7.2.5.2 **Study Plan:**

Objectives: To determine the safety and efficacy of nefazodone, imipramine, and placebo in the treatment of moderately to severely depressed outpatients who met DSM-III-R criteria for Major Depression or Bipolar Disorder, Depressed.

Population to be Studied: Outpatients of either sex, aged 18 or older, with a DSM-III-R diagnosis of moderate or severe Major Depression, Single or Recurrent episode, or Bipolar Disorder, Depressed.

Study Design: Single-center, randomized, double-blind, parallel-group six-week comparison of the safety and efficacy of nefazodone, imipramine, and placebo. Ratings scales included: 28-Item Hamilton Rating Scale for Depression (HAM-D-28), Clinical Global Impressions (CGI) Scale, Patient's Global Assessments (PGA) Scale, Hamilton Rating Scale for Anxiety (HAM-A), and Symptom Checklist-87 (SCL-87).

Plan for Analysis: A one-way analysis of variance (ANOVA) model was used to test for baseline comparability as well as differences between treatments for the change from Baseline in HAM-D and CGI Severity scores. Categorical data such as CGI and PGA Improvement scores were analyzed using Fisher's Exact Permutation Test. The planned sample size of 180 patients had a power of ≥80% to detect an average difference of five points in the HAM-D-17 Total Score between placebo and each of the other treatment groups (nefazodone, imipramine).

7.2.5.3 **Study Conduct/Outcome** (see appendix for related tables)

Patient Disposition: 180 outpatients at one study center received study medication. 169 outpatients were evaluable for efficacy.

Demographics: Of the 180 outpatients, 107 (59%) were women and 73 (41%) men. They ranged in age from (99%) met DSM-III diagnostic criteria for Major Depression (Single or Recurrent) and two (1%) met DSM-III-R criteria for Bipolar Disorder, Depressed; in addition, 36 patients (20%) met DSM-III-R diagnostic criteria for Major Depression, Melancholic Subtype; and 85 (47%) experienced a previous depressive episode.

Dosing Information: One oral capsule given QD or two to six capsules equally divided BID. Recommended dosage ranges: nefazodone 50 to 300 mg/day; imipramine 50 to 300 mg/day; or placebo, two to six capsules/day. For outpatients who had an efficacy evaluation at Week 6, the mean of the Modal Daily Dose at Week 6 was 263.0 mg/day for nefazodone, 206.0 mg/day for imipramine, and 5.5 capsules/day for placebo.

Concomitant Medications: The protocol permitted the use of chloral hydrate for sleep and this was the most frequently used concomitant psychotropic medication. Three outpatients, two in the imipramine group and one in the placebo group, took prohibited concomitant psychotropic medication (diazepam, hydroxyzine HCL, and triazolam), but these outpatients were not excluded from the analyses.

Efficacy Results: Outpatients were considered evaluable for efficacy (i.e., included in the Intent-to-Treat Sample) if they were randomized to treatment, received a dose of study medication, and had an efficacy evaluation during treatment. One hundred sixty-nine outpatients were evaluable for efficacy; 57 received placebo, 55 received imipramine and 57 received nefazodone.

The Nefazodone response is not significant for the HAM-D 17 Total at week

6 LOCF while the imipramine response is. The LOCF results for the CGI and HAM-D depressed mood item suggest some improvement for Nefazodone.

7.2.5.4 Conclusions:
This study failed to show that Nefazodone is more effective than placebo for the treatment of depression. The imipramine response was significant for both LOCF and OC. The study had an absence of dropouts for adverse events and a large number of dropouts due to lack of efficacy suggesting that the dose in the study was too low.

CN 104-002
CN 104-006
-007

7.2.6 Study 030A2-007 (conducted 12/85 to 4/89)
A Multicenter, Double-Blind Comparison of Four Fixed Doses of Nefazodone and Placebo in Patients with Moderate to Severe Depression (Protocol 030A2-0007).

7.2.6.1 Investigators\Locations: (1) Jan Fawcett, M.D., Rush Presbyterian-St. Luke's Medical Center, Chicago, Illinois, USA; (2) Yvon LaPierre, M.D., Royal Ottawa Hospital, Ottawa, Ontario, Canada; (3) Sidney C. Lerfald, M.D., 5600 MacCorkle Ave. S.E., Charleston, West Virginia, USA; (4) C. Leon McGahee, M.D. and Binni Bennett, M.S.W., Marshall University School of Medicine, Huntington, West Virginia, USA; (5) John C. Pecknold, M.D. and (6) Neelakanta P.V. Nair, M.D., St. Mary's Hospital, Montreal, Quebec, Canada, and Douglas Hospital Research Center, Verdun, Quebec, Canada; (7) Gary Tollefson, M.D., Ph.D., St. Paul-Ramsey Medical Center, St. Paul, Minnesota, USA.

7.2.6.2 Study Plan:

Objectives: To determine the safety and efficacy of various doses of nefazodone as compared to placebo in the treatment of depressed patients.

