #	AGE/ SEX	MODAL DOSE (MG/D)	LENGTH OF TREAT- MENT (DAYS)	ADVERSE EVENT/ COMMENTS
303-2380193	49/M	40	183	Grand mal seizure on day 122. Treated with diazepam.
303-2650327	60/F	40	365	Tonic clonic seizure on day 153.

Discontinuations due to seizures in the safety update of 8/29/98 (cut-off 5/15/97)

SUBJECT #	AGE/ SEX	MODAL DOSE (MG/D)	LENGTH OF TREAT- MENT (DAYS)	ADVERSE EVENT/ COMMENTS
302E-3570475*	41/F	Unclear	7	Generalized seizure. No h/o seizure.
306E-3740017*	26/M	80	42	Tonic-clonic seizure. Treated with diazepam. H/o febrile seizure in childhood. No h/o seizure in adolescents and adulthood.
307-3770251*	36/M	40	14	Grand mal seizure. No h/o seizure.
JP-95-601 23-01**	61/M		9	Epileptic seizure. Treated with diazepam and carbamazepine. H/o one prior seizure 2° to polydipsia.

*From Safety Update

**Not in the integrated safety data base

8.1.3 Dropouts and "Other Significant Adverse Events"

8.1.3.1 Overall Profile of Dropouts

According to the original submission, the primary integrated database included 1263 subjects (59%) of the total 2140 who prematurely discontinued treatment in Phase II/III trials. The sponsor did not provide summary data of the discontinuations in the safety update, but a count of the line listings showed that there were 72 new discontinuations. The sponsor's table below provides reasons for discontinuations for the original submission. Please note that this table does not include data from the safety update.

Insufficient clinical response was the reason that the majority of discontinuations occurred for the open label and placebo controlled trials. The sponsor's table below compiles the reason for discontinuations in four of the pivotal short term studies where a placebo comparison can be observed:

Overview of Phase II/III Study Discontinuations
All Oral Dosing Phase II/III Studies

Number (N) of Subjects	Ziprasidone 2140	Haloperidol 407	Risperidone 296	Amisulpride 19	Placebo 354
Discontinuations					
Adverse event	226 (10.6)	64 (15.7)	23 (11.2)	0	18 (5.1)
Insufficient clinical response	609 (28.5)	60 (14.7)	29 (14.1)	1 (5.3)	143 (40.4)
Laboratory findings	16 (0.7)	2 (0.5)	3 (1.5)	0	1 (0.3)
Special safety test finding	2 (0.1)	0	0	0	1 (0.3)
Patient died	3 (0.1)	1 (0.2)	1 (0.5)	0	0
Other	462 (21.1)	82 (20.1)	37 (18.0)	2 (10.5)	57 (16.1)
Total	1308 (61.1)	209 (51.4)	93 (45.1)	3 (15.8)	220 (62.1)

Other reasons for discontinuation may include failure to meet randomization criteria, lost to follow-up, protocol violation, withdrawn consent, etc.

Includes duplicate counting of 45 Ziprasidone subjects who discontinued both the parent and extension study.
Protocols: 615, 101, 102, 104, 104E, 106, 106E, 108, 108E, 109, 109E, 110, 111, 114, 115, 116B, 117, 118, 122, 301, 302, 303, 304, 305

Insufficient clinical response was the reason that the majority of discontinuations occurred for the open label and placebo controlled trials. The sponsor's table below compiles the reason for discontinuations in four of the pivotal short term studies where a placebo comparison can be observed:

Overview of Phase II/III Study Discontinuations
Short-Term Fixed-Dose Placebo-Controlled Oral Dosing Phase II/III Studies

Number (N) of Subjects	Ziprasidone 702	Haloperidol 85	Placebo 273
Discontinuations			
Adverse event	29 (4.1)	7 (8.2)	6 (2.2)
Insufficient clinical response	165 (23.5)	13 (15.3)	95 (34.8)
Laboratory findings	4 (0.6)	0	0
Other	118 (16.8)	17 (20.0)	49 (17.9)
Total	316 (45.0)	37 (43.5)	150 (54.9)

Other reasons for discontinuation may include failure to meet randomization criteria, lost to follow-up, protocol violation, withdrawn consent, etc.

Protocols: 104, 106, 114, 115

As seen above, there was a higher withdrawal rate for insufficient efficacy in the placebo group than in the ziprasidone group; however, the drop out rate for adverse events was higher for the groups receiving ziprasidone.

8.1.3.2 Adverse Events Associated with Dropout

In the integrated safety data base (excluding data from the safety update), 221 subjects (10.3 %) of the 2,140 subjects exposed to ziprasidone discontinued the study due to an adverse event.

In order to establish a comparator control, it is most helpful to focus on data collected from placebo-controlled studies. The following table lists the adverse events which resulted in 2 or more withdrawals from the placebo-controlled pivotal studies (including studies 104, 106, 114, and 115):

Adverse events leading to discontinuations in short term placebo-controlled studies 104, 106, 114, 115

	Ziprasidone n=702	Placebo n=273	Haloperidol n=85
Total # of subjects discontinuing due to adverse events (%)	29 (4.1)	6 (2.2)	7 (8.2)
ADVERSE EVENT			
Rash	7 (1.0)	0	0
Nausea	3 (0.4)	1 (0.4)	0

Adverse events leading to discontinuations in short term placebo-controlled studies 104, 106, 114, 115 (con't)

	<u>Ziprasidone</u> <u>n=702</u>	<u>Placebo</u> <u>n=273</u>	<u>Haloperidol</u> <u>n=85</u>
Hypertension	2 (0.3)	0	0
Tachycardia	2 (0.3)	0	0
Vomiting	2 (0.3)	0	0
Akathisia	2 (0.3)	0	2 (2.4)
Hostility	2 (0.3)	0	0
Insomnia	2 (0.3)	0	0
Somnolence	2 (0.3)	0	1
LFT abnormality	2 (0.3)	0	0

NOTE: It appears from the sponsor's data that individual subjects may have experienced more than one adverse event.

8.1.4 Other Search Strategies

None.

8.1.5 Common Adverse Events

8.1.5.1 Approach to Eliciting Adverse Events in the Development Program

Pfizer did not provide their working definition of an adverse event in the Integrated Summary of Safety. All adverse events presented were classified by organ system using COSTART terminology. The sponsor stated that adverse events were collected by either direct observation by the investigator or by patients volunteering this information. This method may result in an under representation of adverse events, because the schizophrenic population may not be able to spontaneously volunteer and articulate their discomfort.

The sponsor states in the Integrated Summary of Safety (ISS) that investigators categorized adverse events as to whether or not there was a probable relationship to the study medication. The ISS presented tables which addressed events that were judged by the investigators to be related or of unknown relationship to the treatment medication; however, the sponsor stated that all causality tables included all adverse events independent of the investigator's judgment (submitted 4/9/98).

8.1.5.2 Establishing Appropriateness of Adverse Event Categorization and Preferred Terms

The sponsor reports using the COSTART dictionary, coding adverse events by body system and preferred terms. In most cases, the sponsor chose appropriate categories; however, there were several cases in which alternative categories were chosen by this reviewer to better reflect the clinical presentation as described in the patient profiles and case report forms. Serious adverse events and discontinuations which have been re-categorized from the sponsor's original COSTART TERMS are as follows:

1. Subject 116B-553001: a 40 year old female who was taking 60 mg of ziprasidone daily for 830 days began to have an episode of odd and confused behavior, a temperature of 101° F, diaphoresis, bradycardia, urinary incontinence and a CPK level of 944 U/L. Her husband reported that she had had similar episodes in the past. Her urine culture showed an E. coli infection. The sponsor chose to categorize this serious episode as UTI; to be more accurate, it needs to be considered that this case may also have been a manifestation of neuroleptic malignant syndrome.

2. Subject 118-7090001: a 44 year old male who was taking 40 mg ziprasidone daily for 4 days, fell flat backwards 3 ½ hours after his last dose and was found to be hypotensive (70/50). One day after the last

ziprasidone dose, this subject was found on the floor unresponsive; he was found to have a sodium level of 120 (but his baseline was 127) and was re-hospitalized and placed on fluid restriction. EEG and CAT scan were benign. No cardiac work up was done. The sponsor chose to categorize this as a seizure despite that there was no seizure witnessed; therefore, this was recategorized as syncope.

3. Subject 101-5060084: a 52 year old male who was taking 20 mg ziprasidone daily for 4 days was found at home confused and fluid depleted secondary to hyponatremia with sodium level of 111. He was admitted to the hospital and with fluid restriction, and his sodium returned to normal. This was originally cataloged as confusion and this reviewer reclassified it as hyponatremia.

4. Subject 303-0212105: a 56 year old male who was taking 160 mg ziprasidone daily for 280 days who reportedly had a history of essential hypertension (but was normo-tensive throughout the study), fell down the steps, lost consciousness and was noted to have a blood pressure of 220/140. This case was listed as intracranial hemorrhage which actually occurred as a result of this fall; it was recategorized as a hypertensive episode because this event appeared to have preceded the fall.

The following adverse events were listed under reasons for discontinuations, but have been considered to be serious events by this reviewer:

1. Subject 109-5650041: a 51 (age was listed as 48 in the summary, but CRF stated 51) year old male who, within the first few days of treatment with ziprasidone 20 mg qid, became confused with a temperature of 99.9 ° F, a creatinine kinase level of 955, and sinus tachycardia. Within two weeks of discontinuing ziprasidone, the creatinine kinase levels normalized and the tachycardia resolved within 3 days of ziprasidone discontinuation. The sponsor did not list this as a serious adverse event; but as a case of discontinuation due to the event of tachycardia. The presented data more accurately suggests that this was a serious adverse event of probable neuroleptic malignant syndrome.

2. Subject 116B-5230001: a 41 year old male who was taking 80 mg ziprasidone for 80 days experienced mild nausea and an episode of syncope and was taken to the emergency room. The sponsor categorized this as a discontinuation and did not list this as a serious adverse event; the case report form had a notation from the investigator that the emergency room physician thought that this event was due to not eating for a couple of days; however, the work up was not included in this submission. It was felt by this reviewer that this syncopal event should be classified as a serious adverse event.

3. Subject 104-5220146: a 45 year old female (taking 80 mg ziprasidone x 12 days) with a history of hypertension stabilized with nifedipine was hospitalized for a possible hypertensive crisis with a diastolic pressure up to 120. This adverse event was listed in the discontinuations by the sponsor. It is the opinion of this reviewer that this adverse event should be reclassified as a serious adverse event as this event resulted in the subject's being hospitalized.

8.1.5.3 Selecting the Best Adverse Event Tables for Characterizing the Adverse Event Profile

A helpful perspective in the attempt to determine the occurrence of events related to the study medication is to look at incidents of adverse events in placebo-controlled trials. Appendix 8.1.5.3 consists of the sponsor's table of adverse events occurring in 1 % of the subjects taking ziprasidone in the data collected from the placebo-controlled pivotal studies (104, 106, 114, and 115). The proposed labeling include a 1 % table based on this data. Events occurring in this pooled data that are not listed in the proposed labeling are anxiety, tremor, conjunctivitis, and urinary incontinence; these events were seen with equal frequency in the placebo group.

Appendix 8.1.5.4 is extracted from the sponsor's proposed labeling and lists all adverse events occurring in the primary safety data base in the original submission; data from the safety update is not included in this summary.

8.1.5.4 Identifying Common and Drug-Related Adverse Events

Common events were determined by identifying events which occurred in at least 5% of the ziprasidone group and occurred more than twice as frequently in the ziprasidone than in the placebo group. The drug related adverse events fulfilling this criteria were extrapyramidal syndrome and somnolence as seen in the 1% table. Weight gain was observed in 10 % (61/622) of subjects taking ziprasidone in the short term placebo controlled phase II/III studies versus 4 % (9/227) in placebo (see Appendix 8.1.7.3.2); it is noted that weight gain was omitted from the 1% table.

8.1.5.5 Additional Analyses and Explorations

Dose Response

A dose relationship for several adverse events was established when the sponsor applied the Mantel-Haenszel test to the pooled data from pivotal short term studies (104, 106, 114, 115) for doses of <40 mg bid, 40 mg bid, 80 mg bid, and ≤ 100 mg bid. The sponsor's analysis showed a statistically significant dose relationship ($p \leq 0.05$) with the following adverse events: asthenia, postural hypotension, anorexia, diarrhea, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, respiratory tract infection, rhinitis, rash ($p=0.051$), abnormal vision.

Demographic Analyses

The interaction effect of gender, age, or race was determined in the common adverse events that occurred at least 5% in the ziprasidone group and more than twice as frequently than in the placebo group. The sponsor states that using the Breslow-Day Odds Ratio, there was no differences noted in the incidence of somnolence (the only adverse event analyzed) when examining gender ($p=0.89$), age ($p=0.62$) or race ($p=0.89$).

The demographics for this analysis is as follows:

Gender

Women: n=186 ziprasidone, n=71 placebo

Men: n=516 ziprasidone, n=12 placebo

Age

18-64 y.o.: n=693 ziprasidone, n=271 placebo

65-74 y.o.: n=9 ziprasidone, n=2 placebo

Race

Caucasian: n=462 ziprasidone, n=171 placebo

African American: n=175 ziprasidone, n=68 placebo

Asian: n=21 ziprasidone, n=2 placebo

Other: n=44 ziprasidone, n=26 placebo

8.1.6 Laboratory Findings

8.1.6.1 Extent of Laboratory Testing in the Development Program

The review of laboratory findings encompass data from the Phase II/III trials in the integrated safety data base of the original NDA submission. The Integrated Summary of Safety states that routine laboratory tests for all studies included complete blood count, electrolytes, serum hepatic and renal function. The final samples were collected up to six days after the last day of study medication. The frequency of laboratory testing varied amongst the studies; the ISS merely states that routine laboratory tests were collected at baseline and repeated during and/or at the end of the study.

8.1.6.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

This section of the review will concentrate on the pooled clinical laboratory values from the short term placebo-controlled studies 104, 106, 114, 115. This allows for comparison to be made to the placebo group and also may eliminate any confounding variable of time period as the duration of these studies is comparable (studies 104 and 106: 4 weeks; studies 114 and 115: 6 weeks). Laboratory values were collected at different intervals for these studies: 106 and 104 had weekly monitoring, while 114 and 115 had laboratory monitoring about every other week.

