CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-919

Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION

NDA#:	20-919
Applicant:	Pfizer, Inc.
Name of Drug:	Zeldox IM (Intramuscular Ziprasidone Mesylate) for Injection
Indication:	Treatment of acute agitation in psychotic patients
Documents Reviewed:	Vol.1.1, Vols.1.28-1.53
Medical Officer:	Roberta Glass, M.D. (HFD-120)

The following review has been discussed with the medical review team. The tables/figures from the sponsor are labeled as Table/Figure xS, and those from this reviewer's evaluation and analyses are labeled as Table/Figure xR.

1 BACKGROUND

In December 17, 1997, Pfizer Inc. submitted intramuscular ziprasidone mesylate (Trade name: Zeldox IM) NDA for the treatment of acute agitation in psychotic patients. This application consists of five Phase II/III trials (128-120, 128-121, 128-125, 128-126, 128-306). Trials 128-125 and 128-126 were double-blind, fixed-dose studies. Both double-blind studies were multicenter trials. Trials 128-120, 128-121 and 128-306 were open-label studies aimed to study the safety and tolerability of Zeldox IM. This review pertains to Studies 128-125 and 128-126.

2 PIVOTAL TRIALS

2.1 PROTOCOL 128-125 US "A Phase III Randomized Study Comparing 2 Doses of Intramuscular Ziprasidone (2 mg and 10 mg) in Subjects with Psychosis and Acute Agitation" (Study Dates: Feb. 13, 1997 - June 28, 1997)

2.1.1 STUDY DESCRIPTION

TRIAL DESIGN

This was a randomized, double-blind, parallel-group, multicenter (27 centers with 10 sites having no patients randomized) trial. Subjects who fulfilled the screening criteria were to have had all concomitant antipsychotic medication discontinued. At screening and baseline, subjects were to have had scores of 3 (mild) or more on at least three of the following items of the Positive and Negative Syndrome Scale for Schizophrenia (PANSS): anxiety, tension, hostility, and excitement. Eligible patients were randomized in equal ratio to receive doses of either 2 mg

or 10 mg of intramuscular (IM) ziprasidone in equal injection volumes (0.5 ml). Baseline assessments were performed within four hours prior to administration of the first dose of study drug. Screening, baseline, and the first day of double-blind drug treatment could occur on the same day if study criteria were met. Following the initial dose of 2 mg IM or 10 mg IM ziprasidone, successive doses must be administered at least 2 hours apart. The maximum total doses of IM ziprasidone were 8 mg and 40 mg for the 2 mg and 10 mg groups, respectively. Depending on the subject's symptoms, the investigator can choose not to administer any further injections to this subject or to administer injections less frequently.

STUDY OBJECTIVE

The study objective was to compare the efficacy and tolerability of 2 mg and 10 mg doses of IM ziprasidone in subjects with a diagnosis of psychotic disorder and acute agitation. Two protocol amendments were made. The first amendment was related to subject selection criteria, diagnostic eligibility, and flow chart. The Clinical Global Impression Severity (CGI-S) at 4-hr was added as a primary efficacy variable, and subgroup analyses were defined as secondary efficacy analyses in the second amendment.

The primary efficacy variables were to be (1) area under the curve (AUC) for the behavioural assessment scale (BAS) from 0 to 2 hours after first dose of intramuscular drug, (2) changes from baseline of CGI-S score measured at 4 hours, and (3) changes of CGI-S at the study endpoint. The study endpoint was defined as either: at 6 hours after administration of the last dose or at the end of the 24 hour treatment period, whichever is later, OR at the time of early termination. Other secondary analyses to be performed on BAS included: responder rate at 90 minutes after the first administration of the drug (subject "response" is operationally defined as a decrease from baseline of 2 points or more on the BAS score); time-to-response (from first dose); total number of injections; time to second injection; change from baseline of the BAS for each time point up to 2 hours, for each dose. The Last Observation Carried Forward (LOCF) method could be used for imputation of missing data when appropriate. Small centers were to be pooled to form pseduo centers based on pre-specified criteria. Secondary efficacy variables included change in PANSS-total and the sum of the scores of the PANSS agitation items of anxiety, tension, hostility and excitement from baseline; change in CGI improvement scores and change in NOSIE scores (Nurses Observation Scale for Inpatient Evaluation) from baseline.

STATISTICAL PLAN

The primary objective of the study was to test the hypothesis that 10 mg IM ziprasidone is superior to 2 mg IM ziprasidone in the treatment of subjects with psychosis and acute agitation. Treatment contrasts were to be tested **each** at 2-tailed 0.05 level for significance, see Section 2.1.3 Reviewer's Evaluations and Comments.