Population to be Studied: Patients of either sex, aged 18-70 (18-65 at the two Canadian study centers), with a diagnosis of Major Depressive Disorder (Research Diagnostic Criteria - that had been modified to require that dysphoric features be present for at least four weeks).

Study Design: Multicenter, randomized, double-blind, parallel group 6-week comparison of four fixed doses of nefazodone and placebo. Ratings scales included: 25-Item Hamilton Rating Scale for Depression (HAM-D-25), Clinical Global Impressions (CGI) Scale, Patient's Global Assessments (PGA) Scale, Hamilton Rating Scale for Anxiety (HAM-A), and Symptom Checklist-90 (SCL-90).

Plan for Analysis: A two-way analysis of variance (ANOVA) model with study center, treatment, and study center by treatment interaction effects was used to test for baseline comparability as well as differences between treatments for the change from Baseline in HAM-D and CGI Severity scores. Categorical data such as CGI and PGA Improvement Scores were analyzed within the framework of the generalized Cochran-Mantel-Haenszel (CMH) procedure, using study-center as the stratification variable. Both the two-way ANOVA and CMH models were used to test the differences between treatments averaged across the study centers. The planned sample size of 250 patients had a power of ≥ 80% to detect an average difference of 4.9 points in the HAM-D-17 Total Score between a therapeutic dose level of nefazodone and placebo or a significant linear trend across placebo and the four nefazodone dose levels.

7.2.6.3 Study Conduct/Outcome (see appendix for related tables)

Patient Disposition: 234 patients at five study centers received study

Appendix CN104-002

TABLE A
Protocol: CN104-002
Demographic Characteristics for Total Patient Sample

Treatment Groups	n	Age (years)		Sex [n(%)]		Race [n(%)]	
		Mean	Range	Male	Female	White	Non-White
Nefazodone	60	38.2		26 (43)	34 (57)	50 (83)	10 (17)
Imipramine	60	37.6		26 (43)	34 (57)	52 (87)	8 (13)
Placebo	60	38.6		21 (35)	39 (65)	58 (97)	2 (3)

TABLE B
Protocol: CN104-002
Patient Completion Rates

Treatment Groups	Number Randomized	Intent-to-Treat Sample	Completers [n(%)]					
			Wk 1	Wk 2	Wk 3	Wk 4	WK 5	Wk 6
Nefazodone	60	57	53 (93)	52 (91)	49 (86)	49 (86)	47 (82)	46 (81)
Imipramine	60	55	53 (96)	49 (89)	45 (82)	42 (76)	40 (73)	42 (76)
Placebo	60	57	55 (96)	52 (91)	48 (84)	44 (77)	40 (70)	38 (67)

TABLE C
Protocol: CN104-002
Dosing Information

Treatment Groups	Mean Modal Dose (mg/day) for Completers in Active Drug Groups					
	Wk 1	Wk 2	Wk 3	Wk 4	WK 5	Wk 6
Nefazodone	183.0	214.4	223.5	263.3	264.9	263.0
Imipramine	164.2	170.4	182.2	189.3	211.3	206.0

TABLE D
Protocol: CN104-002
Mean Change from Baseline in HAM-D-17 Total Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		WK 5		Wk 6	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone	57	23.3	56	-3.0	56	-5.6	57	-7.3	57	- 9.0	57	-10.1	57	-10.0
Imipramine	55	23.5	55	-3.4	55	-8.3	55	-9.3	55	-11.3	55	-13.5	55	-13.8
Placebo	57	23.1	57	-2.5	57	-5.1	57	-6.5	57	- 6.9	57	- 7.3	57	- 8.2
2-sided p-values for pairwise comparisons														
Nefazodone vs Placebo	0.67		0.47		0.63		0.53		0.10		0.05		0.08	
Imipramine vs Placebo	0.38		0.20		0.00		0.02		0.00		0.00		0.00	

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		WK 5		Wk 6	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone	57	23.3	53	-2.9	52	-5.9	49	-7.2	49	- 9.1	46	-10.4	46	-11.8
Imipramine	55	23.5	53	-3.5	49	-8.3	44	-9.6	42	-12.9	40	-15.0	42	-15.6
Placebo	57	23.1	55	-2.3	52	-5.3	48	-7.0	43	- 8.1	40	- 9.6	38	-11.3
2-sided p-values for pairwise comparisons														
Nefazodone vs Placebo	0.67		0.38		0.61		0.84		0.46		0.63		0.72	
Imipramine vs Placebo	0.38		0.10		0.01		0.04		0.00		0.00		0.01	

TABLE F
Protocol: CN104-002
Mean Change from Baseline in HAM-D Depressed Mood (Item 1) Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		WK 5		Wk 6	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone	57	3.0	56	-0.3	56	-0.6	57	-0.8	57	-0.9	57	-1.2	57	-1.3
Imipramine	55	3.0	55	-0.3	55	-0.8	55	-0.9	55	-1.2	55	-1.5	55	-1.6
Placebo	57	3.0	57	-0.3	57	-0.6	57	-0.8	57	-0.8	57	-0.8	57	-1.0
2-sided p-values for pairwise comparisons														
Nefazodone vs Placebo	0.16		0.90		0.74		1.00		0.47		0.04		0.05	
Imipramine vs Placebo	0.16		0.87		0.15		0.35		0.02		0.00		0.00	