8.1.6.3 Standard Analyses and Explorations of Laboratory Data

8.1.6.3.1 Analyses focused on Measures of Central Tendency

The mean change from baseline of clinical laboratory values for ziprasidone and placebo can be found in Appendix 8.1.6.3.1. The sponsor performed the Kruskal-Wallis test using the RANK and ANOVA procedures with an alpha level of 0.05 to analyze the data; it is inferred from the sponsor's table in Appendix 8.1.6.3.1 that there were no statistically significant findings when comparing the ziprasidone group with the placebo group. Inspection showed that the mean changes of note in the ziprasidone group compared to placebo were values for blood urea nitrogen ($\downarrow 8\%$), bicarbonate ($\uparrow 4.5\%$), and LDH ($\uparrow 3\%$). It is important to keep in mind that the last observation value could be obtained up to six days after discontinuation from the study.

8.1.6.3.2 Analyses focused on Outliers

The sponsor used an elaborate system to determine when a laboratory value had clinical significance; this was not clearly explained in the original NDA submission and a request for further details was made (please refer to submissions of 11/18/97 and 12/17/97). Appendix 8.1.6.3.2a contains the sponsor's laboratory reference ranges used to determine whether the baseline value was normal or abnormal; baseline values were then compared to the worst laboratory value found during the study. The sponsor applied different criteria for subjects who began the study with abnormal laboratory values. Clinical significance was determined using the values in column "A" and "B" in Appendix 8.1.6.3.2b; for subjects with normal baseline values, the worst value was required to be outside the range specified by column "A". Meanwhile, for subjects with an abnormal baseline value it was required that their worst lab value be described by both column "A" and "B" in order to be considered of clinical significance and be included in the number of subjects with laboratory abnormalities.

For reasons explained above, the focus of this section will be the short term placebo controlled trials. Please refer to Appendix 8.1.6.3.2c for the incidence of clinically significant laboratory tests in the short term placebo controlled fixed dose studies 104, 106, 114, 115. Using a Fisher Exact 2-tailed test at the 0.05 alpha level, the sponsor found that statistical significance was seen in the following laboratory values: cholesterol (ziprasidone: 2% versus placebo: 0%) and triglycerides (ziprasidone: 12% versus placebo: 7%).

8.1.6.3.3 Dropouts for Laboratory Abnormalities

Of the 2140 ziprasidone subjects in the phase II/III trials in the original integrated safety data base, the following laboratory abnormalities resulted in early termination in 0.1% or greater of the subjects:

ALT elevation 0.5%
 AST elevation 0.4%
 Alkaline Phosphatase elevation 0.1%

A criteria to determine when a subject should withdraw from the study was not located in this submission. The following table is composed of subjects who did drop out because of laboratory abnormalities. Information for this table was generated from both the original submission and the safety update which encompasses a total of 2565 subjects exposed to ziprasidone in the Phase II/III data base.

Dropouts for laboratory abnormalities

Subject ID #	Age/Sex	Dose/duration	Most extreme levels	Outcome/comments
Abnormal liver enzymes				
117-6550327	58/M	120 mg 37 days	ALT:156,AST:68 U/L AP:250, GGT:1372 Bilirubin: 2.3mg/dl	Jaundice which resolved two weeks after d/c. Five days after d/c labs began to normalized, but remained elevated.
301-2790615*	43/M	120 mg 42 days	ALT:104,AST:217 U/L	Jaundice, mild, with fever and fatigue. Follow up labs reported to be normal.
#117-622-0033	36/M	160 mg 219 days	ALT:58,AST:158, LD:354 IU/L	LFTs reported to be resolved one day after d/c
117-622-0033	36/M	160 mg 219 days	ALT:58,AST:158, LD:354 IU/L	LFTs reported to be resolved one day after d/c
115-6380055	40/M	120 mg 10 days	ALT:116,AST:188 IU/L	LFTs resolved within two days after d/c
116B-6220001	27/M	200 mg 117 days	ALT:77,AST:144 IU/L	LFTs normalized within one month after d/c
106-5390092	35/M	120 mg 9 days	ALT:165,AST:89U/L	ALT returned to normal in 5 days and AST returned to normal in 19 days. LFTs normalized within five days after d/c
109-5720028	34/F	80 mg 9 days	ALT:128,AST:55 U/L	LFTs normalized within eleven days after d/c
101-5090050	37/M	10 mg 7 days	ALT:56,GGT:137 U/L	Within two weeks, ALT normalized and GGT was returning to normal
101-5050065	39/M	40 mg 8 days	ALT:94,AST:197, GGT:128 U/L	LFTs were lowering within 5 days; no other f/u provided
115-6530148	42/M	120 mg 26 days	ALT:194,AST:80 U/L	LFTs were lowering within 8 days; no other f/u provided
116B-5810013*	43/M	200 mg 171 days	AP: 257 U/L	Subject remained in study and elevated AP did not resolve by the end of the study.
114-5290079**	40/M	80 mg 15 days	AST:377 IU/L ALT:582 LDH:784	Labs returned to normal within one month after stopping ziprasidone
304-1890367	27/M	15 days dose not provided	AST: 111 U/L ALT: 290 U/L	Subject was listed in the safety update as participating in the blinded group with laboratory test abnormalities and possible hepatitis. Sponsor revealed that subject was in ziprasidone group. Doses unclear.

Hematologic abnormalities				
303-1800061	65/M	80 mg 89 days	Platelets: 12x 10 ⁹ /L (nl: 160-350)	Value at baseline was 93 x 10 ⁹ /L. Thrombocytopenia resolved 7 days of d/c.
104-5370243	37/M	40 mg 20 days	Neutrophils: 27 % (1242/UL)	Mild neutropenia resolved within day of d/c
303-265-0357	36/M	160 mg 41 days	Eosin: 35.1%	Within two weeks after d/c, eosinophilia resolved.
Dropouts for laboratory abnormalities (con't)				
Subject ID #	Age/Sex	Dose/duration	Most extreme levels	Outcome/comments
Abnormal liver enzymes/hematologic abnormality				
303-02710228	54/M	160mg 87 days	ALT: 70, AST: 85 U/L Prolactin: 0.53 IU/L Hb/Hct: 7.1/0.35	Accompanying symptoms of heartburn and epigastric pain were resolved within four weeks of discontinuation and treatment. Subject diagnosed with chronic gastritis by endoscopy and Helicobacter pylori infection. Follow up labs not included in submission.
Glucose abnormality				
117-05130512	35/M	120 mg 194 days	Glucose: 883 mg/DL	Diabetic ketoacidosis successfully treated with insulin. Subject had one previous episode.

*From Safety Update

**Not included in sponsor's calculations (Sponsor listed this subject as discontinuation due to insufficient clinical response)

As can be seen from the table above, there were several subjects whose liver function studies elevated while on ziprasidone and the pattern of resolution suggests that these episodes were drug related. Two subjects were reported to exhibit symptoms of jaundice with elevated liver functions tests: one subject (117-6550327) had an extremely high level of GGT (1372 IU/L); the other subject (301-2790615) also had symptoms of fever, and fatigue.

Also of note is the one subject (303-01800061) who withdrew because of thrombocytopenia which resolved upon withdraw from ziprasidone. It is possible that this adverse event may have been drug related.

8.1.6.4 Additional Analyses and Explorations

Prolactin studies were monitored in only two subjects in the short-term placebo controlled studies, one of which was found to have abnormal values. Therefore, it is necessary to look at the total pool of oral dosing phase II/III studies; clinically significant abnormalities were identified in 20% of the (148/741) ziprasidone subjects whose prolactin levels were monitored (see Appendix 8.1.6.4). Using the Fisher two tailed statistical test with an alpha level of 0.05, the sponsor determined that this rate of prolactin abnormality was statistically significant when compared with the placebo subjects monitored.

Thyroid function studies were not tested at all in the short-term placebo controlled studies. In referring to Appendix 8.1.6.4, it can be seen that there were only 224 subjects tested for thyroid functions and when compared to the rate of abnormal findings in the 56 placebo group monitored, there was no statistical significance identified.

8.1.7 Vital Signs

8.1.7.1 Extent of Vital Sign Testing in the Development Program

The ISS does not specify which vital signs were included in each study, nor does it state the frequency of vital sign monitoring; the final vital sign monitoring could occur up to six days after the last dose of study medication was given. The sponsor analyzed changes in standing or sitting systolic or diastolic blood pressure and sitting or standing heart rate, and weight gain or loss. Please refer to Appendix 8.1.7.3.2 for vital sign parameters used to determine clinical significance. There is no data comparing changes of supine and standing vital signs; therefore, orthostatic changes could not be adequately assessed.

8.1.7.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

The focus of this section will be on the short-term placebo controlled trials to allow for placebo comparison.

8.1.7.3 Standard Analyses and Explorations of Vital Sign Data

8.1.7.3.1 Analyses Focused on Measures of Central Tendency

Appendix 8.1.7.3.1 contains the sponsor's summary of the median change from baseline to last observation of vital signs. Using the Kruskal-Wallis test with an alpha level of 0.05, the sponsor found a statistically significant change for weight increase (61 of 622 subjects) when comparing the ziprasidone and placebo groups. From these findings, it does not appear that there are significant changes in heart rate or blood pressure reading when comparing placebo and ziprasidone; however, it must be kept in mind that the final reading could have occurred up to six days after the last dose of study medication was administered.

8.1.7.3.2 Analyses focused on Outliers

Appendix 8.7.3.2 includes the sponsor's criterion of clinically significant changes as well as the incidence of these events in the placebo-controlled studies. It can be inferred from this table that statistical significance using the Fisher exact two-tailed test was seen for weight increase only. Again, it must be considered that the baseline values may have been compared to a vital sign measurement that was taken up to six days after the last day of study treatment.

8.1.7.3.3 Dropouts for Vital Sign Abnormalities

The table below presents the number of subjects who withdrew because of vital sign abnormalities in the original NDA submission database. A similar table was not submitted in the sponsor's safety update data.

Subject withdraws for abnormal vital signs or weight measurements in Phase II/III trials (adapted from sponsor's electronic submission)

	Ziprasidone	Haloperidol	Bisperidone	Placebo
Number of Subjects Randomized:	2140	407	206	364
HYPERTENSION	4 (0.2)	0	1 (0.5)	0
HYPOTENSION	1 (0.0)	0	0	0
POSTURAL HYPOTENSION	1 (0.0)	0	0	0
TACHYCARDIA	4 (0.2)	1 (0.2)	0	0
WEIGHT GAIN	1 (0.0)	0	0	0
WEIGHT LOSS	3 (0.1)	0	0	0

The following table itemizes the case reports of subjects who discontinued because of vital sign abnormalities. There is some discrepancy for the number of subjects who discontinued because of weight changes, because there were only two case listed in the sponsor's line listing of subjects for this item; however there were two cases of weight loss listed as serious adverse events (please refer to Appendix 8.1.2 under metabolic).

Subjects who discontinued due to vital sign abnormalities

Subject ID #	Age/Sex	Modal Dose /duration	Reason for d/c	Outcome/comments
116B-0617001	26/F	160 mg 139 days	weight gain	Subject reported weight gain. Investigator did not record weights.
116B-0572000f	37/M	200 mg 127 days	weight loss	Subject's weight fluctuated (baseline: 123 lb.; at discharge: 118.5; overall loss: 4.5 lb.). There was 10 lb. weight gain in first 6 weeks and then 14.5 lb. weight loss within the next two month before d/c.
117-6840608	43/M	80 mg 7 days	hypertension	Termination sitting blood pressure was 160/120 with heart rate 124 bpm. Baseline values: 145/100; 84bpm. No orthostasis.
303-2120222	58/M	160 mg 349 days	hypertension	Syncopal episode: loss of consciousness for 2-3 minutes. Upon recovery, blood pressure was 180/90 with 130 bpm. No significant ECG change. Returned to baseline the next day. CT-scan showed cerebral neoplasm with edema I temporo-parietal region of right hemisphere.
104-5220146	45/F	80 mg 12 days	hypertension	Subject had history of hypertension and diabetes with concurrent medications of nifedipine and glyburide. She awoke in the middle of the night feeling weak and tremulous and had a blood pressure of 195/105. Ziprasidone was d/c and nifedipine was increased. Over the next three days blood pressure fluctuated from 170/90 to 142/84
106-5520124	41/M	40 mg 15 days	hypertension	Blood pressure: baseline: 100/70 (sitting) at d/c: 148/112 (sitting)
Subjects who discontinued due to vital sign abnormalities (con't)				
Subject ID #	Age/Sex	Modal Dose /duration	Reason for d/c	Outcome/comments
303-1970265	68/M	40 mg 7 days	hypotension	Subject was hypotensive at baseline.
106-5420149	31/M	120 mg 14 days	tachycardia	Pulse at baseline: 122 bpm at d/c: 138 bpm
117-7060380	30/M	80 mg 12 days	tachycardia	Recorded as severe tachycardia, but heart rate not available in patient profile or case report.
115-6470383	40/M	80 mg 3 days	tachycardia	Baseline: ECG: possible lateral/inferior infarct with pulse: 74 bpm, but cardiologist determined this was not an infarct. QTc:408.7 At discharge: pulse: 119 bpm, QTc:445.0

8.1.7.4 Additional Analyses and Explorations

There were no additional studies or analyses of vital signs done by the sponsor.

8.1.8 ECGs

8.1.8.1 Extent of ECG testing in the development program

ECGs were recorded in all Phase II/III trials. The tracings were read on site for the short term placebo controlled and most other studies. Study 303, the 52 week placebo controlled study, had ECG tracing initially read on site and then they were sent to Premier Research Worldwide of Cambridge England for blinded reading. In the original NDA submission, the ECG results of study 303 were kept separate as a different data set within the NDA data base. However, a resubmission of the data (11/13/97) included an analysis and consult by Joel Morganroth, M.D. in which the data sets from study 303 were integrated into the entire data base of the NDA, and ECGs suspected of being read by an automated system were reread by a more accurate system of analysis (Please refer to Section 8.1.8.4 for details). The tables of data submitted in Dr. Morganroth's reanalysis (submission of 11/13/97) will be used for the purposes of this review.

As part of the review process, Charles J. Ganley, M.D., cardiology consultant at FDA (review of 11/18/97) stated that ECGs were performed at trough times in some studies and the timing in other studies was unclear. He also addressed concerns regarding the dose dependent response for QT and QTc prolongation observed in some studies within this submission (11/18/97 & 1/6/98).

8.1.8.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

As done in the review of clinical laboratory and vital sign analyses, the main focus of this section of the review will be on pooled ECG data from the short term placebo controlled studies: 104, 106, 114, 115. This allows for comparison to be made to the placebo group and may eliminate any confounding variable of time period since the duration of treatment between the groups in these studies is comparable. Within this pool of data, there were 656 ziprasidone subjects and 250 placebo subjects for comparison. The tables used will reflect the most recent data reanalysis submitted by the sponsor (11/13/97).