The primary efficacy analysis for AUC was to fit linear models including center and treatment and for CGI-S was to fit linear models including center and treatment with baseline score as a covariate, then testing for the linear contrast. Interaction was to be investigated. In case

of gross violations, methods of categorical data analysis were to be used. Rank transformation was to be performed on the change scores if observed data distribution warrant. Log transformations were to be performed on the AUC scores if observed data distribution warrant.

The sponsor was interested in detecting a 1.0 points difference in the mean change from baseline in CGI-S scores between the two treatment groups. Assuming a population standard deviation of the CGI-S score of 1.5 with type I error rate of 5%, it was estimated that 50 subjects per group would provide at least 80% power of declaring such difference based on a two-sided test.

2.1.2 OVERVIEW OF THE SPONSOR RESULTS

In this study, 117 subjects entered the study, of which 113 subjects completed the study: 96.3% (52/54) in 2 mg and 96.8% (61/63) in 10 mg IM ziprasidone. The sponsor performed (1) all subjects, (2) subjects with a first dose between 0600 and 1800 hours, (3) subjects with baseline BAS score of at least 5, and (4) completers analyses. Four subjects out of 117 randomized patients, 2 from 2 mg IM ziprasidone (an insufficient clinical response and an adverse response) and 2 from 10 mg IM ziprasidone (consent withdrawals) prematurely discontinued the study medication during the trial.

Demographic and baseline characteristics were similar between the two treatment arms, male:female ratio of 7:3, mean age of 39.2 yrs (range 18-76 yrs), with majority being White (62% White, 26% Black, 12% others). Over 40% of the subjects in each group had a primary diagnosis of schizophrenic disorder. Diseases and/or syndromes were present at screening in about 85% of subjects in each dose group at screening. More than 80% of subjects in each group took psychotropic medications during the 48 hours before screening.

Primary efficacy variables

- **AUC of BAS score 0-2 hours, CGI-S score at hour 4 and at last observation**

The sponsor stated that "For all subjects and the three subgroups, the AUC of BAS score 0-2 hours of the 10 mg group was significantly ($p<0.001$) less than that of the 2 mg group, indicating that, on average, the BAS scores at multiple timepoints to 2 hours after the first injection were lower in subjects given the 10 mg dose than in those given the 2 mg dose. There were no statistically significant differences between dose groups in the mean change from baseline in CGI-S score at hour 4 or at last observation for all subjects, subjects with baseline BAS >=5, or for completers. For subjects with a first dose between 0600 and 1800 hours, the mean change from baseline in CGI-S score at last observation was significantly ($p<0.05$) greater in the 10 mg group than in the 2 mg group." The sponsor's results based on the all subjects analysis were summarized in Table 1.1S.

Table 1.1S Summary of the results of efficacy outcomes in Trial 128-125

	2 mg (n=54)	10 mg(n=63)	p-val
Primary efficacy outcomes *	mean (SD)(n)	mean (SD)(n)	
AUC^ of BAS scores 0-2 hours	8.30 (1.19) (54)	7.57 (1.41)(62)	**<.001[a]**
CGIC-S change from baseline at 4-hour	-0.74 (1.01) (54)	-0.76 (1.07)(63)	**0.870[c]**
CGIC-S change from baseline at last observation	-0.50 (0.80) (54)	-0.71 (1.01)(63)	**0.214[c]**
Secondary efficacy outcomes			
AUC of BAS 0-4 hours	15.88 (2.72)(45)	13.47(3.03)(55)	<.001
Responder rates@ based on BAS scores	21% (11/52)	45% (28/62)	0.013
PANSS agitation items at 4-hr**	-4.27 (3.77) (52)	-4.44 (4.36)(59)	ns***
PANSS agitation items at last observation	-3.35 (3.89) (54)	-4.02 (4.03)(62)	ns

* protocol specified analysis (all subjects).
^ AUC was computed using the numerical integration technique "trapezoidal rule".
[a] ANOVA with treatment, center.
[c] ANCOVA with treatment, center, baseline covariate.
@ defined as a decrease from baseline of 2 points or more on BAS at 90 minutes post first dose.
** items are hostility, anxiety, tension and excitement.
*** non-significance.

Secondary efficacy variables

For all subjects, the AUC of BAS score 0-4 hours of the 10 mg group was nominally significantly less (nominal $p<0.001$) than that of the 2 mg dose group based on all subjects. An analysis by timepoint showed that the mean change from baseline in BAS scores of subjects given the 10 mg dose was consistently greater than that of subjects given the 2 mg dose from one to two hours after the first injection, see Figure 1S. Among selected list of secondary efficacy variables, responder rates showed a nominal significance ($p=0.013$) in favor of 10 mg arm. However, PANSS agitation items at 4-hr and at last observation were no different between the 2 mg and the 10 mg arms.

A summary of the sponsor's analyses on the primary and secondary efficacy variables based on all subjects can be found in Table 1.2S.