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		WK 5		Wk 6	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone	57	3.0	53	-0.3	52	-0.7	49	-0.8	49	-1.0	46	-1.3	46	-1.5
Imipramine	55	3.0	53	-0.3	49	-0.8	44	-1.0	42	-1.5	40	-1.8	42	-1.9
Placebo	57	3.0	55	-0.3	52	-0.6	48	-0.8	43	-1.0	40	-1.1	38	-1.3
2-sided p-values for pairwise comparisons														
Nefazodone vs Placebo	0.16		0.94		0.60		0.92		0.89		0.22		0.33	
Imipramine vs Placebo	0.16		0.92		0.11		0.33		0.01		0.00		0.01	

TABLE H
Protocol: CN104-002
Mean Change from Baseline in CGI Scale: Doctor's Opinion of Severity

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		WK 5		Wk 6	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone	57	4.2	56	-0.2	56	-0.5	57	-0.6	57	-0.8	57	-1.0	57	-1.2
Imipramine	55	4.2	55	-0.1	55	-0.6	55	-0.9	55	-1.2	55	-1.5	55	-1.6
Placebo	57	4.1	57	-0.1	57	-0.4	57	-0.5	57	-0.6	57	-0.7	57	-0.8
2-sided p-values for pairwise comparisons														
Nefazodone vs Placebo	0.36		0.51		0.39		0.56		0.17		0.07		0.04	
Imipramine vs Placebo	0.44		0.96		0.06		0.03		0.00		0.00		0.00	

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		WK 5		Wk 6	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone	57	4.2	53	-0.2	52	-0.5	48	-0.6	49	-0.9	46	-1.1	46	-1.4
Imipramine	55	4.2	53	-0.1	49	-0.6	45	-1.0	42	-1.4	40	-1.7	42	-1.9
Placebo	57	4.1	55	-0.1	52	-0.4	48	-0.6	44	-0.8	40	-0.9	38	-1.1
2-sided p-values for pairwise comparisons														
Nefazodone vs Placebo	0.36		0.36		0.34		0.80		0.55		0.44		0.20	
Imipramine vs Placebo	0.44		0.80		0.07		0.03		0.00		0.00		0.00	

TABLE I
Protocol: CN104-002
Mean Score in CGI Scale: Doctor's Opinion of Improvement

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Wk 1		Wk 2		Wk 3		Wk 4		WK 5		Wk 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Nefazodone	50	3.6	56	3.3	57	3.0	57	2.7	57	2.5	57	2.4
Imipramine	53	3.6	55	2.8	55	2.6	55	2.3	55	2.1	55	2.1
Placebo	55	3.7	57	3.4	57	3.2	57	3.1	57	3.0	57	2.9
2-sided p-values for pairwise comparisons												
Nefazodone vs Placebo	0.29		0.47		0.24		0.06		0.02		0.02	
Imipramine vs Placebo	0.23		<0.01		<0.01		<0.01		<0.01		<0.01	

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Wk 1		Wk 2		Wk 3		Wk 4		WK 5		Wk 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Nefazodone	50	3.6	52	3.?	48	2.9	49	2.7	46	2.3	46	2.1
Imipramine	53	3.6	49	2.8	45	2.5	42	2.1	40	1.9	42	1.8
Placebo	54	3.7	51	3.3	48	3.1	43	3.0	39	2.7	38	2.4
2-sided p-values for pairwise comparisons												
Nefazodone vs Placebo	0.31		0.55		0.40		0.15		0.11		0.14	
Imipramine vs Placebo	0.25		<0.01		<0.01		<0.01		<0.01		0.01	

Study CN104-002 (Conducted 7/88 to 11/90)

Study CN104-002 was a randomized, parallel, 3-armed, dose titration study of 6 weeks duration with a 46-week extension. A total of 180 patients (60 in each treatment group) were randomized to one of three treatment groups (nefazodone 300 mg/day peak dose allowed, imipramine 300 mg/day peak dose allowed or placebo) at 3 psychiatric sites. One site (Dixon) enrolled 78% of the patients. For all three sites, the study was conducted under the direction of Dr. Feighner.

Since all 3 sites were administered under the same investigator and the results by site were consistent across the 3 sites, pooling the patients from all sites for analysis seems justified to this reviewer. (The same approach was taken for Study 104-005 where small sites were pooled to form one center under the direction of a single investigator.)

The treatment groups were comparable with regard to demographics and psychiatric history. Nearly all the patients (99%) were diagnosed with major depression; 47% had recurrent depression. Only 22% of the patients had used antidepressants previously.