8.1.8.3 Standard Analyses and Explorations of ECG Data

8.1.8.3.1 Analyses Focused on Measures of Central Tendency

Appendix 8.1.8.3.1 presents the mean change from baseline to the most abnormal value of ECGs from the short term placebo controlled studies. It is important to compare baseline to the most abnormal value, because the last observed value was collected up to six days after the last dose which may reflect less drug effect due to the half life. The sponsor did not provide a statistical analysis comparing placebo with the treatment groups with this reanalyzed data. From observation, it appears that subjects in the ziprasidone groups manifest more frequent ECG changes of QTc increase and heart rate than is seen in the placebo and haloperidol group. Below is a table summarizing these two parameters.

Summary of maximum mean changes in ECG of Short term placebo control studies

	Ziprasidone Daily Dose (mg/day)					Placebo (n=250)	Haloperidol (n=76)
	<80 (n=230)	80 (n=138)	120 (n=111)	160 (n=100)	≥200 (n=77)		
QTc	8.6	12.6	15.2	19.8	15.0	4.3	4.1
Heart rate	7.8	6.6	5.4	6.7	4.4	4.5	4.4

As observed by Dr. Ganley's review (11/18/97 & 1/6/98), it can be seen that there is a dose response for the mean QTc change for doses less than 200 mg of ziprasidone.

8.1.8.3.2 Analyses focused on Outliers

Appendix 8.1.8.3.2 presents the sponsor's reanalysis of the incidence by percent of QTc changes collected from ECGs in the short term placebo controlled studies. The sponsor only submitted data on the incidences of QTc changes and did not submit information regarding the incidence of change in other ECG parameters.

In the original submission, the sponsor included a consult from [redacted] His observation based on the original data base was that the most frequent ECG changes were from normal ST-T to abnormal ST-T with instances of isolated prolongation of the P-R, QRS, appearance of LVH, LAFB and rare PVC; Dr. Fisch did not feel that these findings were significant and he did not observe them to be dose related.

8.1.8.3.3 Dropouts for ECG Abnormalities

The sponsor did not provide information specifically itemizing subjects who withdrew because of ECG changes. The following table of subjects who discontinued due to ECG abnormalities was generated from the pool of all oral dosing phase II/III subjects.

ECG-Related Withdrawals

SUBJECT #	AGE/ SEX	DOSE (MG/D)	LENGTH OF TREATMENT	SERIOUS ADVERSE EVENT/ COMMENTS
116B-6360004	69/F	80	approx. 8 months	Arrhythmia; Holter monitor showed frequent ventricular ectopy with ventricular couplets and bigeminy and supraventricular ectopy.
106-5420149	31/M	120	14 days	sinus tachycardia (138 bpm)
109-5650041	51/M	80	3 days	tachycardia-discussed as Possible NMS (See section 8.1.2.1)
117-7060380	30/M	80	12 days	sinus tachycardia (from CRF: 132 bpm) QT: minimal change from baseline
115-6470383	40/M	80-200	3 days	sinus tachycardia (119 bpm) QTc:screening:396 baseline: 408.7 termination 445.0 post study:423.8 post study: 396.2

8.1.8.4 Additional Analyses and Explorations

The sponsor's submission dated 11/13/97 included a copy of a cardiology consult prepared by [redacted]. Within this submission, [redacted] reported his additional analysis of the ECG data from the integrated safety data base; this included a blinded rereading of 3,883 ECGs using a central laboratory for purportedly more accurate QTc duration measurement to correct inaccuracies caused by automated readings of the ECG data. Using this method, [redacted] concluded that of the 34 subjects originally identified as demonstrating QTc interval of ≥ 500 or having an increase of ≥ 75 msec, only one subject (116B-6220003) actually fulfilled the criteria of a QTc interval increase of ≥ 75 msec. No subjects were found to have a QTc measurement greater than 450 msec.

Dr. C. Ganley of HFD-110 also reviewed the ECG data in the integrated safety data base. Please refer to his reviews dates 11/18/97 & 1/6/98.

Because the sponsor allowed for the final ECGs to be recorded up to six days after the administration of the last dose, Dr. Boehm (HFD-120: 1/23/98) conducted an analysis that excluded any QTc value of subjects whose final ECG was recorded at one day or more after discontinuing ziprasidone in study 101 (the protocol required that the time of the ECGs be recorded); a comparison of baseline-to-final QTc was then recalculated. Dr. J. Boehm's results suggest that the mean baseline-to-final QTc changes recorded less than 1 day after discontinuing the drug were similar to the mean QTc measurements when the final ECG reading was taken up to 6 days after discontinuing the drug.

In the submission of 3/20/98, the sponsor expressed concern that the methodology of recording the initial QTc affects the determination of QTc prolongation. The sponsor explained that they recorded both screening and baseline values (with a wash out period in between) and claim that there was a dose dependent relationship of QTc prolongation observed with the baseline-to-final QTc measurements, but not with the screening-to-final. They expressed their concern that NDA data bases from recently approved anti-psychotic agents utilized measurements of screening value to determine if QTc prolongation was present. It is important to note that according to [redacted] report (sponsor's submission of 11/13/97), there was a dose dependent QTc prolongation observed in both screening-to-maximum QTc value and the baseline-to-maximum value in ziprasidone treatment groups (although, the screening-to-maximum is of a lower magnitude).

Both Dr. Ganley and [redacted] report present data suggesting a dose dependent increase in QTc for doses up to and including 160 mg daily of ziprasidone in the short term placebo controlled studies. Both reports also discuss that a QTc increase is not demonstrated in the analysis of the 52 week study 303.

Based on the evidence that ziprasidone has been shown to cause an increase in the QTc interval as a function of dose within the proposed therapeutic range (80-160 mg daily), Dr. Ganley concludes that the risks of arrhythmia, syncope, and sudden death may exist for ziprasidone, because these risks have been observed with other drugs which also prolong the QTc interval. He stated also that the labeling should clearly reflect this risk and that it may be necessary to consider this drug as a second line therapy if approved.

8.1.9 Special Studies

8.1.9.1 Ophthalmology

The sponsor did ophthalmology examinations including slit lamp exam in some of the long term studies (Studies 104E, 106E, 108, 108E, 109E, 116B, 117, 303). The sponsor provided the following superficial analysis of this data in the ISS:

Ophthalmology Data: Incidence of Significant Changes from Baseline
All Evaluable Oral Dosing Phase II/III Studies

Number of Subjects	Ziprasidone 1168						Haloperidol 104						Risperidone 147						Placebo 84						
	Yes			No			Yes			No			Yes			No			Yes			No			
Changes From Baseline	N	S	%	N	S	%	N	S	%	N	S	%	N	S	%	N	S	%	N	S	%	N	S	%	
	43	(8.0)	491	(91.9)	3	(6.0)	47	(94.0)	3	(5.4)	52	(94.6)	4	(6.1)	61	(93.8)									

* Visit day relative to start of open label treatment.
Protocols: 104E, 106E, 108, 108E, 109E, 116B, 117, 303

A review of the incidence of all adverse events in the original integrated safety data base (not including the update) revealed that there were no prominent patterns of eye dysfunction that would merit a more detailed analysis at this time. Of note, there was one subject reported with cataract and 87 subjects (4% of 2140 subjects) who reported abnormal vision, not otherwise specified.

8.1.9.2 Extrapyramidal Symptoms

Extrapyramidal symptoms (EPS) were assessed through the use of the Simpson Angus Rating Scale (SARS) and the amount of use of benztropine in subjects participating in studies 114 and 115, two of the pivotal six week placebo controlled studies. The following were the results observed:

1. When considering only subjects not treated with benztropine in study 114, a higher percentage of subjects in the 80 mg bid dose group had SARS scores (indicating more symptomatology) than in the 40 mg bid dose group. Both ziprasidone treatment groups had consistently higher scores than placebo. (see Appendix 8.1.9.2a). In study 114, twice as many subjects in the ziprasidone groups (40 and 80 mg bid) required the use of benztropine than in the placebo group (see Section 7.2.2 for details).
2. Results of study 115 showed a higher percentage of subjects with an increased SARS score in all ziprasidone groups compared to placebo. In study 115, benztropine was required in the 100 mg bid group approximately 1.5 times more often than in placebo group subjects; the 20 and 60 mg bid ziprasidone group's use was comparable to placebo use (see Section 7.2.3 for details).

Akathisia, a symptom of EPS, was measured using the Barnes Akathisia Scale (BAS) in both studies 114 and 115; propranolol was the medication identified to treat akathisia in the study 114 protocol and was listed as the concomitant medication to be used for EPS in study 115. The following were the results observed:

- 1) In study 114, the percentage of subjects who had an increase in the BAS (including only subjects who had not taken beta-blockers) showed higher scores (indicating more symptomatology) in both ziprasidone treatment groups compared to the placebo group at the last visit (see Appendix 8.1.9.2b). In study 114, beta blocker use in the ziprasidone treatment groups increased with higher dosing and was utilized more frequently than in the placebo group (see section 7.2.2).
- 2) In study 115, fewer subjects in the ziprasidone treatment group had an increase in BAS scores in the compared to placebo (see Appendix 8.1.9.2b), while blocker use in the ziprasidone groups was similar in slightly lower than in the placebo group (see section 7.2.3).

In conclusion, results from study 114 reveal that subjects in the ziprasidone groups consistently experienced EPS and akathisia more than subjects in the placebo group. Results from study 115 show a higher experience of EPS in ziprasidone groups versus placebo, but not akathisia.

8.1.10 Withdrawal Phenomena/Abuse Potential

The sponsor did not study the abuse potential nor the effects of sudden or gradual discontinuation of ziprasidone treatment. There were no reported case of withdrawal reaction.

8.1.11 Human Reproduction Data

The sponsor did not address this topic in the ISS and a request for information was required. The following table summarizes the subjects known to become pregnant while taking ziprasidone .

Subject #	age	ziprasidone exposure	Outcome and comments
304(E)-00390345	33	Subject had taking ziprasidone 80 mg for eight months; undetermined when pregnancy occurred.	Uterine bleeding: 1 day after stopping ziprasidone Spontaneous abortion: 2 days after stopping ziprasidone.
115-07350541	26	1 st trimester (single 40 mg dose)	Term Infant with Tetralogy of Fallot
116B-0523003*	31	1 st trimester (160 mg x 8 days)	Abortion; no medical complications reported
301-02730246	28	1 st trimester (20 mg x 7 days)	Healthy baby girl

This represents a limited number of exposures during pregnancy; therefore, no definitive conclusions can be drawn from this data.

8.1.12 Overdose Experience

The sponsor reports in the Integrated Summary of Safety that there were three subjects taking ziprasidone who experienced an overdose; the sponsor does not offer a specific definition of overdose. It is possible that one subject (116B6220002) experienced the sequela of ataxia; otherwise, there is no apparent sequela in the subjects who overdosed with ziprasidone. The following table summarizes the overdose cases:

Subjects with overdose of ziprasidone

SUBJECT #	AGE/SEX	OVERDOSE MG	CONCOMITANT MEDICATIONS	COMMENTS
116B5870007	22/M	640 mg	lorazepam	Hospitalized for nausea, vomiting, shakiness, sweats, headache. Event resolved 4 days later, but treatment not recorded in submission.
116B6220002	28/M	480 mg	lorazepam, ranitidine, aluminum hydroxide/magnesium hydroxide	Leukocytosis (also observed one month prior to overdose), slowed speech and unsteady gait. Subject was hospitalized for observation and discharged 3 days later with ataxia. Follow-up information was not located in this submission.
116B5950022	29/M	1880 mg	lorazepam, acetaminophen, topical starch suppository	Reported to also take alcohol and paroxetine. No signs or symptoms present. ECG reported to be normal. Gastric lavage revealed no pills.

Subject who was over accidentally overmedicated with ziprasidone

SUBJECT #	AGE	OVERDOSE MG	CONCOMITANT MEDICATIONS	COMMENTS
116B06820005	52/M	200 mg qd x 2 weeks	lorazepam, benztropine, chloral hydrate	Dosage was supposed to be 80 mg qd. Subject hospitalized for ↑ insomnia, restlessness, and Parkinsonism.

8.1.13 Pediatric Studies

There were two studies (044 and 122) described in the user fee extension submission (1/23/98) in which pediatric subjects diagnosed with Tourette's Syndrome were exposed to ziprasidone (note: there was no data submitted for a trial in pediatric subjects suffering with psychosis).

In study 044, an open label single dose (up to 20 mg ziprasidone of a liquid suspension) pharmacokinetic study in 15 children ages 7-16 y.o. with Tourette's Syndrome, adverse events were: 1) a 15 year old with a

syncopal event 3 hours and 41 minutes after a single oral dose of 20 mg (which corresponds to the $t_{1/2}$ range of 3.3-4.7 hours determined in this study), 2) postural hypotension observed in 2 subjects, 3) somnolence seen in 10 of the 15 subjects, 4) an increase in prolactin levels observed in all subjects with a peak elevation at 2-4 hours post dosing, and 5) other events including nervousness, dizziness, nausea and abdominal pain. Of note, one subject (07440011) demonstrated pharmacokinetic data that reflected an exposure of up to 10 times greater than the exposure of subjects from the same treatment group of 10 mg ziprasidone; this subject's data was not incorporated into the preliminary report's calculations of mean pharmacokinetic data.

In study 122, a double blind, placebo controlled, 8 week flexible dose (maximum: 20 mg bid ziprasidone) trial, 16 pediatric subject (ages 7-16) with Tourette's Syndrome were exposed to ziprasidone. All of the subjects treated with ziprasidone experienced adverse events during the study; the most commonly reported was somnolence (12 of 16 subjects). Of note, one subject (07440020) developed a new onset of abnormal involuntary tongue movements (suggestive of a dyskinesia) on day 59 of ziprasidone treatment which continued until day 80 when he was treated with risperidone and buspirone and was discontinued from the study. Another subject (07430014) a 15 y.o. male developed gynecomastia. Other adverse events included: akathisia, insomnia, depression, dizziness, headache, arthralgia, urinary incontinence, and dysuria.

8.2 Adequacy of Patient Exposure and Safety Assessments

8.2.1 Adequacy of Clinical Experience

The clinical data of this NDA appears to be based on an adequate subject exposure of the adult population. The duration of exposure and the total number of subjects is comparable to other recently submitted NDAs for the indication of psychosis. The sponsor submitted more than one adequate and well controlled study to support the efficacy claims of ziprasidone.