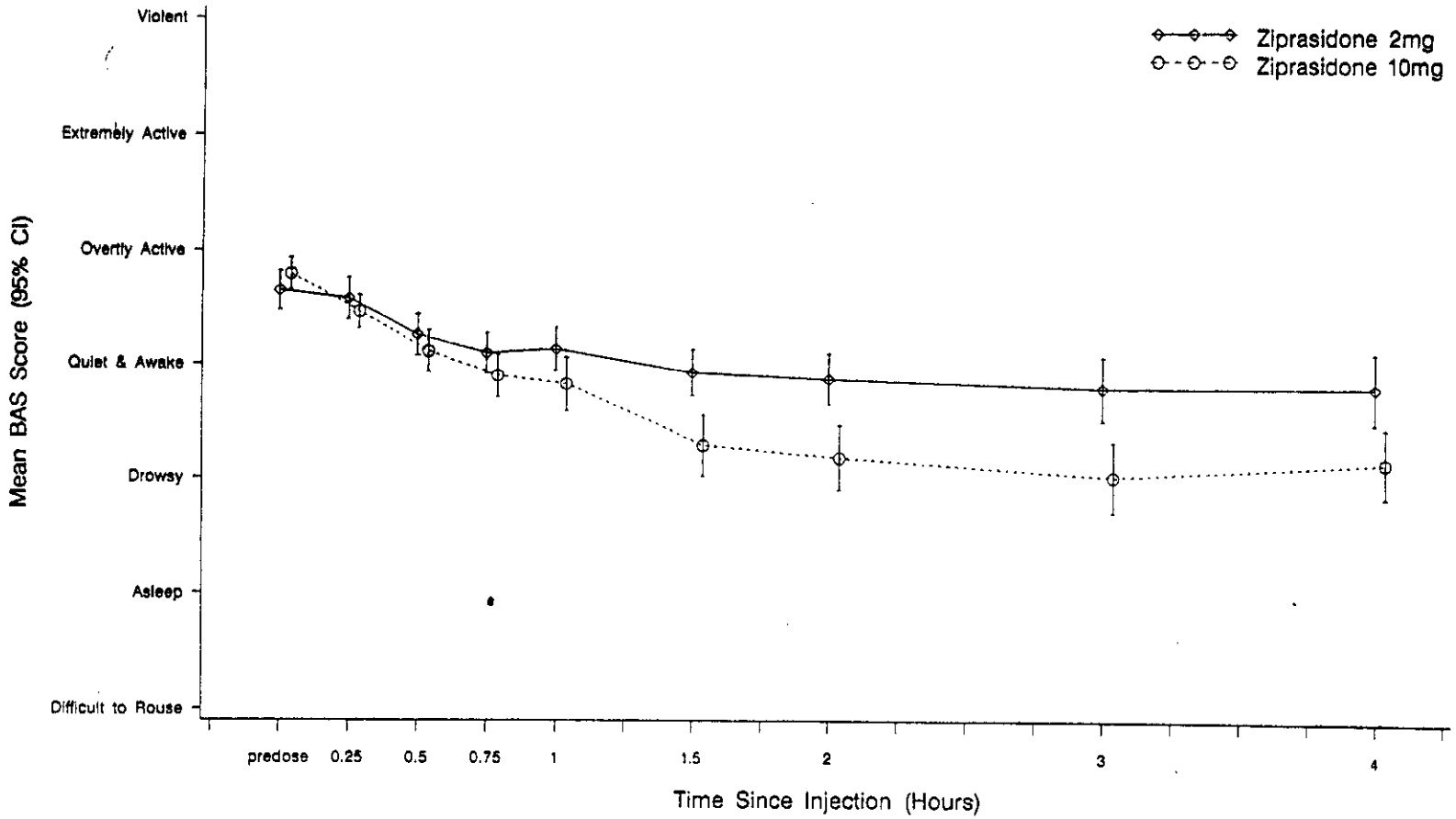
2.1.3.REVIEWER'S EVALUATIONS AND COMMENTS

The sponsor's results based on the all subjects analysis have been confirmed by this reviewer.

- Correlation between baseline PANSS agitation items versus baseline BAS scores

The medical reviewer was concerned about whether there was a direct correlation between baseline PANSS agitation items versus baseline BAS scores. One of the psychiatric inclusion criteria was that "at screening and at baseline subjects were to have scores of 3 (mild) or more on at least three of the PANSS agitation items (anxiety, tension, hostility, and excitement)." The

Figure 1
Mean BAS Scores Over Time 0 – 4 Hours Post First Injection – All Subjects, Observed Cases
Ziprasidone Protocol 125



Source Data: Appendix V Table 15. Date of Data Extraction: 16SEP97. Date of Figure Generation: 01OCT97.