Patient Disposition

From the table below it can be seen that in the two drug groups at least 70% of the patients completed the study while in the placebo group 63% of the patients were completers. No patients dropped out in the nefazodone group due to adverse experiences while 6 (10%) patients dropped due to lack of efficacy. Seven of the 11 adverse events for the imipramine group occurred during Week 1. In the placebo group, the primary reasons for withdrawal were lack of efficacy (13%) and patient withdrawal of consent (10%).

Table 16. Study CN104-002
Patients on Study

WEEK	NEFAZODONE	PLACEBO	IMIPRAMINE
Randomized	60	60	60
1	56 (93%)	52 (87%)	49 (82%)
2	53 (88%)	50 (83%)	47 (78%)
3	50 (83%)	45 (75%)	45 (75%)
4	49 (82%)	41 (68%)	42 (70%)
5	46 (77%)	38 (63%)	42 (70%)
6	46 (77%)	38 (63%)	42 (70%)

Table 17. Study CN104-002
Reasons for Dropouts

Reason for Dropout	NEFAZODONE	PLACEBO	IMIPRAMINE
Lack of Efficacy	6 (10%)	8 (13%)	1 (2%)
Adverse Experience	0 (0%)	2 (3%)	11 (18%)
Lost-to-Followup	4 (7%)	4 (7%)	5 (8%)
Other	4 (7%)	8 (13%)	1 (2%)

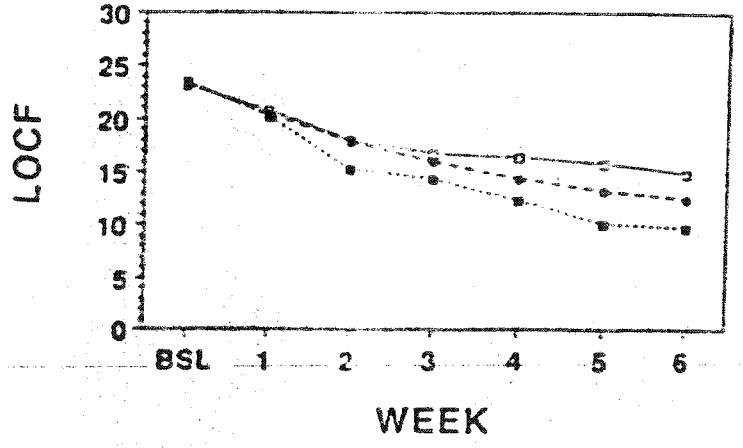
Results

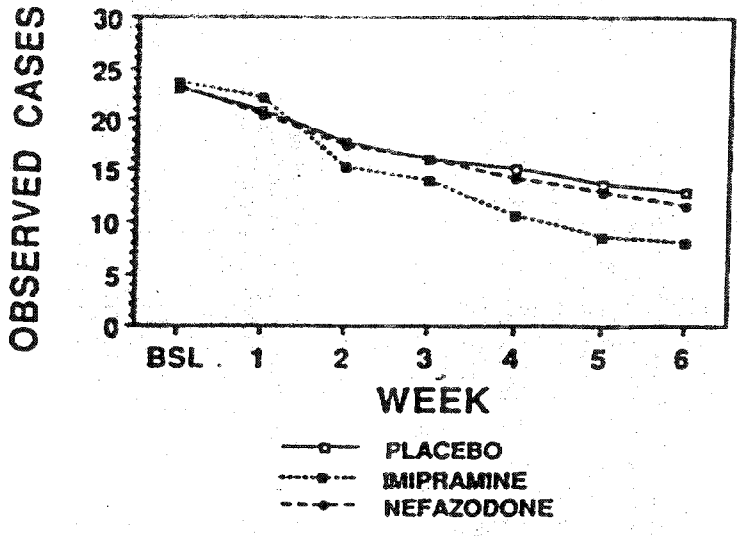
For the HAM-D 17 Total Week 6 LOCF, the nefazodone response is not statistically significantly greater than placebo while the imipramine response is significantly greater than both placebo ($p < .0002$) and nefazodone ($p = .05$). In spite of the large number of patients that remained on study, the LOCF and the observed cases results for nefazodone are not consistent for any variable (Figure 6). However, the imipramine response was highly significant for all comparisons for both LOCF and observed cases with p-values generally less than .001.

Table 18. Study CN104-002
Sponsor's Results

	NEFAZODONE Mean	PLACEBO Mean	IMIPRAMINE Mean	P-VALUE NEF vs PLA
HAM-D 17 Total				
Baseline	23.3	23.1	23.5	.67
Week 6				
LOCF	-10.8	-8.2	-13.8	.08
OC	-11.8	-11.3	-15.6	.72
HAM-D Item 1				
Baseline	3.0	3.0	3.0	.16
Week 6				
LOCF	-1.3	-1.0	-1.6	.05
OC	-1.5	-1.3	-1.9	.33
CGI Severity of Illness				
Baseline	4.2	4.1	4.2	.35
Week 6				
LOCF	-1.2	-0.8	-1.6	.03
OC	-1.4	-1.1	-1.9	.18
CGI Global Improvement				
Week 6				
LOCF	2.1	2.9	2.1	.02
OC	2.1	2.4	1.8	.18

Figure 6: Study CN104 - 002
HAM-D 17 Total by Week
Means





Reviewer's Comments on Study CN104-002

The absence of dropouts for adverse events and the large number of dropouts due to lack of efficacy suggest, as the HAM-D 17 Total data does (Figure 6), that the dose in this study was too low to provide convincing evidence of efficacy. (Also, it should be noted that the imipramine group beat placebo for all comparisons.) These findings for low dose nefazodone are consistent with the responses observed in the low dose arm of Studies 030A0A-003, 03A0A-004A and 03A0A-004B.