Data from two pediatric studies (Studies 044 and 050) exposing ziprasidone to children with Tourette's Syndrome were included as part of the major amendment to the NDA which extended the User Fee Date by 3 months. The material submitted for this new molecular entity entailed an exposure of ziprasidone in 15 children with a single dose and 18 children exposed to ziprasidone for less than 60 days. Also, this amendment did not include any studies in children diagnosed with psychotic disorders, the indication for which this NDA has been submitted. Therefore, the pediatric data submitted thus far is not adequate to provide appropriate safety labeling for children and adolescents at this time.

8.2.2 Adequacy of Animal and/or In Vitro Testing

With respect to QTc prolongation, the preclinical cardiovascular testing in the original NDA submission did not include in vitro studies to assess ziprasidone's effect on potassium channels or on duration of action potential in Purkinje fibers. The sponsor was requested in a letter on October 3, 1997 to conduct these in vitro studies and to characterize the action potential duration in Purkinje fibers for ziprasidone, the major metabolites of ziprasidone and an active comparison group such as sotalol or terfenadine. The request suggested using multiple concentrations of each agent to generate dose response curves.

In a meeting package (2/13/98), the sponsor concluded that ziprasidone and the metabolite ziprasidone-sulfoxide did not demonstrate significant effects on the action potentials of Purkinje fibers in dogs; FDA cardiology consultants (HFD-110) expressed concern that the sponsor did not test a high enough concentration of ziprasidone in this study to fully characterize the effects of ziprasidone in the therapeutic dosage range (note: the sponsor has not submitted a study report for review). In a meeting with FDA and the sponsor (3/27/98), the sponsor presented a brief summary of data which suggested that ziprasidone may inhibit the I_{Kr} channel, an ion channel implicated in the process of QTc prolongation (no data was submitted for review).

8.2.3 Adequacy of Routine Clinical Testing

This submission was of adequate quality to be submitted for review. There were some concerns of what categories the sponsor chose for some serious adverse events; this is discussed in detail in section 8.1.2.1. Originally the sponsor submitted the data with the inclusion of clinical trials conducted by Drs.

....., it was requested that the sponsor re-evaluate the data excluding data from these sites. The sponsor concluded that the safety profile from Dr. site was consistent with the overall NDA data base. They also reported that the efficacy data was not significantly affected by the exclusion of Dr. data.

Most of the ECG recordings obtained in this data base were performed without regard for timing. There was no study which observed ECG recordings/QTc measurements at times of peak concentrations of ziprasidone. Also of concern is that no subject in these studies wore a Holter monitor. There is a possibility that QTc changes may have been more pronounced or perhaps evidence to the contrary could have been collected if ECGs had been collected just after peak doses were administered. A Holter monitor might have also provided insight into the multiple episodes of syncope observed if those patients had been monitored.

There were also a methodological flaw in the collection of the vital signs. Most of the vital signs recorded were done with sitting blood pressure rather than blood pressure recorded in the supine position; this does not allow for the most accurate assessment of orthostatic effects of ziprasidone. Also, in looking at the median changes from baseline of vital signs, the sponsor used observations that could have been recorded up to six days after the last day of study treatment; this may provide less accurate comparisons than could have been made if these measurements were recorded sooner given the half-life of this drug ($t_{1/2} = 6.6$ hours).

The elaborate system used by the sponsor for reporting clinical significance of laboratory values set up many restrictions that may not have captured laboratory abnormalities of interest. The criteria for a change from baseline for a baseline-abnormal subject appears extreme, and changes that may be concerning would not be picked up using this system. It would perhaps be more helpful to identify changes from baseline and use that as the criteria. It is curious that there were a significant number of subjects who had an abnormal baseline to merit different criterion; however, their laboratory values were not so abnormal that they were excluded from enrolling in the study. Also of note is that the last laboratory value was performed up to 6 days after the end of the study; some subjects may no longer have had appreciable plasma concentrations when the tests were performed, and the maximum effect of ziprasidone may not have been appreciated.

In the placebo controlled studies, there were only two subjects evaluated for prolactin studies; no thyroid studies were conducted in the placebo controlled studies. It would have provided more accurate information to assess these changes with placebo control studies; instead inference had to be made from a pool of data that included studies of different designs and duration.

8.2.4 Adequacy of Metabolic Workup

The sponsor conducted phase I studies in healthy adults testing the concomitant use of ziprasidone and carbamazepine, cimetidine, or Maalox ® in healthy adults. However, conclusions regarding concomitant use of carbamazepine was based on results from a study which used a dose which was lower than the recommended dosage range (please refer to Section 6.0 for detail). It would be most useful for the sponsor to test concomitant use of therapeutic doses of carbamazepine to make a more accurate conclusion of its effect.

8.2.5 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by New Drug; Recommendations for Further Study

For reasons discussed above, it would be helpful to assess ECG monitoring more closely with a Holter monitor to assess QTc changes during concentration peaks. One suggestion is to challenge subjects with higher doses to prove or disprove the existence of a dose effect changes of the QTc.

To further investigate the sponsor's claim that the QTc was not adequately tested in recently approved antipsychotic medications, it would be helpful to have a study characterizing the QTc of ziprasidone and other marketed drugs in which all ECGs were evaluated at a baseline after a wash out period. If all subjects in such a study were using a Holter monitor, it might provide clarity regarding each of these drugs effect on the QTc interval.

8.2.6 Assessment of Quality and Completeness of Data

No electronic data sets were made available as part of the electronic submission, and all data was assessed from the grouping done by the sponsor's tables. Therefore, the laboratory abnormalities were determined by the sponsor's fixed criterion.

There were some items that did not offer consistency in the NDA. As an example: the listing of cataracts in a summary analysis: in Table H.5.2a, there are no incidents of cataract reported in all phase I/II/III studies. However, in Table H.5.8a there is one listing for cataract in this pool of all phase II/III studies. The ISS gave only a cursory summary of rashes experienced in this data base, and more detail would be necessary to help characterize this adverse event.

Another example of inconsistency was the reporting of syncopal episodes. There were 3 subjects experiencing syncope found by review of the patient narratives (108-6050002, 108E-5550096, 108E-5780052) who were not listed in the sponsor's listing of subjects with adverse events (Appendix VI table 1b of sponsor's submission of 3/18/97). This leaves some question as to whether all syncopal episodes were considered when the calculation the total of subjects with syncope listed in their calculations of incidence (Table H.5.8a of sponsor's submission 3/18/97).

Given that there is so much concern for the effects of ziprasidone on QTc measurements, it would be most helpful for the sponsor to analyze and submit results of all ECGs that have been performed when a subject has been taking ziprasidone whether they have been obtained by scheduled or unscheduled visits. It would also be helpful to have subjects on Holter monitors especially if they are subjects who have already shown that they have ECG changes or symptoms such as syncope associated with the use of ziprasidone.

8.3 Summary of Selected Drug-Related Adverse Events

8.3.1 Sudden Death

The sudden unexpected death rate for the ziprasidone safety update is 9.1 SUD per 1000 subject years (7/2565) [note: the cut-off date for the deaths was 5/15/97; the sponsor did not respond to requests to specify the cut-off date for calculating the subject years (i.e. the denominator)] (see section 8.1.1, p.28).

There are a variety of classification schemes to determine sudden unexpected deaths. However, under the scrutiny of different classification schemes, ziprasidone's rate of SUD rate continues to present a signal of risk. As discussed in Section 8.1.1 (p.28), using the scheme of classification by Dr. J Boehm (HFD-120: 2/3/98), ziprasidone was found to have a SUD rate that was 6 times higher than the SUD rate from a pool of combined data of recently approved antipsychotic NDAs. The SUD rate calculated in section 8.1.1 (p.27) of this review utilized a less inclusive classification, and resulted in a similar SUD count as that provided by the sponsor (submission of 3/20/98: using 5/15/98 cut-off). Using this less inclusive SUD

count, ziprasidone continues to surpass the SUD rate of the recently approved antipsychotics olanzapine, risperidone, and quetiapine. The SUD rate of ziprasidone is comparable to sertindole, an antipsychotic NDA withdrawn by the sponsor because of safety concerns regarding QTc prolongation, high sudden death rates in clinical trials and post marketing data from the U.K. showing a high SUD reporting rate (see section 2.2, p. 2). Since ziprasidone is not currently marketed in any country, the SUD rate of ziprasidone used in the less monitored and less restricted environment of a marketed drug is not available at this time.

8.3.2 QTc prolongation

Clinically, Ziprasidone has been shown to prolong the QTc interval in a pool of the short term placebo controlled studies (see section 8.1.8.3.1, p. 45) compared to both placebo and haloperidol in a dose dependent manner. It must also be mentioned that there was no regard for the timing of the ECG in those studies and the effect of ziprasidone on the QTc at peak concentration of ziprasidone remains unknown. The sponsor expressed concern that NDA data bases from recently approved anti-psychotic agents utilized a different methodology to ascertain QTc prolongation--using screening ECGs rather than baseline readings which are recorded after a wash out period (see section 8.1.8.4, p. 46). However, when either screening or baseline QTc values are compared to the maximum QTc, ziprasidone increases the QTc values in a dose related fashion (although, the screening-to-maximum is of a lower magnitude).

Drug induced QTc prolongation may be correlated with the development of ventricular arrhythmia, syncope, and sudden death (Morganroth, 1993). Though the ziprasidone safety data base is limited, there is already a signal of a higher SUD rate when compared to other recently approved antipsychotic NDAs. No subject--not even subjects who experienced syncope--underwent Holter monitoring. Holter monitoring may have provided insight into the multiple episodes of syncope observed in this data base (see section 8.2.3 p.51).

Based on the evidence that ziprasidone has been shown to cause an increase in the QTc interval as a function of dose within the proposed therapeutic range (80-160 mg daily), Dr. C. Ganley, FDA cardiology consultant (HFD-110) concluded that there may be the usual risks observed with drugs which prolong the QT interval. He stated also that the labeling should clearly reflect this risk and that it may be necessary to consider this drug as a second line therapy if approved.

8.3.3 Hypotension/Syncope

Because ziprasidone demonstrates alpha adrenergic properties, it is not unexpected that orthostatic hypotension and syncope were observed as adverse events in this data base (see section 8.1.2.1, p. 29). It should be noted that most of the vital signs recorded in this data base were done with sitting blood pressure rather than blood pressure recorded in the supine position; therefore, orthostatic changes may not be completely appreciated (see section 8.2.3, p.51). Despite this methodological flaw, postural hypotension was seen to have a statistically significant dose response relationship (see section 8.1.5.5, p. 39).

Syncope was reported to occur in 0.7% (15/2140) of subjects in the phase II/III safety data base (cutoff 10/31/96), while hypotension (combining postural hypotension and hypotension) occurred in 2.5% (53/2140) of subjects in the phase II/III safety data base (as per sponsor's submission of 3/18/97: Table H.5.8). Postural hypotension occurred at a higher frequency in ziprasidone groups (1.3%) compared to placebo (0.4%) in the short term placebo controlled studies (Appendix 8.1.5.3).

There were 5 syncopal events and one hypotensive event considered to be serious adverse events (see section 8.1.2.1: p.29 and section 8.1.5.2 p. 37); however, it is unclear what criteria the sponsor used to report a syncopal event as a serious event. There were at least thirteen episodes of syncope in the Phase II/III data base that were not reported by the sponsor as a serious adverse event (see section 8.1.2.1: p.29). It is possible that the actual incidence of syncope may be higher than 0.7% because of an inconsistency found in the presentation of the safety data base (see section 8.2.6 p. 52).

It is also noted that syncope is associated with other drugs which prolong the QTc interval. Unfortunately, subjects who experienced syncope were not monitored more closely with a Holter to determine possible etiology of their syncopal events.

8.3.4 Rash

Rash was the most common adverse event resulting in withdrawal from the ziprasidone treatment groups (see 8.1.3.2, p.36). When viewing the sponsor's table of incidence of treatment emergent adverse events (submission 3/18/97: Table H.5.8a), events related to skin and appendages occurred in 10.2 % (218/2140) of subjects. The 1 % table states that rashes occurred in 4.1% (29/702) of ziprasidone subjects in the short term placebo controlled studies, compared to the placebo rate at 3.3% (see Appendix 8.1.5.3). There also was a dose response relationship seen with the occurrence of rashes (see section 8.1.5.5 p. 39).

There were 21 subjects who discontinued for rashes in the originally submitted integrated safety data base; the haloperidol group only had 2 withdrawals, while the placebo group had 1 withdrawal. It was left to the investigator's discretion as to whether or not an event was reported as serious, and there did not appear to be any consistent feature that merited reporting a rash as a serious event (see section 8.1.2.2, p.30).

It was necessary for this reviewer to go through the line listings of subjects with adverse events (sponsor's submission of 3/18/98: Appendix VI Table 1b) and then follow this up with relevant patient profiles in order to gain a better understanding of the rashes in this NDA data base. This review revealed that there were several subjects whose rash was accompanied by an elevated white blood count, and at least two subjects with rash whose eosinophil count was elevated. Most cases of rash resolved within one week of discontinuing ziprasidone; one subject experienced "bullous drug eruptions/ pruritic blisters with post-excoriated papules" on the hands, wrist, scalp, and neck which resolved 24 days after discontinuing ziprasidone. Medications used to treat rashes included steroids (oral and topical) and antihistamines. Three subjects required prolonged hospitalization to observe their rashes. (See section 8.1.2.2, p.31)

Since the sponsor's summary of the rashes in the ISS was found to be inadequate, it is recommended that the sponsor compile a detailed and thorough summary of the description, duration, related hospitalizations, severity, accompanying symptoms, treatment and resolution history of all cases of rashes observed in this NDA safety data base.

8.3.5 Seizure

In the safety update (submitted 8/29/97), the sponsor reported that 1.8 subjects per 100 subject years (12/772) or 0.54 % (12/2588) of the subjects in the NDA data base experienced a seizure while taking ziprasidone. The original NDA-submission (3/18/97) includes six subjects who discontinued as a result of their seizure or possible seizure activity. The safety update did not include specific subject information (see section 8.1.2.7, p. 34). If using ziprasidone, caution would be required for patients with a history of seizure disorder.