Figure 15

Table 1.2S

Table H.3.3
Study Summary of Outcomes* for Protocol 125 - All Subjects, Observed Cases

		Ziprasidone 2 mg	Ziprasidone 10 mg
AUC of BAS 0-2	Mean	8.30	7.57
	p-value		<0.001
	N	54	62
CGI Severity at Hour 4	Mean baseline	4.24	4.37
	Mean change	-0.74	-0.76
	% change	-17.47	-17.45
	p-value		0.870
	N	54	63
CGI Severity at Last Obs.	Mean baseline	4.24	4.37
	Mean change	-0.50	-0.71
	% change	-11.79	-16.36
	p-value		0.214
	N	54	63
AUC of BAS 0-4	Mean	15.88	13.47
	p-value		<0.001
	N	45	55
BAS Score at Hour 2 (LOCF)+	Mean baseline	4.65	4.81
	Mean change	-0.78	-1.63
	% change	-16.73	-33.89
	p-value		<0.001
	N	54	62
Responder Rate++	# responders	11	28
	% responders	21.15	45.16
	p-value		0.013
	N	52	62

*Data based on last visit, unless otherwise specified, except for AUC, which is based on 0-2 hours or 0-4 hours post first injection.
+BAS score at hour 2 is the the last assessment taken up to 2 hours post first injection.
++Defined as a decrease from baseline of 2 points or more on the Behavioural Assessment Scale at 90 minutes post first dose.
**PANSS Agitation Items Score equals the sum of items P4 (Excitement), P7 (Hostility), G2 (Anxiety) and G4 (Tension).
Source Data: Protocol 125. Date of Table Generation: 20OCT97.

Table H.3.3
Study Summary of Outcomes* for Protocol 125 - All Subjects, Observed Cases

		Ziprasidone 2 mg	Ziprasidone 10 mg
CGI Improvement	Mean	3.09	2.89
	p-value		0.109
	N	54	63
PANSS Total	Mean baseline	89.38	90.00
	Mean change	-12.30	-13.55
	% change	-13.76	-15.05
	p-value		0.379
	N	53	62
PANSS Agitation**	Mean baseline	14.93	15.03
	Mean change	-3.35	-4.02
	% change	-22.46	-26.72
	p-value		0.162
	N	54	62
NOSIE	Mean baseline	37.63	37.98
	Mean change	-4.28	-5.41
	% change	-11.37	-14.25
	p-value		0.349
	N	54	63

*Data based on last visit, unless otherwise specified, except for AUC, which is based on 0-2 hours or 0-4 hours post first injection.
+BAS score at hour 2 is the the last assessment taken up to 2 hours post first injection.
++Defined as a decrease from baseline of 2 points or more on the Behavioural Assessment Scale at 90 minutes post first dose.
**PANSS Agitation Items Score equals the sum of items P4 (Excitement), P7 (Hostility), G2 (Anxiety) and G4 (Tension).
Source Data: Protocol 125. Date of Table Generation: 20OCT97.

study efficacy endpoint was the AUC of BAS at Hour 2 after first IM injection. This reviewer performed a correlation analysis. The estimated correlation between PANSS agitation items vs. BAS scores at baseline was 0.40 (95%CI 0.24, 0.54). It appeared that baseline PANSS agitation items was mildly to moderately correlated with baseline BAS scores. The baseline BAS scores between the 2 mg and 10 mg IM arms were summarized in Table 1R.

Table 1R. Distribution of baseline BAS scores between 2 mg and 10 mg IM ziprasidone arms

Trial 128-125	Baseline Behavior Assessment Scale (BAS)			total
	4 quiet and awake	5 signs of overt activity calms down w/ instructions	6 extremely active, not requiring restraint	
2 mg	24 (45%)	25 (46%)	5 (9%)	59
10 mg	18 (29%)	40 (63%)	5 (8%)	63

Numerically, patients in the 10 mg IM ziprasidone arm appeared to be more severe than those in the 2 mg arm based on patients' baseline BAS scores. However, the baseline PANSS agitation items were well balanced between the two groups with mean (range) of 14.93 (10,24) in the 2 mg arm and 15.02 (10,23) in the 10 mg arm, respectively.

- multiple endpoints (AUC of BAS at 2-hr, CGI-S at 4-hr, and CGI-S at study endpoint)

Based on this reviewer's analysis, CGI-S at 4-hr and CGI-S at study endpoint appeared to be highly correlated [sample correlation estimate was 0.64 (95% CI 0.47, 0.77) and 0.52 (95%CI 0.30, 0.69) for the 10 mg and 2 mg IM ziprasidone, respectively].

The sponsor stated that "Treatment contrasts were to be tested **each** at 2-tailed 0.05 level for significance." No multiplicity adjustment was mentioned in the protocol or amendments given the three co-primary efficacy variables, AUC of BAS at 2-hr, CGI-S at 4-hr, and CGI-S at study endpoint. The sponsor's all subjects analyses showed that $p<0.001$ (2-way ANOVA) for AUC of BAS score, $p=0.870$ (2-way ANCOVA) for CGI-S at 4-hour, and $p=0.214$ for CGI-S at last observation (2-way ANCOVA).