The LOCF results of the CGI and HAM-D Depressed Mood Item suggest that nefazodone offers some improvement over placebo however the OC results show no statistically significant differences between the groups.

This study failed to show that nefazodone is more effective than placebo for the treatment of depression presumably due to inadequate dosing.

7.0 Efficacy Findings

7.1 Overview of Studies Pertinent to Efficacy

There were eleven controlled trials in the NDA including eight placebo-controlled trials and three two-arm, active-control trials conducted during Nefazodone's clinical development. These trials were primarily conducted in adult out-patients meeting RDC, DSM-III or DSM-IIIR criteria for major depressive episode. The eight double-blind, placebo-controlled trials were conducted in the United States and Canada.

Seven of the short-term, placebo-controlled studies, one was a fixed-dose study and the other seven were flexible-dose designs. These studies compared Nefazodone in doses from 50 mg up to 600 mg, although a number of subjects did not reach the higher dose ranges.

These trials tended to look at the same group of efficacy variables; the HAM-D total, the HAM-D depressed mood item, the clinical global impression severity of illness score and the global improvement score.

For these primary studies the sponsor provided data from the intent-to-treat sample and results for both last observation carried forward and completer cases analyses were presented.

There was good consistency of demographic data throughout all of the studies. Seventy-five percent of the patients enrolled in these trials were women. Eighty-five percent of the patients were white and the average age was about 39 years.

Patients were required to have a score of at least 20 on the HAMD-17 to enter these trials.

There were 7 completed and 3 on-going active-controlled trials which do not show differences between treatment groups and do not contribute to the evaluation of efficacy.

7.2 Summaries of Placebo Controlled Studies Pertinent to Efficacy

7.2.1 Study CN104-005 (conducted 2/89 to 6/90)
A Double-Blind Trial of Nefazodone, Imipramine, and Placebo in the Treatment of Depressed Outpatients (Protocol CN104-005).

7.2.1.1 Investigators and Location

Two centers under the auspices of a single principal investigator, Karl Rickels, M.D., University Hospital, Philadelphia, Pennsylvania, U.S.A. Center 001 comprised six Psychiatric Practices located in Pennsylvania, Delaware, New Jersey, and West Virginia; Center 002 comprised seven Family Practices located in Pennsylvania, Delaware, and New Jersey.

7.2.1.2 Study Plan:

Objectives\Rational: To investigate the safety and efficacy of nefazodone, imipramine, and placebo in the treatment of patients with a non-psychotic Major Depressive Episode or Bipolar Disorder, Depressed, and

to provide data on the effective dose range.

Population to be Studied: Outpatients of either sex, 18 years of age or older, with a diagnosis of Major Depression (Single Episode or Recurrent) or Bipolar Disorder, Depressed (DSM-III-R).

Study Design: Multicenter, randomized, double-blind, parallel-group, 8-week comparison of the safety and efficacy of nefazodone, imipramine, and placebo. Rating scales included: 28-item Hamilton Rating Scale for Depression (HAM-D-28); Symptom Checklist-87 (SCL-87); Clinical Global Impression (CGI) Scale, Patient's Global Assessments (PGA) Scale, and the Hamilton Rating Scale for Anxiety (HAM-A). Two distinct practice settings, a Family Practice Group and a Psychiatric Practice Group, were established a priori to permit analyses of the relationship of response to treatment setting.

Analysis Plan: A two-way analysis of variance (ANOVA) model with study center (Family Practice or Psychiatric Practice), treatment, and study center by treatment interaction effects was used to test for baseline comparability as well as differences between treatments for the change from Baseline in HAM-D and CGI Severity scores. Categorical data such as CGI and PGA Improvement scores were analyzed within the framework of the generalized Cochran-Mantel-Haenszel (CMH) procedure. Both the two-way ANOVA and CMH models tested the differences between treatments averaged across the study centers. The planned sample size of 240 patients had a power of ≥ 80% to detect an average difference of 4 points in the HAM-D-17 Total Score between placebo and each of the other treatment groups (nefazodone, imipramine).

7.2.1.3 Study Conduct/Outcome (see appendix for related tables)

Patient Disposition: 283 patients at two study centers were randomized to three treatment groups. 260 patients were evaluable for efficacy.