8.3.6 Cholesterol/triglyceride elevation

In the short term placebo controlled trials, the ziprasidone groups were shown to have statistically significant increases in both cholesterol and triglyceride when compared to placebo with respect to numbers of patients exceeding threshold values. Cholesterol levels were observed in 2 % (16/685) whereas placebo had 0%. Triglycerides increased in 12 % (85/684) of the ziprasidone subjects in these trials compared to an increase in 7 % observed in the placebo group (see section 8.1.6.3.2, p. 40 and Appendix 8.1.6.3.2c). The increase in cholesterol and triglyceride levels is not listed in the sponsor's 1 % table (Appendix 8.1.5.3) which should be corrected. Increased cholesterol and triglyceride levels may be considered risks for the development of atherosclerosis.

8.3.7 Hyperprolactinemia

Prolactin studies were monitored in only two subjects in the short-term placebo controlled studies, one of which was found to have abnormal values. Therefore, it is necessary to look at the total pool of oral dosing phase II/III studies; clinically significant abnormalities were identified in 20% (148/741) of ziprasidone subjects whose prolactin levels were monitored (see section 8.1.6.4, p. 42 and Appendix 8.1.6.4).

Amongst the sponsor's literature review were two studies (Bench, 1996; Bench, 1993) which reported large elevations of prolactin levels when comparing baseline and peak plasma levels of ziprasidone in twelve normal volunteers taking between 5 and 60 mg of a single dose of ziprasidone (see section 5.2.3 p.6).

An increase in prolactin levels was observed in all subjects with a peak elevation at 2-4 hours post dosing in a single dose pediatric study of 15 children ages 7-16 y.o (Study 044). Gynecomastia was observed in one 15 y.o. male with Tourette's Syndrome in Study 122. (see section 8.1.13, p. 49)

As many neuroleptics are associated with hyperprolactinemia, it is not surprising to observe this effect with use of ziprasidone.

8.3.8 Transaminases elevation

An elevated SGOT (AST) levels were observed in 0.3 % (6/1780) of subjects in the phase II/III study data base. Elevated levels of SGPT (ALT), a more specific enzyme indicative of hepatic cell activity, was observed in 2% (17/1776) of the subject in the phase II/III data base (sponsor's submission 3/18/97: Table H.5.18a.2).

Section 8.1.6.3.3 (p.41) provides a listing of subjects who dropped out because of abnormal liver enzymes; there were several subjects whose liver function studies elevated while taking ziprasidone and normalized one to twenty days after discontinuing ziprasidone, suggesting a positive dechallenge and drug relatedness. There were two subjects in this listing who were noted to have jaundice accompanying elevated LFTs; there was inadequate follow up reported for subject 301-2790615 (safety update) which would be required for complete assessment. Cases which the sponsor considered to manifest serious adverse event of elevated transaminase is found in section 8.1.2.4 (p.32). It is unclear how the sponsor determined whether or not a laboratory value was considered a serious adverse event.

Also of note is the case of a 49 y.o. female (subject 307-2690047) who eventually died of hepatic coma, cholestatic jaundice and malignant neoplasm 95 days after stopping ziprasidone. Her initial symptoms of jaundice and elevated AST (244 U/L) and ALT (375 U/L) first appeared after 196 days of taking a daily dose of 100 mg ziprasidone. It may be possible that the ziprasidone aggravated her already compromised liver.

8.3.9 Weight Gain

Weight gain of $\geq 7\%$ was observed in 10 % (61/622) of subjects taking ziprasidone in the short term placebo controlled phase II/III studies (see section 8.1.7.3.1, p. 43). There was a statistically significant increase in weight gain found in subjects taking ziprasidone compared to placebo. It is noted that weight gain in not recorded in the sponsor's 1 % table (Appendix 8.1.5.3) and fits the criteria to be considered a common and drug-related adverse event (see 8.1.5.4, p.39).

8.3.10 Extrapyramidal Symptoms (EPS)

EPS was observed often enough in the ziprasidone safety data base to be considered a common and drug-related adverse event (see 8.1.5.4, p.39). Its incidence was found to be 5 % (33/702) of the ziprasidone subjects in the short term placebo controlled phase II/III studies . As can be seen in the 1 % table, associated symptoms of akathisia, dystonia, and hypertonia were observed at higher rates in the ziprasidone group compared to the placebo group (see Appendix 8.1.5.3).

EPS and akathisia, a symptom of EPS, were assessed in studies 114 and 115 using rating scales and use of concomitant medications (see section 8.1.9.2, p.48). It was found in studies 114 and 115 that subjects in the ziprasidone groups consistently experienced EPS to a greater magnitude than in the placebo groups. Study 114 results revealed that akathisia was experienced more often in the ziprasidone treatment groups, whereas study 115 did not support this conclusion.

A listing of subjects whose EPS was considered a serious adverse event can be found in Section 8.1.2.6 (p.33).

8.3.11 Neuroleptic Malignant Syndrome (NMS)

Although the ISS did not identify any cases of NMS, a review of the patient narratives revealed two subjects whose adverse event description could be categorized as NMS. These cases are also summarized in section 8.1.2.5 (p.31).

8.3.12 Somnolence

Somnolence was found to be a common and drug-related adverse event (see 8.1.5.4, p.39). It was also found to have a dose response relationship (see Section 8.1.5.5, p. 39). Somnolence was observed in 14.4% (101/702) of subjects in the ziprasidone group in the short term placebo controlled phase II/III studies (see Appendix 8.1.5.3)

8.3.13 Tardive Dyskinesia

Tardive Dyskinesia is associated with the use of most neuroleptics and the symptoms may be masked by the use of antipsychotics. It is difficult to determine ziprasidone's potential to cause tardive dyskinesia as most of the controlled safety data base is of short duration of exposure.

Of note, one subject (07440020) in pediatric study 122 developed a new onset of abnormal involuntary tongue movements (suggestive of a dyskinesia) on day 59 of ziprasidone treatment which continued until day 80 when he was treated with risperidone and buspirone and was discontinued from the study (see Section 8.1.13, p. 49). More information is needed from the sponsor to characterize this episode more clearly.

8.3.14 Aspiration Pneumonia

Aspiration pneumonia has been associated with neuroleptic use and should be considered as a possible adverse event. There were two cases of pneumonia seen in the ziprasidone safety data base (see section 8.1.2.6, p. 33). As a related symptom, cough was seen to increase in 2.6 % (18/702) of the ziprasidone subjects (compared to 0.7 % placebo subjects) in the short term placebo controlled phase II/III studies (see 1 % table: Appendix 8.1.5.3).

9.0 Labeling

If approved, the sponsor's labeling will need considerable revision. Please see section 8.3 for important concerns that need to be addressed in labeling.

10.0 Conclusions

In the wake of the uncertainty and disagreement in the cardiology community of the effects of a dose dependent QTc prolongation caused by a drug, it is difficult to determine whether this quality of ziprasidone presents a major health hazard. Clearly, more understanding and research (using consistent methodology) are needed to clarify this issue for ziprasidone as well as any antipsychotic which may have this potential. What is striking about ziprasidone is that an effect of QTc prolongation was observed in the short term placebo controlled studies irrespective of methodology (i.e. the QTc interval is prolonged when both screening-to-maximum and baseline-to-maximum measurements are made). Another relevant detail regarding ziprasidone's ability to prolong the QTc is that it has been found to be dose-dependent within the therapeutic dosing range in short term placebo controlled studies.

An important factor that must be considered in reviewing the safety of this drug is the sudden unexpected death (SUD) rate. It is concerning and alarming to view the ziprasidone safety data base against other recently reviewed antipsychotic NDA safety data bases. Even under different methods of SUD analysis, the rate of ziprasidone's SUDs clearly surpass similar drugs that have been recently approved.

In clinical practice, it is always important to weigh the balance of risks and benefits for each medication prescribed to a patient. There are currently 15 antipsychotic medications marketed in the USA, and physicians continue to struggle with finding adequate treatment for many schizophrenic patients who do not respond or cannot be treated by the available armamentarium of medications. It may be that ziprasidone would offer a unique treatment in individual cases. However, thus far, the sponsor has not shown that ziprasidone is of benefit to subjects who are refractory towards treatment with other available antipsychotic medications.

Although the sponsor may be claiming that the mean weight gain observed in the ziprasidone NDA safety data base reflects less of an increase than other marketed antipsychotics, ziprasidone is associated with weight gain. Weight gain of $\geq 7\%$ was observed in 10% of subjects taking ziprasidone in the short term placebo controlled phase II/III studies, and this was shown to be statistically significant when compared to placebo.

Also, ziprasidone possesses the ability to induce extrapyramidal symptoms.

Ziprasidone has been shown to be effective in the treatment of schizophrenia in two placebo controlled studies. However, the risks appear numerous. Of most concern are the qualities it shares with sertindole, an antipsychotic NDA which was withdrawn by the sponsor because of safety concerns regarding QTc prolongation and high sudden death rates in clinical trials and post marketing data from the U.K. Since ziprasidone is not currently marketed in any country, we do not have the insight as to how this drug would affect a large population in an environment less monitored, less restricted and without a mechanism for informed consent.

11.0 Recommendations

According to Section 505 [355] of the Federal Food, Drug, and Cosmetic Act (July, 1993), approval of an application may be denied if the sponsor has not employed "adequate tests by all methods reasonably applicable" to show that the drug is "safe for use under the conditions prescribed, recommended or suggested in the proposed labeling," or if there is "insufficient information to determine whether such drug

is safe for use under such conditions." In the ziprasidone safety data base, there are still many uncertainties regarding the QTc prolongation, the etiologies of syncopal episodes (no Holter monitoring was used in the current safety data base), and the signal presented by the high sudden unexpected death rate.

Ziprasidone has been shown to be effective in schizophrenic patients yet it presents safety risks of unknown magnitude. Given that there are many antipsychotic drugs available whose NDA data base did not possess the qualities of both a high SUD rate and the ability to cause a dose dependent QTc prolongation, the risk benefit ratio does not support ziprasidone as a first line drug. To overcome the risk/benefit ratio, the sponsor would need to show that it can effectively treat patients who fail on other drugs. Even if approved as a second line drug, the risks of syncope, ventricular arrhythmias, or sudden unexpected death need to be clearly stated in the labeling so as to alert physicians, thus enabling them to monitor patients appropriately. In light of the uncertainty of its safety profile and the unknown effectiveness in refractory patients, it is recommended that ziprasidone not be approved at this time.

/S/

4/30/98

Roberta L. Glass, M.D.
Medical Officer, Division of Neuropharmacological Drug Products

NDA 20-825
Div File
HFD-120:Laugren/Hardeman/Mosholder/Burkhart/Boehm/Glass

5-8-98

While I am also concerned about the potential for cardiovascular risk associated with the use of ziprasidone, I do not believe this potential risk precludes entirely the possibility of approving this product. In my memo to the file, I have provided an alternative discussion of the data and issues pertinent to cardiovascular risk for ziprasidone, and I have provided a draft of labeling that I believe adequately describes the potential risks with ziprasidone and restricts its use in a way that makes it possible for it to be used in a reasonably safe manner for patients who fail on other products.

/S/

Team Leader, PDP

MD

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Appendix 5.1.1.1 Summary of all trials (adapted from the sponsor's submission of 10/27/97; cut off date is 5/15/97).

	Ziprasidone	Haloperidol	Risperidone	Amisulpride	Other	Placebo
Phase I Studies (Clinical Pharmacology)						
Single Dose Studies	409	4			38	71
Multiple Dose Studies	333				11	78
Subtotal: Phase I Studies	742	4			49	149
Phase II/III Studies						
Oral Studies						
Placebo Controlled Studies						
Short-term Fixed-Dose Studies (1)	702					273
Long-term Fixed-Dose Studies (2)	246 [27]					84 [9]
Short-term Flexible-Dose Studies (3)	16					12
Long-term Flexible-Dose Studies (4)	17					10
Active Controlled Studies						
Short-term Fixed-Dose Studies (5)	683	340				
Short-term Flexible-Dose Studies (6)	199	6	147	49		
Long-term Flexible-Dose Studies (7)	1252 [609]	267 [28]	156 [8]			
Uncontrolled Studies						
Short-term Studies (8)	86					
Long-term Studies (9)	6 [6]					
Subtotal: Oral Studies	2565*	585	295	49		370
Dementia Patient Studies						
Short-term Flexible-Dose Studies (10)	11					12
Single Dose Total	409	4			38	71
Multiple Dose Total	2909	585	295	49	11	531
Grand Total	3318	589	295	49	49	602

Numbers in brackets represent the number of subjects included in the unbracketed number whose participation was in a continuation study under the same treatment as the parent study and are also counted in the parent study category for that treatment. These subjects are counted only once in totals and subtotals. Protocol 115 subjects taking ziprasidone are counted in categories (1) and (4) but are counted only once in totals and subtotals.