Given the three pre-specified primary efficacy endpoints, if the rule for win is that at least one endpoint shows statistical significance, then the study appeared to show that 10 mg IM ziprasidone is superior to 2 mg IM ziprasidone based on the result of AUC of BAS at 2-hr after first IM dose injection. However, if the rule for win is that at least two endpoints or all three endpoints show statistical significance, then the study failed to show a statistically significant 10 mg IM ziprasidone effect.

This reviewer consulted with Dr. Laughren, the medical team leader, and Dr. Glass, the medical reviewer, regarding this issue. According to Dr. Laughren, AUC for BAS seemed to be the most reasonable primary outcome as a basis for declaring each study a success or failure. The rationale of not including CGI-S, according to Dr. Laughren, is that if patients were so sedated, it would be difficult to distinguish a no change or improved CGI-S from heavy sedation, which

might not necessarily translate into patients' clinical benefit from IM ziprasidone.

- Subgroup analysis by gender

This reviewer performed a by-gender subgroup summary on the primary efficacy variable, see Table 2R. Although the male:female ratio was approximately 7:3, there seemed to be no by-gender difference within a given dosage arm, either in patients treated with 2 mg or 10 mg IM ziprasidone.

Table 2R. Summary of AUC of BAS at 2-hr by-gender of IM ziprasidone treated patients

Trial 128-125	2 mg			10 mg		
	Male	Female	Total	Male	Female	Total
n	38	16	54	42	20	62
mean	8.38	8.09	8.30	7.58	7.53	7.57
sd	1.20	1.16	1.19	1.48	1.29	1.41

2.2 PROTOCOL 128-126 US "A Phase III Randomized Study Comparing 2 Doses of Intramuscular Ziprasidone (2 mg and 20 mg) in Subjects with Psychosis and Acute Agitation" (Study Dates: Feb. 19, 1997 - June 28, 1997)

2.2.1 STUDY DESCRIPTION

STUDY DESIGN

The study design, study objective, protocol amendments, and statistical plan were essentially the same as those in Trial 128-125US except the following: the higher dose group was administered with 20 mg of IM ziprasidone, one of the primary efficacy variable of interest was AUC of BAS from 0 to 4 hours after first dose of intramuscular drug, an additional secondary analyses on BAS was performed, viz., AUC for the BAS from 0 to 2 hours, and the sample size was estimated to be 30 subjects per group, which was targeted to detecting a 1.5 points difference in the mean change from baseline in CGI severity scores between the two treatment groups.

In this trial, eligible patients were randomized in equal ratio to receive doses of either 2 mg or 20 mg of IM ziprasidone in equal injection volumes (1.0 ml). Following the initial dose of 2 mg IM or 20 mg IM ziprasidone, successive doses must be administered at least 4 hours apart. The maximum total doses of IM ziprasidone were 8 mg and 80 mg for the 2 mg and 20 mg groups, respectively.

2.2.2 OVERVIEW OF THE SPONSOR RESULTS

Demographic and baseline characteristics for all randomized subjects were generally comparable for the two dosage treatment groups (2mg ziprasidone: n=38, 20mg ziprasidone: n=41). A total of 62 males aged 20 to 62 years and 17 females aged 29 to 57 years received study

medications with majority being White (75%) followed by Black (13%), others (9%), and Asian (3%). Over 53% of the subjects in each group had a primary diagnosis of schizophrenic disorder. Disease and/or syndromes were present at screening in more than 82% of subjects in each of the treatment groups. There were no notable differences between the dose groups in either past or present medical history. More than 84% of subjects took psychotropic medications during the 48 hours before screening. A total of 20 centers were initially identified for participation and received study drug, 2 sites did not randomize any subjects.

Five subjects out of 79 randomized patients, 2 from 2 mg IM ziprasidone arm (an insufficient clinical response and an adverse response) and 3 from 20 mg IM ziprasidone arm (all due to withdrew consent) prematurely discontinued study medication during the trial.

Primary efficacy variable

- **AUC of BAS score 0-4 hours, CGI-S score at hour 4 and at last observation**

The sponsor stated that "For the all subjects group and the three subgroups, differences between the 20 mg dose and the 2 mg dose were statistically significant for all three primary efficacy variables. The AUC of BAS score 0-4 hours of the 20 mg dose group was significantly ($p<0.001$) less than that of the 2 mg dose group, indicating that, on average, the BAS scores at multiple timepoints to 4 hours after the first injection were lower for the 20 mg dose than the 2 mg dose. The mean decreases from baseline in CGI Severity scores of the 20 mg dose group were significantly greater than those of the 2 mg dose group at Hour 4 ($p=0.008$) and last observation ($p=0.004$)." The sponsor's results based on the all subjects analysis were summarized in Table 2.1S.