Demographics: Of the 283 patients, 179 (63%) were women and 104 (37%) men. Patient age ranged from 19 to 81 years. 271 (96%) patients met DSM-III-R criteria for moderate to severe Major Depression (Single or Recurrent Episode) and 12 (4%) met the diagnostic criteria for Bipolar Disorder, Depressed; 159 (56%) patients experienced a previous depressive episode.

Dosing Information: Oral capsules administered QD or BID. Recommended dosage ranges: nefazodone (100-mg capsule) 100 to 600 mg/day; imipramine (50-mg capsule) 50 to 300 mg/day; placebo, one capsule/day to six capsules/day. The mean modal dose at Week 8 was 375.4 mg/day for the nefazodone group, 164.9 mg/day for the imipramine group, and 4.5 capsules/day for the placebo group.

Concomitant Medications: The protocol permitted the use of chloral hydrate for sleep and this was the most frequently used concomitant psychotropic medication. Seventeen patients took prohibited concomitant psychotropic medications (alprazolam, diazepam, lorazepam, amitriptyline, Librax, hydroxyzine HCl, fluoxetine HCl, caffeine, doxepin HCl, and prochlorperazine); however, these patients were not excluded from the analyses.

Efficacy Results: Patients were considered evaluable for efficacy (i.e., included in the Intent-to-Treat Sample) if they were randomized to

treatment, received a dose of study medication, and had an efficacy evaluation during treatment. Of the 260 patients evaluable for efficacy, 91 received placebo, 83 received imipramine, and 86 received nefazodone. Sixteen patients were lost to follow up.

There are no differences in the week 8 LOCF nefazodone and placebo results for center one. In Center 2 the nefazodone group was significantly different ($p<.001$) from placebo on the 4 efficacy measures. These differences are first apparent at week 3. The LOCF and OC results are also consistent.

Data is provided for the combined analysis in the appendix.

7.2.1.4 Conclusion: Center one, in this study, did not differentiate Nefazodone or Imipramine from placebo. Center two clearly does differentiate Nefazodone from placebo and the combined analysis isalso postive

CN 104-005

7.2.2 Study 03A0A-004B (8/87 to 5/89) A Double-Blind Trial of Two Daily Dose Ranges of Nefazodone and Placebo in the Treatment of Depressed Outpatients

7.2.2.1 Investigator/Locations: Joseph Mendels, M.D., Philadelphia Medical Institute, Philadelphia, PA (Study 2408); Frederick Reimherr, M.D., University of Utah, College of Medicine, Salt Lake City, UT (Study 2531).

7.2.2.2 Study Plan:

Objectives: To determine the safety and efficacy of nefazodone titrated in two dose ranges (recommended low-dose range 150-300 mg/day and recommended high-dose range 300-600 mg/day) as compared to placebo in the treatment of outpatients with moderate to severe depression.

Population to be Studied: Outpatients of either sex, 18 years of age or older, with a diagnosis of Major Depressive Episode or Bipolar Disorder, Depressed (DSM-III).

Study Design: Multicenter, randomized, double-blind, parallel group, 6-week comparison of the safety and efficacy of two dose ranges of nefazodone and placebo. Rating scales included: 17-Item Hamilton Rating Scale for Depression (HAM-D-17); Clinical Global Impressions (CGI) Scale; Inventory for Depressive Symptomatology - Clinician (IDS-C); and Inventory for Depressive Symptomatology -Self Report (IDS-SR). A narrative of the physician's overall assessment was collected on the End-of-Study Evaluation Form.

Plan for Analysis: A two-way analysis of variance (ANOVA) model with study center, treatment, and study center by treatment interaction effects was used to test for baseline comparability as well as differences between treatments for the change from Baseline in HAM-D and CGI Severity scores. Categorical data such as CGI Improvement scores were analyzed within the framework of the generalized Cochran-Mantel-Haenszel (CMH) procedure, using study center as the stratification variable. Both the two-way ANOVA and CMH models tested the differences between treatments averaged across the study centers. The planned sample size of 240 patients had a power of $\geq 80\%$ to detect an average difference of four points in the HAM-D-17 Total score between nefazodone and placebo.

TABLE A
Protocol: CN104-005
Demographic Characteristics for Total Patient Sample

Treatment Groups	n	Age (years)		Sex (n(%))		Race (n(%))	
		Mean	Range	Male	Female	White	Non-White
Nefazodone	96	44.7		31 (32)	65 (68)	83 (86)	13 (14)
Imipramine	92	42.7		35 (38)	57 (62)	82 (89)	10 (11)
Placebo	95	42.6		38 (40)	57 (60)	87 (92)	8 (8)

TABLE B
Protocol: CN104-005
Patient Completion Rates

Treatment Groups	Number Randomized	Intent-to-Treat Sample	Completers [n(%)]					
			Wk 1	Wk 2	Wk 3	Wk 4	WK 6	Wk 8
Nefazodone	96	86	81 (94)	75 (87)	73 (85)	68 (79)	64 (74)	65 (76)
Imipramine	92	83	76 (92)	67 (81)	60 (72)	50 (60)	51 (61)	47 (57)
Placebo	95	91	86 (95)	77 (85)	81 (89)	68 (75)	71 (78)	61 (67)