- (1) Includes studies 104, 106, 114, 115
- (2) Includes studies 104E, 106E, 303
- (3) Includes studies 122
- (4) Includes studies 307
- (5) Includes studies 101, 115, 301
- (6) Includes studies 111, 302, 305
- (7) Includes studies 116B, 117, 108, 108E, 304, 302E, 304E
- (8) Includes studies 015, 102, 109, 110, 118
- (9) Includes studies 109E
- (10) Includes studies 105

*Does not include Studies 105 (n=11) and 120 (n=12)

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Appendix 5.1.1.2 Table of all studies (adapted from sponsor's submission of 10/24/97)

Pfizer Central Research Sponsored Phase I Clinical Pharmacology Studies	
128-001-US	Double-blind, placebo-controlled, parallel, single rising oral dose trial; healthy men (Ziprasidone: n=40, pbo: n=20); ziprasidone doses (0.5, 1, 2.5, 10, 20, 40, 60, 80, 100 mg oral suspension).
128-002-US	Double-blind, pbo-controlled, multiple oral dose trial; healthy men (Ziprasidone: n=18, pbo n=5); ziprasidone dose range (20 mg qd to 40 mg bid) 18 days.
128-004-US	Open, randomized, 3-way crossover, single oral dose trial; healthy men (n=9); ziprasidone dose (suspension-fasting: 20 mg, capsule fasting: 20 mg, capsule-fed: 20mg).
128-005-US	Double-blind, pbo-controlled, multiple oral dose, parallel trial; healthy men (ziprasidone n=18, pbo: n=4); Ziprasidone dose range (20 mg qd to 80 mg bid), 18 days.
128-006-US	Open, non-randomized, 6-way crossover, single oral dose trial; healthy men (n=45); Ziprasidone dose (capsule-fed: 20mg; capsules-fasting: 40mg; capsules-fasting: 80mg; capsules-fed: 80 mg).
128-007-US	Open, three-way, crossover, oral single dose trial; healthy men (n=28); Ziprasidone dose (fasting: 20mg; fed: 20mg; 2 hr after meal: 20mg).
128-008-US	Open, non-randomized, crossover oral single dose trial comparative to Haloperidol; healthy men (n=5); Doses (Ziprasidone: 40mg; Haloperidol: 75 mg).
128-009-US	Double-blind, pbo-controlled, randomized, single oral dose, parallel trial comparative to Diazepam; healthy subjects (Ziprasidone: n=30, Diazepam: n=30; Pbo n=30); doses (Ziprasidone 20mg; Diazepam: 10mg).
128-010-US	Open, randomized, two-way crossover, single oral/IV dose; healthy men (Oral: n=12, IV: n=12); dose (capsules 20mg; IV: 6mg)
128-011-US	Open, randomized three-way crossover, oral single dose trial; healthy men (n=90); Ziprasidone dose (4x6 mg tablet, 1x20 mg tablet, 1x20 mg capsule).
128-013-US	Double-blind, pbo-controlled, multiple oral dose trial; healthy men (Ziprasidone n=29; pbo: n=10); Ziprasidone dose range (5 mg qd to 60 mg bid).
128-014-US	Open, randomized, two-way crossover, single oral dose trial, healthy men (n=12); Ziprasidone dose (2x20 mg capsule, 1x40 mg capsule).
128-015-US	Double-blind, pbo-controlled, multiple oral dose trial; subjects with schizophrenia or schizoaffective disorder (n=33); Ziprasidone dose (titrated to 160 mg/day), 24 days.
128-016-US	Open, randomized, six-way crossover single oral/IV/Nasocentrio infusion trial; Healthy men (n=28); Ziprasidone dose (20 mg).
128-017-US	Open, parallel, oral single dose, PET Scan study; healthy men (n=10); Ziprasidone dose (2x40mg capsule); PET Scan performed at 4, 8, 12, and 18 hours post-dosing.
128-018-US	Open, randomized, two-way crossover, oral single dose, healthy men (n=12); Ziprasidone dose (3x20 mg capsules and 1x 60 mg capsule).
128-019-US	Open, randomized, two-way crossover oral single dose, healthy men (n=11); Ziprasidone dose (4x20 mg capsules and 1x80 mg capsule).
128-020-US	Open, non-randomized, single oral dose trial; healthy men (n=4); ¹⁴ C/ ³ H-ziprasidone dose (20 mg oral suspension).
128-021-US	Open, randomized, two-way crossover, single oral dose fasting/fed trial; healthy men (n=12); Ziprasidone dose (40 mg tablet).
128-022-US	Open, randomized, two-way crossover, single oral dose fasting / fed trial; healthy men (n=12); ziprasidone dose (40 mg tablet).
128-023-US	Open, randomized, two-way crossover, single oral dose fasting / fed trial; healthy men (n=12); ziprasidone dose (40 mg tablet).
128-024-US	Open, randomized, two-way crossover, single oral dose fasting / fed trial; healthy men (n=12); ziprasidone dose (40 mg tablet).
128-025-US	Open, randomized, placebo-controlled, parallel, lithium interaction trial; healthy men (Ziprasidone + Lithium: n=12, pbo + Lithium: n=13); ziprasidone dose (2 x 20 mg capsules bid).
128-026-US	Open, parallel, multiple dose steady-state PK trial; healthy and renally impaired subjects (Group 1 CL _r >70: n=10, Group 2 CL _r 30-60: n=9, Group 3 CL _r 10-29: n=11, Group 4 hemodialysis: n=9); ziprasidone dose (20 mg capsules bid).
128-027-US	Open, non-randomized, single oral dose trial; healthy men (n=4); ¹⁴ C/ ³ H-ziprasidone dose (20 mg oral suspension).
128-028-US	Open, parallel, multiple dose PK trial; healthy elderly (n=16) and young (n=19) subjects; ziprasidone dose (20 mg capsules bid).
128-029-US	Open, randomized, two-way crossover, single oral dose fasting / fed trial; healthy men (n=12); ziprasidone dose (40 mg oral suspension).
128-030-US	Open, parallel, multiple dose PK trial; healthy (n=14) and cirrhotic (n=16) subjects; ziprasidone dose (20 mg capsules bid).
128-031-US	Open, randomized, two-way crossover, single oral dose trial; healthy subjects (n=23); ziprasidone dose (capsules: 20 mg research vs, 20 mg commercial).
128-032-US	Open, non-randomized, cross-over, single intravenous escalating dose trial; subjects with schizophrenia or schizoaffective disorder (n=6); ziprasidone doses (2.5, 5, 10, 20, 40 mg).
128-033-UK	Investigator-blind, placebo-controlled, single escalating intramuscular dose trial; healthy males (Ziprasidone: n=16, pbo: n=6); ziprasidone doses (5, 10, 20 mg).
128-034-US	Open, randomized, two-way crossover, single oral dose trial; healthy subjects (n=12); ziprasidone doses (2 x 20 mg capsules vs 40 mg oral suspension).
128-035-US	Open, randomized, two-way crossover, multiple oral dose trial; healthy subjects (n=12); ziprasidone dose (20 mg research capsules bid vs. 20 mg commercial capsules bid).

Ongoing Japanese Trials Contributing Safety Data in Original NDA Submission
 (Japanese data reported separately and not incorporated into the NDA project database)

Pfizer Japan Sponsored Phase I Clinical Pharmacology Studies	
Pfizer Japan Sponsored Phase II/III Clinical Studies	

Additional Trials Reflected in Four-Month Safety Update
 ("n" reflects number of subjects in project database as of May 15, 1997 data cutoff)

Pfizer Central Research Sponsored Phase I Clinical Pharmacology Studies	
128-045-US	Open, randomized, three-way crossover, multiple dose trial; healthy subjects (n=13); ziprasidone doses (cross-linked capsules: 20 mg, uncross-linked capsules: 20mg).
128-050-US	Open, randomized, two-way crossover, multiple dose ketoconazole interaction trial; healthy subjects (n=14); ziprasidone dose (2 x 20mg capsules).
Pfizer Central Research Sponsored Phase II/III Studies	
128-307-EU	Fifty-two week, double-blind, randomized, flexible-dose, placebo-controlled trial; subjects with chronic or subchronic schizophrenia (Ziprasidone: n=17, pbo: n= 10); ziprasidone doses (40-60, or 80-100 mg qd).
128-308-EU	Open, flexible-dose, extension trial; subjects with non-organic psychosis (n=0); ziprasidone dose (20-100 mg bid).
Pfizer Japan Sponsored Phase II/III Clinical Studies	
JP-06-602	Fifty-two week, open, flexible-dose, extension trial (n=0); ziprasidone dose (20-60mg bid).

Trials Contributing Safety Data to Original NDA but not to Four-Month Safety Update
 (Data from these trials are now contained in a separate intramuscular database)

128-120-South Africa	Five-day, open, non-randomized intramuscular to oral dose trial; subjects with psychosis (n=12); ziprasidone doses (intramuscular: 2.5 to 20 mg bid to qid, oral: 20 to 60 mg bid).
128-121-US	Open, randomized, haloperidol-controlled, multiple dose intramuscular and oral trial; subjects with psychotic disorder (n=0); ziprasidone doses (20 to 80 mg IM up to qid, 20 to 100 mg oral capsules bid).

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Appendix 5.1.2.1 Demographics of subjects exposed to ziprasidone in Phase I clinical trial (adapted from sponsor's electronic submission)

Demographic Characteristics
All Clinical Pharmacology Studies

	Ziprasidone			Haloperidol			Other		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number of Subjects	596	119	715	4	0	4	44	5	49
Age (years):									
<18 years	4	2	6	0	0	0	0	0	0
18-64 years	576	104	680	4	0	4	44	5	49
65-74 years	16	12	28	0	0	0	0	0	0
>=75 years	0	1	1	0	0	0	0	0	0
Mean age (years)	29.5	36.0	30.6	30.0		30.0	27.2	27.0	27.2
Age range	14-74	11-76	11-76	25-40		25-40	18-40	20-37	18-40
Race:									
Asian	5	1	6	0	0	0	2	1	3
Black	69	5	74	0	0	0	4	2	6
Caucasian	458	102	560	4	0	4	33	2	35
Other	64	11	75	0	0	0	5	0	5
Mean weight (kg)	76.0	64.6		79.5			78.0	59.7	
Weight range	49-115	34-92		68-93			57-98	48-69	

(CONTINUED)

The numbers in each treatment group may not match the sum of the IM, IV and ORAL groups in the Route of Administration table, since some subjects are counted in more than one of these groups.

Protocols: 001,002,004,005,006,007,008,009,010,011,013,014,016,017,018,019,020,021,022,023,024,025,026,027,028,029,030,031,032,033,034,035,036,037,038,039,040,041,043,044,047,048,049,201,202,203

	Placebo		
	Male	Female	Total
Number of Subjects	111	24	135
Age (years):			
<18 years	0	0	0
18-64 years	111	24	135
65-74 years	0	0	0
>=75 years	0	0	0
Mean age (years)	28.0	28.5	28.1
Age range	18-45	22-45	18-45
Race:			
Asian	1	0	1
Black	15	1	16
Caucasian	86	23	109
Other	9	0	9
Mean weight (kg)	76.0	64.8	
Weight range	54-98	50-82	

The numbers in each treatment group may not match the sum of the IM, IV and ORAL groups in the Route of Administration table, since some subjects are counted in more than one of these groups.

Protocols: 001,002,004,005,006,007,008,009,010,011,013,014,016,017,018,019,020,021,022,023,024,025,026,027,028,029,030,031,032,033,034,035,036,037,038,039,040,041,043,044,047,048,049,201,202,203

Date of Table Generation: 10JAN97

Appendix 5.1.2.2 Demographic profile for Phase II/III trials (adapted from sponsor's submission of 8/29/97)

Demographic Characteristics

All Oral Dosing Phase II/III Studies

	Ziprasidone			Haloperidol			Risperidone		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number of Subjects	1824	741	2565	391	194	585	203	92	295
Age (years):									
<18 years	15	2	17	0	0	0	0	0	0
18-64 years	1774	711	2485	387	189	576	203	87	290
65-74 years	31	24	55	3	4	7	0	4	4
>=75 years	4	4	8	1	1	2	0	1	1
Mean age (years)	38.1	41.9	39.2	37.2	41.0	38.5	35.7	39.6	36.9
Age range	7-78	11-82	7-82	18-75	18-82	18-82	18-64	18-75	18-75
Race:									
Asian	32	10	42	9	4	13	4	4	8
Black	267	110	377	48	24	72	11	11	22
Caucasian	1403	598	2001	323	163	486	169	76	245
Other	122	23	145	11	3	14	19	1	20
Mean weight (kg)	79.2	72.8		80.0	73.0		82.2	72.6	
Weight range	27-163	35-145		38-149	40-151		48-159	40-123	

(CONTINUED)

Protocols: 015, 101, 102, 104, 104E, 106, 106E, 108, 108E, 109, 109E, 110, 111, 114, 115, 116B, 117, 118, 122, 301, 302, 302E, 303, 304, 304E, 305, 307

Date of Table Generation: 27JUN97

Four month safety update - cumulative
Demographic Characteristics

All Oral Dosing Phase II/III Studies

	Amsulpride			Placebo		
	Male	Female	Total	Male	Female	Total
Number of Subjects	29	20	49	281	89	370
Age (years):						
<18 years	1	0	1	8	4	12
18-64 years	28	20	48	266	82	348
65-74 years	0	0	0	6	3	9
>=75 years	0	0	0	1	0	1
Mean age (years)	38.0	34.8	36.7	39.1	41.8	39.7
Age range	8-55	24-48	8-55	8-76	10-70	8-76
Race:						
Asian	0	0	0	6	2	8
Black	0	0	0	50	18	68
Caucasian	29	20	49	203	64	267
Other	0	0	0	22	5	27
Mean weight (kg)	74.8	67.4		78.3	70.4	
Weight range	50-103	55-86		25-133	35-118	

Protocols: 015, 101, 102, 104, 104E, 106, 106E, 108, 108E, 109, 109E, 110, 111, 114, 115, 116B, 117, 118, 122, 301, 302, 302E, 303, 304, 304E, 305, 307

Date of Table Generation: 27JUN97

Appendix 5.1.3.1 Number of all subjects in phase I trials taking ziprasidone (adapted from sponsor's submission)

Modal Daily Dose and Duration of Ziprasidone Treatment
All Multiple Dose Clinical Pharmacology Studies

	<40mg	40mg	80mg	Modal Total Daily Dose Per Subject			240mg	320mg	Total (%)	
				120mg	160mg	200mg				
Number of Subjects with Treatment Duration										
<= 1 day	6	2	0	0	0	0	0	0	8	(2.6)
2-7 days	2	70	1	0	0	0	0	0	73	(23.9)
8-14 days	0	122	47	0	0	0	0	0	169	(55.2)
15-28 days	6	14	15	13	8	0	0	0	56	(18.3)
29-60 days	0	0	0	0	0	0	0	0	0	(0.0)
61-90 days	0	0	0	0	0	0	0	0	0	(0.0)
91-180 days	0	0	0	0	0	0	0	0	0	(0.0)
181-360 days	0	0	0	0	0	0	0	0	0	(0.0)
>= 361 days	0	0	0	0	0	0	0	0	0	(0.0)
Number of Subjects (%)	14 (4.6)	208 (68.0)	63 (20.6)	13 (4.2)	8 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	306 (100.0)	
Mean Duration	8	8	13	1R	1R	n	n	n	1n	
Range										

Subjects with a modal daily dose not represented above are included in the next lowest dose category.
Protocols: 002,005,013,025,026,028,030,035,040,041,043,047,049,203
Date of Table Generation: 10JAN97

Appendix 5.1.3.2 Number of all subjects in phase II/III trial taking ziprasidone (adapted from sponsor's submission)

Four month safety update - cumulative
Modal Daily Dose and Duration of Ziprasidone Treatment
All Oral Dosing Phase II/III Studies

	<40mg	40mg	80mg	Modal Total Daily Dose Per Subject			240mg	320mg	Total (%)	
				120mg	160mg	200mg				
Number of Subjects with Treatment Duration										
<= 1 day	5	7	2	0	0	0	0	0	14	(0.5)
2-7 days	43	84	77	16	5	1	0	0	226	(8.8)
8-14 days	18	59	86	32	20	13	0	0	228	(8.9)
15-28 days	47	103	126	51	64	26	0	0	417	(16.3)
29-60 days	15	59	182	105	116	74	1	0	552	(21.5)
61-90 days	0	91	62	84	52	88	0	0	377	(14.7)
91-180 days	0	21	101	30	45	21	0	0	218	(8.5)
181-360 days	2	24	126	47	62	20	0	0	281	(11.0)
>= 361 days	1	40	89	28	78	16	0	0	252	(9.8)
Number of Subjects (%)	131 (5.1)	488 (19.0)	851 (33.2)	393 (15.3)	442 (17.2)	259 (10.1)	1 (0.0)	0 (0.0)	2565 (100.0)	
Mean Duration	30	80	119	108	156	98	59	0	110	
Range										

Subjects with a modal daily dose not represented above are included in the next lowest dose category.
Protocols: 015,101,102,104,104E,106,106E,108,108E,109,109E,110,111,114,115,116B,117,118,122,301,302,302E,303,304,304E,305,307
Date of Table Generation: 27JUN97

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Appendix 7.2.1.2
(from Sponsor's Submission)

Subject Disposition
Ziprasidone Protocol 106

Treatment Group	Number of Subjects		Number of Subjects Completing Each Period of Study*			
	Randomized	Treated	Week 1	Week 2	Week 3	Week 4
Ziprasidone, 20 mg BID	44	44	42	39	33	28
Ziprasidone, 60 mg BID	47	47	42	38	28	24
Placebo	48	48	44	38	28	24
Total:	139	139	128	115	89	76

*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, 15, 16. Date of Data Extraction: 18SEP95. Date of Table Generation: 15JAN96.