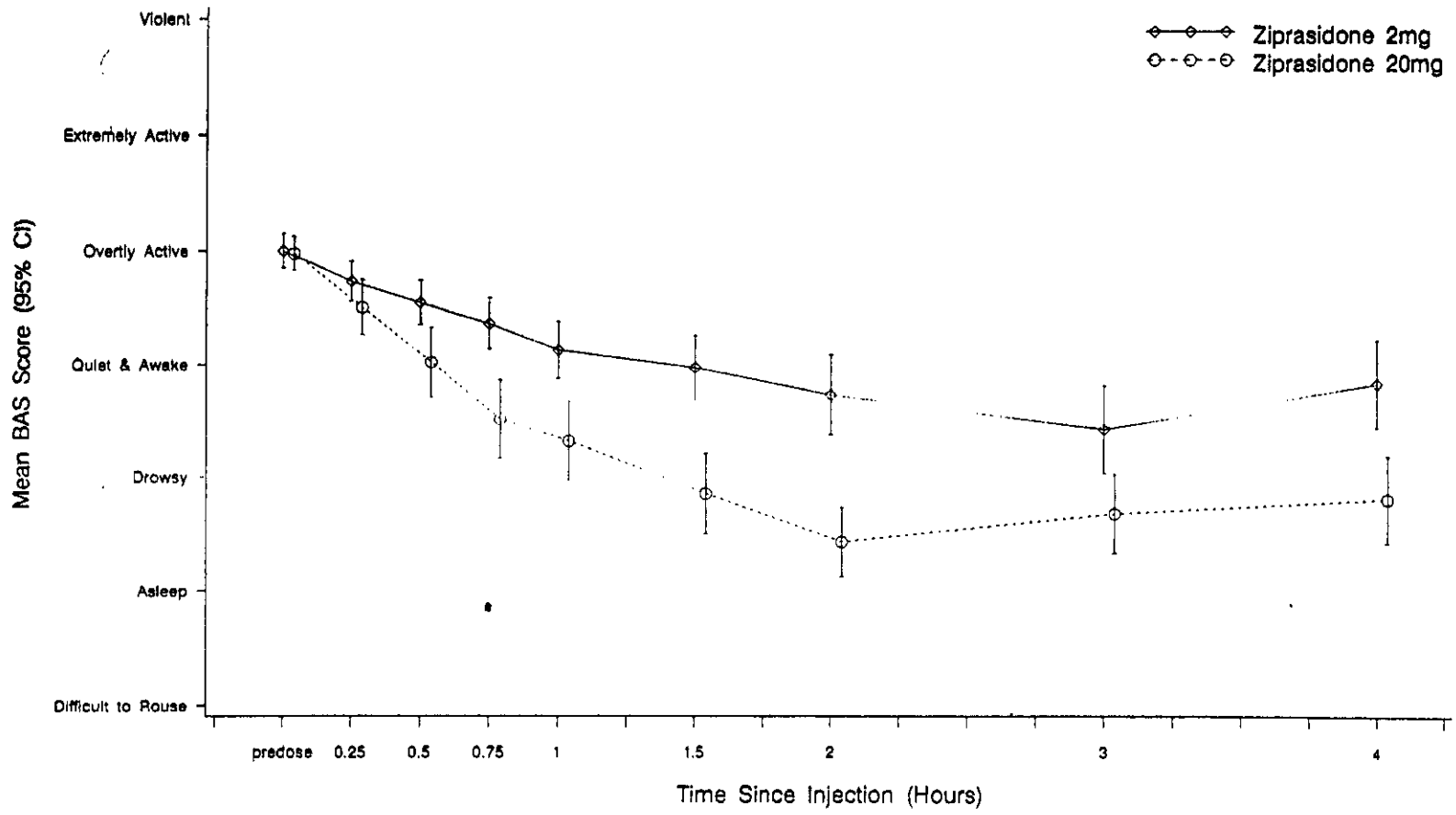
Table 2.1S Summary of the results of primary efficacy outcomes in Trial 128-126

	2 mg (n=38)	20 mg (n=41)	p-val
Primary efficacy outcomes*	mean (SD) (n)	mean (SD) (n)	
AUC^ of BAS scores 0-4 hours	15.73 (3.06) (38)	12.23(3.17)(40)	**<.001[a]**
CGIC-S change from baseline at 4-hour	-1.16 (1.28) (38)	-1.88 (1.45)(40)	**0.008[c]**
CGIC-S change from baseline at last observation	-0.92 (1.22) (38)	-1.58 (1.30)(40)	**0.004[c]**
Secondary efficacy outcomes			
AUC of BAS 0-2 hours	8.48 (1.20) (37)	6.95 (1.57)(40)	<.001
Responder rates@ based on BAS scores	26% (10/38)	65% (26/40)	0.001
PANSS agitation items at 4-hr**	-4.03 (3.48) (35)	-6.64 (3.93)(33)	<0.05
PANSS agitation items at last observation	-4.03 (4.09) (38)	-5.70 (3.95)(40)	n.s.