LOCF = same as ITT total started in Rickels 1994

TABLE C
Protocol: CN104-005
Dosing Information

Treatment Groups	Mean Modal Dose (mg/day) for Completers in Active Drug Groups					
	Wk 1	Wk 2	Wk 3	Wk 4	WK 6	Wk 8
Nefazodone	223.5	286.7	321.9	380.9	384.4	375.4
Imipramine	109.2	143.3	160.0	169.0	170.6	164.9

TABLE D
Protocol: CN104-005
Mean (Least Squares) Change from Baseline in HAM-D-17 Total Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		WK 6		Wk 8	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone	86	24.4	86	-3.3	86	-5.8	86	-8.5	86	-10.0	86	-10.9	86	-12.0
Imipramine	83	24.3	82	-2.5	82	-4.9	82	-6.9	83	- 8.6	83	- 9.9	83	-10.2
Placebo	90	23.5	88	-3.0	88	-5.0	90	-7.0	90	- 7.4	90	- 7.3	90	- 8.0
2-sided p-values for pairwise comparisons														
Nefazodone vs Placebo	0.08		0.71		0.37		0.12		0.01		0.00		0.00	
Imipramine vs Placebo	0.11		0.44		0.85		0.97		0.26		0.02		0.06	

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANCOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		WK 6		Wk 8	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone	86	24.4	86	-3.2	86	-5.8	86	-8.4	86	-9.9	86	-10.7	86	-11.8
Imipramine	83	24.3	82	-2.5	82	-4.8	82	-6.9	83	-8.5	83	-9.8	83	-10.1
Placebo	90	23.5	88	-3.1	88	-5.1	90	-7.1	90	-7.7	90	-7.5	90	-8.3
2-sided p-values for pairwise comparisons														
Nefazodone vs Placebo	0.08		0.81		0.49		0.19		0.03		0.00		0.00	
Imipramine vs Placebo	0.11		0.37		0.70		0.78		0.43		0.03		0.12	

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(1) Rule for how to render this precise
(2) Tx-by-center interaction. See 1 of these similar cases.

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TABLE D
Protocol: CN104-005
Mean (Least Squares) Change from Baseline in HAM-D-17 Total Score

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		WK 6		Wk 8	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone	86	24.4	80	-3.4	75	-6.6	73	-9.6	68	-10.9	64	-12.1	64	-14.3
Imipramine	83	24.3	75	-2.6	67	-5.4	58	-8.6	50	- 9.8	50	-13.5	47	-14.3
Placebo	90	23.5	85	-3.0	75	-5.5	81	-7.4	68	- 7.9	71	- 8.3	60	- 9.7
2-sided p-values for pairwise comparisons														
Nefazodone vs Placebo	0.08		0.63		0.24		0.04		0.01		0.00		0.00	
Imipramine vs Placebo	0.11		0.58		0.96		0.29		0.13		0.00		0.00	

TABLE F

Protocol CN104-005

Mean (Least Squares) Change from Baseline in HAM-D Depressed Mood (Item 1) Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		WK 6		Wk 8	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone	86	3.0	86	-0.4	86	-0.7	86	-0.9	86	-1.1	86	-1.3	86	-1.4
Imipramine	83	2.9	82	-0.3	82	-0.6	82	-0.8	83	-1.1	83	-1.2	83	-1.3
Placebo	90	2.9	88	-0.4	88	-0.7	90	-0.8	90	-0.9	90	-0.9	90	-0.9
2-sided p-values for pairwise comparisons														
Nefazodone vs Placebo	0.33		0.89		0.93		0.26		0.06		0.01		0.00	
Imipramine vs Placebo	0.68		0.78		0.42		0.96		0.11		0.03		0.01	

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		WK 6		Wk 8	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone	86	3.0	80	-0.4	75	-0.8	73	-1.0	68	-1.2	64	-1.4	64	-1.7
Imipramine	83	2.9	75	-0.3	67	-0.6	58	-0.9	50	-1.2	50	-1.6	47	-1.8
Placebo	90	2.9	85	-0.4	75	-0.7	81	-0.8	68	-1.0	71	-1.0	60	-1.1
2-sided p-values for pairwise comparisons														
Nefazodone vs Placebo	0.33		0.78		0.54		0.11		0.17		0.01		0.00	
Imipramine vs Placebo	0.68		0.85		0.68		0.66		0.15		0.00		0.10	

TABLE H
Protocol: CN104-005
Mean (Least Squares) Change from Baseline in CGI: Doctor's Opinion of Severity

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		WK 6		Wk 8	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone	86	4.5	86	-0.2	86	-0.6	86	-0.9	86	-1.1	86	-1.3	86	-1.6
Imipramine	83	4.5	82	-0.2	82	-0.5	82	-0.7	83	-0.9	83	-1.1	83	-1.3
Placebo	91	4.4	89	-0.3	89	-0.5	91	-0.7	91	-0.8	91	-0.9	91	-1.0
2-sided p-values for pairwise comparisons														
Nefazodone vs Placebo	0.16		0.45		0.38		0.23		0.12		0.02		0.01	
Imipramine vs Placebo	0.12		0.24		0.79		0.87		0.62		0.13		0.15	