Appendix 7.2.1.3
(from Sponsor's Submission)

Demographic Characteristics
Ziprasidone Protocol 106

	Ziprasidone 20 mg BID			Ziprasidone 60 mg BID			Placebo		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number of Subjects Randomized	30	14	44	39	8	47	41	7	48
Age (years):									
18-44	24	7	31	29	2	31	32	4	36
44-64	5	7	12	10	6	16	8	3	11
>=65	1	0	1	0	0	0	1	0	1
Mean age (years)	38.6	44.6	40.5	37.0	47.5	38.8	38.2	43.7	39.0
Age range	25-65	21-60	21-65	19-59	23-57	19-59	21-67	29-57	21-67
Race:									
Caucasian	22	9	31	26	8	34	29	6	35
Black	5	5	10	9	0	9	7	1	8
Oriental	0	0	0	2	0	2	3	0	3
Other	3	0	3	2	0	2	2	0	2
Mean weight (kg)	79.9	67.8		79.0	74.0		80.3	64.5	
Weight range	59-138	41-91		56-126	44-108		52-108	54-79	

Source Data: APPENDIX V - TABLE 2 Date of Data Extraction: 05SEP95 Date of Table Generation: 12SEP95

BPRS Total Score Study 106
(from Sponsor's Submission)

BPRS Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 106

Treatment Groups	Treatment Week									
	Baseline		Week 1		Week 2		Week 3		Week 4	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone										
20 mg BID	43	36.5	42	-3.8	39	-5.4	33	-9.0	28	-8.9
60 mg BID	41	36.6	41	-5.6	38	-7.3	27	-12.4	24	-16.0
Placebo	47	37.0	44	-4.0	37	-6.1	28	-8.0	24	-9.4

2-Sided P-Values for Pairwise Comparisons

Ziprasidone 20 mg BID vs placebo	0.838	0.923	0.767	0.395	0.747
Ziprasidone 60 mg BID vs placebo	0.874	0.423	0.373	0.098	0.018

Source Data: Appendix V Table 15. Date of Data Extraction: 15DEC95.
Date of Table Generation: 23MAY96.

BPRS Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 106

Treatment Groups	Treatment Week									
	Baseline		Week 1		Week 2		Week 3		Week 4	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone										
20 mg BID	43	36.5	43	-3.7	43	-4.9	43	-5.7	43	-5.2
60 mg BID	41	36.6	41	-5.6	41	-7.2	41	-8.2	41	-10.1
Placebo	47	37.0	47	-3.8	47	-4.3	47	-4.0	47	-4.1

2-Sided P-Values for Pairwise Comparisons

Ziprasidone 20 mg BID vs placebo	0.838	0.990	0.773	0.468	0.657
Ziprasidone 60 mg BID vs placebo	0.874	0.380	0.208	0.108	0.022

Source Data: Appendix V Table 15. Date of Data Extraction: 15DEC95.
Date of Table Generation: 23MAY96.

BPRS Core Items Study 106
(from Sponsor's Submission)

BPRS Core Items Score - Mean Change From Baseline and P-Values by Week -
All Subjects, Observed Cases
Ziprasidone Protocol 106

Treatment Groups	Treatment Week									
	Baseline		Week 1		Week 2		Week 3		Week 4	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone										
20 mg BID	43	13.4	42	-2.1	39	-2.8	33	-4.1	28	-3.5
60 mg BID	41	13.6	41	-2.4	38	-2.9	28	-4.7	24	-5.8
Placebo	47	13.9	44	-2.0	38	-2.0	28	-3.5	24	-3.9

2-Sided P-Values for Pairwise Comparisons

Ziprasidone 20 mg BID vs placebo	0.526	0.645	0.178	0.368	0.619
Ziprasidone 60 mg BID vs placebo	0.661	0.555	0.209	0.210	0.096

Source Data: Appendix V Table 15. Date of Data Extraction: 28JUL95.
Date of Table Generation: 23MAY96.

BPRS Core Items Score - Mean Change From Baseline and P-Values by Week -
All Subjects, LOCF
Ziprasidone Protocol 106

Treatment Groups	Treatment Week									
	Baseline		Week 1		Week 2		Week 3		Week 4	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone										
20 mg BID	43	13.4	43	-2.0	43	-2.7	43	-3.1	43	-2.6
60 mg BID	41	13.6	41	-2.4	41	-3.0	41	-3.5	41	-4.1
Placebo	47	13.9	47	-2.0	47	-1.9	47	-2.2	47	-2.3

2-Sided P-Values for Pairwise Comparisons

Ziprasidone 20 mg BID vs placebo	0.526	0.812	0.271	0.322	0.677
Ziprasidone 60 mg BID vs placebo	0.661	0.587	0.213	0.186	0.059

Source Data: Appendix V Table 15. Date of Data Extraction: 28JUL95.
Date of Table Generation: 23MAY96.

CGI Severity Score Study 106
(from Sponsor's Submission)

CGI Severity Score - Mean Change From Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 106

Treatment Groups	Treatment Week									
	Baseline		Week 1		Week 2		Week 3		Week 4	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone										
20 mg BID	43	4.7	42	-0.1	39	-0.5	33	-0.8	28	-0.7
60 mg BID	42	4.7	42	-0.3	38	-0.5	28	-0.8	24	-1.0
Placebo	47	4.7	44	-0.1	38	-0.3	28	-0.3	24	-0.5

2-Sided P-Values for Pairwise Comparisons

Ziprasidone 20 mg BID vs placebo	0.978	0.690	0.105	0.012	0.330
Ziprasidone 60 mg BID vs placebo	0.824	0.215	0.233	0.024	0.033

Source Data: Appendix V Table 16. Date of Data Extraction: 28JUL95.
Date of Table Generation: 23MAY96.

CGI Severity Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 106

Treatment Groups	Treatment Week									
	Baseline		Week 1		Week 2		Week 3		Week 4	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone										
20 mg BID	43	4.7	43	-0.1	43	-0.4	43	-0.5	43	-0.4
60 mg BID	42	4.7	42	-0.3	42	-0.5	42	-0.5	42	-0.6
Placebo	47	4.7	47	-0.1	47	-0.2	47	-0.1	47	-0.2

2-Sided P-Values for Pairwise Comparisons

Ziprasidone 20 mg BID vs placebo	0.978	0.805	0.169	0.034	0.209
Ziprasidone 60 mg BID vs placebo	0.824	0.167	0.238	0.040	0.039

Source Data: Appendix V Table 16. Date of Data Extraction: 28JUL95.
Date of Table Generation: 23MAY96.

SANS Total Score Study 106
(from Sponsor's Submission)

SANS Total Score - Mean Change from Baseline and P-Values by Week-
All Subjects, Observed Cases
Ziprasidone Protocol 106

Treatment Groups	Treatment Week					
	Baseline		Week 2		Week 4	
	n	Mean	n	Mean	n	Mean
Ziprasidone	42	52.2	38	-7.7	26	-11.5
20 mg BID	40	50.9	37	-3.8	22	-14.0
60 mg BID						
Placebo	42	49.1	34	-2.1	22	-7.6

2-Sided P-Values for Pairwise Comparisons

Ziprasidone 20 mg BID	0.503	0.166	0.462
vs placebo			
Ziprasidone 60 mg BID	0.706	0.642	0.204
vs placebo			

Source Data: Appendix V Table 17. Date of Data Extraction: 30MAY96.
Date of Table Generation: 31MAY96.

SANS Total Score - Mean Change From Baseline and P-Values by Week-
All Subjects, LOCF
Ziprasidone Protocol 106

Treatment Groups	Treatment Week					
	Baseline		Week 2		Week 4	
	n	Mean	n	Mean	n	Mean
Ziprasidone	42	52.2	42	-6.5	42	-8.6
20 mg BID	40	50.9	40	-3.6	40	-7.4
60 mg BID						
Placebo	42	49.1	41	-1.3	42	-2.4

2-Sided P-Values for Pairwise Comparisons

Ziprasidone 20 mg BID	0.503	0.192	0.165
vs placebo			
Ziprasidone 60 mg BID	0.706	0.534	0.197
vs placebo			

Source Data: Appendix V Table 17. Date of Data Extraction: 30MAY96.
Date of Table Generation: 31MAY96.

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Appendix 7.2.2.2
(from Sponsor's Submission)

Subject Disposition
Ziprasidone Protocol 114

Treatment Group	Number of Subjects		Number of Subjects Completing Each Period of Study*					
	Randomized	Treated	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Ziprasidone, 40 mg BID	106	106	103	94	78	69	57	54
Ziprasidone, 80 mg BID	104	104	103	97	92	80	73	67
Placebo	92	92	88	77	68	58	50	45
Total:	302	302	294	268	238	207	180	166

*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; Week 5 similarly counts those with visit 35; Week 6 similarly counts those with visit 42.
Source Data: Appendix V Tables 6, 15, 16. Date of Data Extraction: 29MAR96. Date of Table Generation: 01APR96.

Appendix 7.2.2.3
(from Sponsor's Submission)

Demographic Characteristics
Ziprasidone Protocol 114

	Ziprasidone 40 mg BID			Ziprasidone 80 mg BID			Placebo		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number of Subjects Randomized	75	31	106	77	27	104	63	29	92
Age (years):									
18-44	60	23	83	66	19	85	51	20	71
45-64	14	7	21	11	7	18	12	9	21
>=65	1	1	2	0	1	1	0	0	0
Mean age (years)	35.6	39.6	36.8	34.6	39.1	35.8	35.7	40.4	37.2
Age range	19-65	24-67	19-67	18-58	24-65	18-65	18-63	18-64	18-64
Race:									
White	52	25	77	55	18	73	39	17	56
Black	15	4	19	11	6	17	15	9	24
Asian	1	1	2	3	0	3	2	0	2
Other	7	1	8	8	3	11	7	3	10
Mean weight (kg)	77.9	68.6		78.6	72.0		82.4	73.1	
Weight range	57-137	50-111		49-127	44-101		51-122	49-118	

Source Data: APPENDIX V - TABLE 2 Date of Data Extraction: 26MAR96 Date of Table Generation: 27MAR96

BPRSd Total Score Study 114
(from Sponsor's Submission)

BPRSd Total Score - Mean Change From Baseline and P-Values by Week - All Subjects, Observed Cases
Ziprasidone Protocol 114

Treatment Groups	Treatment Week*													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
40 mg BID	104	56.5	103	-4.1	94	-4.0	78	-9.1	69	-11.6	57	-15.8	54	-15.5
80 mg BID	103	55.0	103	-6.3	96	-8.4	92	-11.2	80	-12.1	73	-13.3	67	-13.9
Placebo	91	55.1	87	-1.1	77	-4.9	68	-6.0	58	-8.5	50	-10.7	45	-12.2

2-Sided P-Values for Pairwise Comparisons**

Ziprasidone 40 mg BID vs placebo	0.4521	0.0381	0.6611	0.1020	0.1574	0.0147	0.1747
Ziprasidone 80 mg BID vs placebo	0.9250	0.0001	0.0127	0.0021	0.0315	0.1566	0.4410

*Baseline = last visit prior to double-blind treatment; Week 1 = visit 7; Week 2 = visit 14; Week 3 = visit 21; Week 4 = visit 28; Week 5 = visit 35; Week 6 = visit 42. Missing values are imputed using value of previous non-missing visit, planned or unplanned.
**Estimates of treatment effects are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response as covariate and (fixed effect) terms for center and treatment. The p-values are derived from the respective t-tests.
Source Data: Appendix V Table 15. Date of Data Extraction: 29MAR96. Date of Table Generation: 17APR96.

BPRSd Total Score - Mean Change From Baseline and P-Values by Week - All Subjects, LOCF
Ziprasidone Protocol 114

Treatment Groups	Treatment Week*													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
40 mg BID	104	56.5	104	-4.1	104	-3.4	104	-6.2	104	-7.2	104	-8.0	104	-7.7
80 mg BID	103	55.0	103	-6.3	103	-8.1	103	-10.6	103	-10.5	103	-10.5	103	-10.3
Placebo	91	55.1	90	-0.8	91	-2.6	91	-2.3	91	-2.9	91	-3.2	91	-3.4

2-Sided P-Values for Pairwise Comparisons**

Ziprasidone 40 mg BID vs placebo	0.4521	0.0236	0.6489	0.0419	0.0439	0.0240	0.0472
Ziprasidone 80 mg BID vs placebo	0.9250	0.0001	0.0003	0.0001	0.0001	0.0001	0.0003

*Baseline = last visit prior to double-blind treatment; Week 1 = visit 7; Week 2 = visit 14; Week 3 = visit 21; Week 4 = visit 28; Week 5 = visit 35; Week 6 = visit 42. Missing values are imputed using value of previous non-missing visit, planned or unplanned.
**Estimates of treatment effects are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response as covariate and (fixed effect) terms for center and treatment. The p-values are derived from the respective t-tests.
Source Data: Appendix V Table 15. Date of Data Extraction: 29MAR96. Date of Table Generation: 03APR96.