* protocol specified analysis (all subjects).
^ AUC was computed using the numerical integration technique "trapezoidal rule".
[a] ANOVA with treatment, center.
[c] ANCOVA with treatment, center, baseline covariate.
@ defined as a decrease from baseline of 2 points or more on BAS at 90 minutes post first dose.
** items are hostility, anxiety, tension and excitement.
*** non-significance.

Figure 1

Mean BAS Scores Over Time 0 – 4 Hours Post First Injection – All Subjects, Observed Cases
Ziprasidone Protocol 126



Source Data: Appendix V Table 15. Date of Data Extraction: 30SEP97. Date of Figure Generation: 01OCT97.

Figure 25

Table 2.2S

Table H.3.5
Study Summary of Outcomes* for Protocol 126 - All Subjects, Observed Cases

		Ziprasidone 2 mg	Ziprasidone 20 mg
AUC of BAS 0-4	Mean	15.73	12.23
	p-value		<0.001
	N	38	40
CGI Severity at Hour 4	Mean baseline	4.74	4.63
	Mean change	-1.16	-1.88
	% change	-24.44	-40.54
	p-value		0.008
	N	38	40
CGI Severity at Last Obs.	Mean baseline	4.74	4.63
	Mean change	-0.92	-1.58
	% change	-19.44	-34.05
	p-value		0.004
	N	38	40
AUC of BAS 0-2	Mean	8.48	6.95
	p-value		<0.001
	N	37	40
BAS Score at Hour 4 (LOCF)+	Mean baseline	6.00	4.98
	Mean change	-1.17	-2.17
	% change	-23.42	-43.63
	p-value		<0.001
	N	38	41
Responder Rate++	# responders	10	26
	% responders	26.32	65.00
	p-value		0.001
	N	38	40

*Data based on last visit, unless otherwise specified, except for AUC, which is based on 0-2 hours or 0-4 hours post first injection.
+BAS score at hour 4 is the the last assessment taken up to 4 hours post first injection.
++Defined as a decrease from baseline of 2 points or more on the Behavioural Assessment Scale at 90 minutes post first dose.
**PANSS Agitation Items Score equals the sum of items P4 (Excitement), P7 (Hostility), G2 (Anxiety) and G4 (Tension).
Source Data: Protocol 126. Date of Table Generation: 20OCT97.

Table H.3.5
Study Summary of Outcomes* for Protocol 126 - All Subjects, Observed Cases

		Ziprasidone 2 mg	Ziprasidone 20 mg
CGI Improvement	Mean	3.32	2.38
	p-value		<0.001
	N	38	40
PANSS total	Mean baseline	84.00	86.65
	Mean change	-12.08	-18.30
	% change	-14.38	-21.12
	p-value		0.074
	N	38	40
PANSS Agitation**	Mean baseline	14.29	14.88
	Mean change	-4.03	-5.70
	% change	-28.18	-38.32
	p-value		0.102
	N	38	40
NOSIE	Mean baseline	34.71	35.90
	Mean change	-2.29	-4.70
	% change	-6.60	-13.09
	p-value		0.323
	N	38	40

*Data based on last visit, unless otherwise specified, except for AUC, which is based on 0-2 hours or 0-4 hours post first injection.
+BAS score at hour 4 is the the last assessment taken up to 4 hours post first injection.
++Defined as a decrease from baseline of 2 points or more on the Behavioural Assessment Scale at 90 minutes post first dose.
**PANSS Agitation Items Score equals the sum of items P4 (Excitement), P7 (Hostility), G2 (Anxiety) and G4 (Tension).
Source Data: Protocol 126. Date of Table Generation: 20OCT97.

Secondary efficacy variable

For all subjects, the AUC of BAS score 0-2 hours of the 20 mg group was significantly less ($p<0.001$) than that of the 2 mg dose group. An analysis by timepoint showed that the mean change from baseline in BAS scores of subjects from 0.5 to 4 hours after the first injection of the 20 mg dose was consistently greater ($p<0.05$) than that in the 2 mg dose group, see Figure 2S. Among selected list of secondary efficacy variables, responder rates (nominal $p=0.001$), the PANSS agitation items at 4-hr (nominal $p<0.05$) showed a nominal significance in favor of 20 mg arm, but PANSS agitation items at last observation did not show statistical significance at nominal level of 0.05.

A summary of the sponsor's analyses on the primary and secondary efficacy variables based on all subjects can be found in Table 2.2S.

2.2.3 REVIEWER'S EVALUATIONS AND COMMENTS

This reviewer confirmed the sponsor results on the all subject analysis.