BPRSd Core Items Study 114
(from Sponsor's Submission)

BPRSd Core Items Score - Mean Change From Baseline and P-Values by Week - All Subjects, Observed Cases
Ziprasidone Protocol 114

Treatment Groups	Treatment Week*													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
40 mg BID	104	16.9	103	-1.9	94	-2.0	78	-3.6	69	-4.5	57	-5.6	54	-5.9
80 mg BID	103	16.6	103	-2.5	96	-3.7	92	-4.5	80	-5.1	73	-5.8	67	-5.8
Placebo	91	16.4	87	-1.0	77	-2.2	68	-2.6	58	-3.2	50	-4.0	45	-4.5

2-Sided P-Values for Pairwise Comparisons**

Ziprasidone 40 mg BID vs placebo	0.3573	0.0380	0.6995	0.1487	0.1123	0.0507	0.1714
Ziprasidone 80 mg BID vs placebo	0.7136	0.0003	0.0045	0.0025	0.0071	0.0088	0.1533

*Baseline = last visit prior to double-blind treatment; Week 1 = visit 7; Week 2 = visit 14; Week 3 = visit 21; Week 4 = visit 28; Week 5 = visit 35; Week 6 = visit 42. Missing values are imputed using value of previous non-missing visit, planned or unplanned.
**Estimates of treatment effects are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response as covariate and (fixed effect) terms for center and treatment. The p-values are derived from the respective t-tests.
Source Data: Appendix V Table 15. Date of Data Extraction: 29MAR96. Date of Table Generation: 02APR96.

BPRSd Core Items Score - Mean Change From Baseline and P-Values by Week - All Subjects, LOCF
Ziprasidone Protocol 114

Treatment Groups	Treatment Week**													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
40 mg BID	104	16.9	104	-1.8	104	-1.8	104	-2.7	104	-3.1	104	-3.3	104	-3.4
80 mg BID	103	16.6	103	-2.5	103	-3.5	103	-4.2	103	-4.3	103	-4.5	103	-4.4
Placebo	91	16.4	90	-0.9	91	-1.6	91	-1.6	91	-1.7	91	-1.9	91	-2.0

2-Sided P-Values for Pairwise Comparisons*

Ziprasidone 40 mg BID vs placebo	0.3573	0.0256	0.5929	0.0553	0.0260	0.0207	0.0396
Ziprasidone 80 mg BID vs placebo	0.7136	0.0002	0.0002	0.0001	0.0001	0.0001	0.0002

**Baseline = last visit prior to double-blind treatment; Week 1 = visit 7; Week 2 = visit 14; Week 3 = visit 21; Week 4 = visit 28; Week 5 = visit 35; Week 6 = visit 42. Missing values are imputed using value of previous non-missing visit, planned or unplanned.
*Estimates of treatment effects are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response as covariate and (fixed effect) terms for center and treatment. The p-values are derived from the respective t-tests.
Source Data: Appendix V Table 15. Date of Data Extraction: 29MAR96. Date of Table Generation: 01APR96.

CGI Severity Score Study 114
(from Sponsor's Submission)

CGI Severity Score - Mean Change From Baseline and P-Values by Week - All Subjects, Observed Cases
Ziprasidone Protocol 114

Treatment Groups	Treatment Week*													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
40 mg BID	104	4.8	103	-0.3	94	-0.2	78	-0.5	69	-0.6	57	-0.9	54	-1.0
80 mg BID	103	4.8	103	-0.3	97	-0.6	92	-0.7	80	-1.0	73	-1.0	67	-1.1
Placebo	92	4.8	88	-0.1	77	-0.3	68	-0.3	58	-0.5	50	-0.6	45	-0.8

2-Sided P-Values for Pairwise Comparisons**

Ziprasidone 40 mg BID vs placebo	0.9477	0.1244	0.9983	0.0677	0.2355	0.0162	0.2157
Ziprasidone 80 mg BID vs placebo	0.5024	0.0166	0.0111	0.0101	0.0010	0.0040	0.0281

*Baseline = last visit prior to double-blind treatment; Week 1 = visit 7; Week 2 = visit 14; Week 3 = visit 21; Week 4 = visit 28; Week 5 = visit 35; Week 6 = visit 42. Missing values are imputed using value of previous non-missing visit, planned or unplanned.
**Estimates of treatment effects are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response as covariate and (fixed effect) terms for center and treatment. The p-values are derived from the respective t-tests.
Source Data: Appendix V Table 16. Date of Data Extraction: 29MAR96. Date of Table Generation: 02APR96.

CGI Severity Score - Mean Change From Baseline and P-Values by Week - All Subjects, LOCF
Ziprasidone Protocol 114

Treatment Groups	Treatment Week*													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
40 mg BID	104	4.8	104	-0.3	104	-0.2	104	-0.4	104	-0.4	104	-0.5	104	-0.5
80 mg BID	103	4.8	103	-0.3	103	-0.5	103	-0.6	103	-0.8	103	-0.8	103	-0.8
Placebo	92	4.8	91	-0.1	92	-0.1	92	-0.1	92	-0.2	92	-0.2	92	-0.2

2-Sided P-Values for Pairwise Comparisons**

Ziprasidone 40 mg BID vs placebo	0.9477	0.0864	0.6033	0.0324	0.0649	0.0096	0.0299
Ziprasidone 80 mg BID vs placebo	0.5024	0.0115	0.0007	0.0002	0.0001	0.0001	0.0001

*Baseline = last visit prior to double-blind treatment; Week 1 = visit 7; Week 2 = visit 14; Week 3 = visit 21; Week 4 = visit 28; Week 5 = visit 35; Week 6 = visit 42. Missing values are imputed using value of previous non-missing visit, planned or unplanned.
**Estimates of treatment effects are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response as covariate and (fixed effect) terms for center and treatment. The p-values are derived from the respective t-tests.
Source Data: Appendix V Table 16. Date of Data Extraction: 29MAR96. Date of Table Generation: 17APR96.

PANSS Total Score Study 114
(from Sponsor's Submission)

PANSS Total Score - Mean Change From Baseline and P-Values by Week - All Subjects, Observed Cases
Ziprasidone Protocol 114

Treatment Groups	Treatment Week*													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
40 mg BID	104	98.2	103	-7.0	94	-6.5	78	-14.3	69	-18.4	57	-25.3	54	-25.6
80 mg BID	103	95.8	103	-9.9	96	-14.0	92	-18.6	80	-20.2	73	-22.2	67	-23.5
Placebo	91	97.3	86	-1.6	77	-7.7	68	-9.3	58	-13.8	50	-19.0	44	-21.0

2-Sided P-Values for Pairwise Comparisons**

Ziprasidone 40 mg BID vs placebo	0.7859	0.0169	0.8971	0.0743	0.1126	0.0265	0.1217
Ziprasidone 80 mg BID vs placebo	0.6324	0.0001	0.0058	0.0005	0.0120	0.1721	0.3418

*Baseline = last visit prior to double-blind treatment; Week 1 = visit 7; Week 2 = visit 14; Week 3 = visit 21; Week 4 = visit 28; Week 5 = visit 35; Week 6 = visit 42. Missing values are imputed using value of previous non-missing visit, planned or unplanned.
**Estimates of treatment effects are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response as covariate and (fixed effect) terms for center and treatment. The p-values are derived from the respective t-tests.
Source Data: Appendix V Table 15. Date of Data Extraction: 29MAR96. Date of Table Generation: 03APR96.

PANSS Total Score - Mean Change From Baseline and P-Values by Week - All Subjects, LOCF
Ziprasidone Protocol 114

Treatment Groups	Treatment Week*													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone														
40 mg BID	104	98.2	104	-6.9	104	-5.5	104	-9.7	104	-11.3	104	-12.6	104	-12.4
80 mg BID	103	95.8	103	-9.9	103	-13.4	103	-17.4	103	-17.2	103	-17.0	103	-17.1
Placebo	91	97.3	89	-1.2	91	-3.8	91	-3.2	91	-4.3	91	-5.0	91	-5.4

2-Sided P-Values for Pairwise Comparisons**

Ziprasidone 40 mg BID vs placebo	0.7859	0.0100	0.5010	0.0274	0.0307	0.0250	0.0478
Ziprasidone 80 mg BID vs placebo	0.6324	0.0001	0.0002	0.0001	0.0001	0.0001	0.0002

*Baseline = last visit prior to double-blind treatment; Week 1 = visit 7; Week 2 = visit 14; Week 3 = visit 21; Week 4 = visit 28; Week 5 = visit 35; Week 6 = visit 42. Missing values are imputed using value of previous non-missing visit, planned or unplanned.
**Estimates of treatment effects are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response as covariate and (fixed effect) terms for center and treatment. The p-values are derived from the respective t-tests.
Source Data: Appendix V Table 15. Date of Data Extraction: 29MAR96. Date of Table Generation: 01APR96.

PANSS Negative Score Study 114
(from Sponsor's Submission)

PANSS Negative Subscale Score - Mean Change From Baseline and P-Values by Week - All Subjects, Observed Cases
Ziprasidone Protocol 114

Treatment Groups	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone 40 mg BID	104	25.4	103	-2.1	94	-1.9	78	-3.3	69	-3.9	57	-5.7	54	-5.7
80 mg BID	103	24.3	103	-2.4	96	-3.1	92	-4.1	80	-4.7	73	-5.1	67	-5.2
Placebo	91	24.9	86	0.3	77	-1.3	68	-1.7	58	-2.6	50	-5.0	45	-5.4

2-Sided P-Values for Pairwise Comparisons**

Ziprasidone 40 mg BID vs placebo	0.6687	0.0004	0.4771	0.1164	0.0615	0.1300	0.2144
Ziprasidone 80 mg BID vs placebo	0.5793	0.0001	0.0097	0.0016	0.0021	0.4064	0.5720

*Baseline = last visit prior to double-blind treatment; Week 1 = visit 7; Week 2 = visit 14; Week 3 = visit 21; Week 4 = visit 28; Week 5 = visit 35; Week 6 = visit 42. Missing values are imputed using value of previous non-missing visit, planned or unplanned.
**Estimates of treatment effects are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response as covariate and (fixed effect) terms for center and treatment. The p-values are derived from the respective t-tests.
Source Data: Appendix V Table 15. Date of Data Extraction: 29MAR96. Date of Table Generation: 02APR96.

PANSS Negative Subscale Score - Mean Change From Baseline and P-Values by Week - All Subjects, LOCF
Ziprasidone Protocol 114

Treatment Groups	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Ziprasidone 40 mg BID	104	25.4	104	-2.1	104	-1.6	104	-2.4	104	-2.7	104	-3.2	104	-3.2
80 mg BID	103	24.3	103	-2.4	103	-3.0	103	-4.0	103	-4.0	103	-3.8	103	-3.9
Placebo	91	24.9	89	0.3	91	-0.3	91	-0.4	91	-0.4	91	-1.0	91	-0.9

2-Sided P-Values for Pairwise Comparisons*

Ziprasidone 40 mg BID vs placebo	0.6687	0.0004	0.1566	0.0267	0.0109	0.0238	0.0236
Ziprasidone 80 mg BID vs placebo	0.5793	0.0001	0.0007	0.0001	0.0001	0.0009	0.0006

*Baseline = last visit prior to double-blind treatment; Week 1 = visit 7; Week 2 = visit 14; Week 3 = visit 21; Week 4 = visit 28; Week 5 = visit 35; Week 6 = visit 42. Missing values are imputed using value of previous non-missing visit, planned or unplanned.
*Estimates of treatment effects are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response as covariate and (fixed effect) terms for center and treatment. The p-values are derived from the respective t-tests.
Source Data: Appendix V Table 15. Date of Data Extraction: 29MAR96. Date of Table Generation: 01APR96.

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Appendix 7.2.3.2
(from Sponsor's Submission)

Subject Disposition
Ziprasidone Protocol 115

Treatment Group	Number of Subjects		Number of Subjects Completing Each Period of Study*					
	Randomized	Treated	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Ziprasidone, 20 mg BID	87	87	84	77	62	57	51	50
Ziprasidone, 60 mg BID	78	78	75	69	62	57	50	39
Ziprasidone, 100 mg BID	86	86	82	77	69	60	57	47
Haloperidol	85	85	77	72	67	58	50	47
Placebo	83	83	77	65	48	35	32	27
Total:	419	419	395	360	308	267	240	210

*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; Week 5 similarly counts those with visit 35; Week 6 similarly counts those with visit 42.
Source Data: Appendix V Tables 6, 15, 16. Date of Data Extraction: 22OCT96. Date of Table Generation: 22OCT96.

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Appendix 7.2.3.3
(from Sponsor's Submission)

Demographic Characteristics
Ziprasidone Protocol 115

	Ziprasidone 20 mg BID			Ziprasidone 60 mg BID			Ziprasidone 100 mg BID		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number of Subjects Randomized	53	34	87	55	23	78	55	31	86
Age (years):									
18-44	35	25	60	42	15	57	43	20	63
45-64	18	7	25	11	8	19	12	10	22
>=65	0	2	2	2	0	2	0	1	1
Mean age (years)	41.1	39.1	40.3	39.7	40.7	40.0	36.9	40.5	38.2
Age range	22-60	21-68	21-68	21-72	20-58	20-72	19-60	21-71	19-71
Race:									
White	32	23	55	37	17	54	37	21	58
Black	14	9	23	16	5	21	13	8	21
Asian	2	2	4	2	1	3	0	1	1
Other	5	0	5	0	0	0	5	1	6
Mean weight (kg)	78.5	79.9		78.7	78.5		81.9	72.8	
Weight range	54-117	40-125		51-109	45-110		50-130	46-104	

Source Data: APPENDIX V - TABLE 2 Date of Data Extraction: 22OCT96 Date of Table Generation: 22OCT96

Demographic Characteristics
Ziprasidone Protocol 115

	Haloperidol			Placebo		
	Male	Female	Total	Male	Female	Total
Number of Subjects Randomized	60	25	85	54	29	83
Age (years):						
18-44	44	18	62	40	20	60
45-64	16	5	21	13	9	22
>=65	0	2	2	1	0	1
Mean age (years)	38.1	40.6	38.8	38.3	40.0	38.9
Age range	18-64	21-69	18-69	18-65	18-56	18-65
Race:						
White	37	18	55	30	20	50
Black	18	6	24	13	6	19
Asian	2	1	3	1	1	2
Other	3	0	3	10	2	12
Mean weight (kg)	84.4	73.6		79.7	75.9	
Weight range	51-141	49-110		51-133	50-112	

Source Data: APPENDIX V - TABLE 2 Date of Data Extraction: 22OCT96 Date of Table Generation: 22OCT96