- Correlation between baseline PANSS agitation items versus baseline BAS scores

To address the medical reviewer's concern about whether there was a direct correlation between baseline PANSS agitation items versus baseline BAS scores (also see the first paragraph of Section 2.1.3), this reviewer performed a correlation analysis. The estimated correlation between PANSS agitation items vs. BAS scores at baseline was 0.30 (95%CI 0.08, 0.49). Thus, as also was the case in Trial 128-125, baseline PANSS agitation items appeared to be mildly to moderately correlated with baseline BAS scores. The baseline BAS score between the 2 mg and 20 mg IM arms were summarized in Table 3R.

Table 3R. Distribution of baseline BAS scores between 2 mg and 20 mg IM ziprasidone arms

Trial 128-126	Baseline Behavior Assessment Scale (BAS)				total
	4 quite and awake	5 signs of overt activity calms down w/ instructions	6 extremely active, not requiring restraint	7 violent, requires restraint	
2 mg	4 (10.5%)	30 (79%)	4 (10.5%)	0 (0%)	38
20 mg	3 (8%)	35 (88%)	1 (2.5%)	1 (2.5%)	40

Baseline BAS scores seemed reasonably balanced between the 2 mg and 10 mg IM ziprasidone arms. Baseline PANSS agitation items also seemed balanced with mean (range) of 14.29 (11,23) in the 2 mg arm and 14.90 (10,22) in the 20 mg arm, respectively.

- multiple endpoints (AUC of BAS by 4-hr, CGIC-S at 4-hr, and CGIC-S at study endpoint)

The sponsor stated that "Treatment contrasts were to be tested **each** at 2-tailed 0.05 level for significance." No multiplicity adjustment was mentioned in the protocol or amendments given the three co-primary efficacy variables, AUC of BAS at 4-hr, CGI-S at 4-hr, and CGI-S at study

endpoint. The results from the all subjects analysis were $p<0.001$ for AUC of BAS score at 4-hr, $p=0.008$ for CGI Severity score at 4-hr, and $p=0.004$ for CGI-S score at last observation. Since all three endpoints had very small p-values, clearly 20 mg dose is significantly more effective than that of 2 mg dose with respect to AUC of BAS at 4-hr, CGI-S at 4-hr and CGI-S at study endpoint.

- Subgroup analysis by gender

This reviewer performed a by-gender subgroup summary on the primary efficacy variable, see Table 4R. Although the male:female ratio was approximately 8:2, there seemed to be no by-gender difference within a given dosage arm, either in patients treated with 2 mg or 20 mg IM ziprasidone.

Table 4R. Summary of AUC of BAS at 4-hr by-gender of IM ziprasidone treated patients

Trial		2 mg			20 mg	
128-126	Male	Female	Total	Male	Female	Total
n	30	8	38	31	9	40
mean	15.53	16.47	15.73	12.13	12.51	12.23
sd	3.24	2.30	3.06	3.22	3.14	3.17

CONCLUSION

Two double-blind, active-controlled (2 mg IM ziprasidone) studies (Trials 128-125 and 128-126), indicated for the treatment of acute agitation in psychotic patients, were reviewed.

In Trial 128-126, the 20 mg IM dose is clearly significantly more effective than that of 2 mg IM dose with respect to AUC of BAS at 4-hr, CGI-S at 4-hr, and CGI-S at study endpoint. In Trial 128-125, if AUC of BAS at 2-hr can be used as a basis for showing effectiveness, the 10 mg IM dose is significantly more effective than that of 2 mg IM dose. If it is required to show statistical significance on at least two endpoints or all three endpoints, then the study failed to conclude that 10 mg IM dose is more effective than that of 2 mg IM dose. Thus, the choice of rule will depend on the appropriateness of AUC of BAS by designated time point as the primary efficacy variable for evaluating that efficacy.

/S/

Sue-Jane Wang, Ph.D.
Mathematical Statistician

Concur: Dr. Jin

Dr. Chi 10/26/98

cc:
NDA 20-919
HFD-120/Dr. Leber
HFD-120/Dr. Laughren
HFD-120/Dr. Glass
HFD-120/Mr. Purvis
HFD-120/Mr Hardeman
HFD-344/Dr. Barton
HFD-710/Dr. Chi
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SWANG/443-4252/October 13, 1998/zeldoxim.nda

This document consists of 14 pages, including 4 tables 2 figures from the sponsor, 2 figures from the sponsor, and 4 tables from this reviewer.

Chi

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 13, 1998

FROM: Director, Division of Biometrics II (HFD-715)

SUBJECT: Review of Zeldox IM (Intramuscular Ziprasidone Mesylate), NDA 20-919

TO: Director, Division of Biometrics I (HFD-710)

Attached is Sue-Jane Wang's statistical review of NDA 20-919 for your secondary and tertiary review.

S. Edward Nevius

S. Edward Nevius, Ph.D.

cc:
HFD-710/Jin
HFD-715/Wang, division file