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		WK 6		Wk 8	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone	86	4.5	81	-0.2	75	-0.7	72	-1.0	68	-1.2	62	-1.4	65	-2.0
Imipramine	83	4.5	76	-0.2	67	-0.5	60	-0.9	49	-1.1	51	-1.6	47	-2.1
Placebo	91	4.4	86	-0.3	76	-0.5	81	-0.7	68	-0.9	70	-1.0	60	-1.3
2-sided p-values for pairwise comparisons														
Nefazodone vs Placebo	0.16		0.49		0.24		0.04		0.09		0.05		0.00	
Imipramine vs Placebo	0.12		0.33		0.98		0.22		0.29		0.00		0.00	

TABLE I
Protocol: CN104-005
Mean (Least Squares) Score in CGI Scale: Doctor's Opinion of Improvement

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week											
	Wk 1		Wk 2		Wk 3		Wk 4		WK 6		Wk 8	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Nefazodone	81	3.6	86	3.2	86	2.8	86	2.6	86	2.5	86	2.2
Imipramine	76	3.7	82	3.4	82	3.1	83	2.8	83	2.7	83	2.6
Placebo	86	3.6	89	3.3	91	3.1	91	3.0	91	3.1	91	3.0
2-sided p-values for pairwise comparisons												
Nefazodone vs Placebo	0.93		0.61		0.07		0.01		<0.01		<0.01	
Imipramine vs Placebo	0.27		0.60		0.82		0.31		0.02		0.07	

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week											
	Wk 1		Wk 2		Wk 3		Wk 4		WK 6		Wk 8	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Nefazodone	81	3.6	75	3.1	72	2.7	68	2.5	62	2.4	65	1.9
Imipramine	76	3.7	67	3.2	60	2.8	49	2.7	51	2.1	47	1.9
Placebo	86	3.6	76	3.2	81	3.1	78	2.7	70	2.9	66	2.6
2-sided p-values for pairwise comparisons												
Nefazodone vs Placebo	0.93		0.35		0.03		0.02		<0.01		<0.01	
Imipramine vs Placebo	0.27		0.93		0.18		0.03		<0.01		<0.01	

Study CN104-005 (Conducted 2/89 to 6/90)

Study CN104-005 was a randomized, parallel, 3-armed, dose titration study of 8 weeks duration with a 44-week open label extension. The three treatment groups were nefazodone (600 mg/day peak allowable dose), placebo and imipramine (300 mg/day peak allowable dose).

A total of 283 patients were enrolled at 13 different sites; all under the auspices of Dr. Rickels. In concurrence with the protocol, these sites were grouped into two "centers" (referred to as studies by the sponsor) according to the type of site; psychiatric practice site or family practice site. Six psychiatric sites constituted Center 1 while 7 family practice sites constituted Center 2. Due to the consistency of the results by site within centers and the small number of patients at each site, this review will focus on the center results.

The results for the 2 centers differed significantly on the 4 efficacy measures. For the HAM-D 17 Total the treatment difference for Center 1 was 0.7 while for Center 2 the treatment difference was 6.9. P-values for tests of treatment by center interaction ranged from .02 to .11. These center results, therefore, are presented separately here. (The sponsor presented the results of the 2 centers combined and reported a p-value of less than .01 for the HAM-D Total comparison at Week 8 LOCF.)

Center 1

The treatment groups in this study were comparable with regard to demographics. About 60% of the patients in each group were diagnosed with recurrent depression; 57% of the patients had previously used antidepressants.

Patient Disposition

Less than 60% of the patients completed the study in the nefazodone and imipramine groups while about 70% of the placebo patients were completers (Table 19). Of the 20 dropouts in the nefazodone group, 10 patients dropped during the first week of the study; the major reasons for discontinuing at Week 1 were adverse event (5 patients) and withdrawal of consent (3 patients). In the placebo group, the major reason for dropout was lack of efficacy (5 of the 8 patients dropped during Week 6). In the imipramine group, patients dropped during the first 3 weeks predominately due to adverse events while for the last 5 weeks of the study the main reason for dropout was lack of efficacy.

Table 19. Study CN104-005
Center 1
Patients on Study

WEEK	NEFAZODONE	PLACEBO	IMIPRAMINE
Randomized	48	48	49
1	38 (79%)	46 (96%)	44 (90%)
2	36 (75%)	45 (94%)	40 (82%)
3	34 (71%)	42 (88%)	35 (71%)
4	33 (69%)	41 (85%)	33 (67%)
6	28 (58%)	35 (73%)	27 (55%)
8	28 (58%)	33 (69%)	27 (55%)

Table 2. Study CN104-005/Center 1
Reasons for Dropouts

Reason for Dropout	NEFAZODONE	PLACEBO	IMIPRAMINE
Lack of Efficacy	4 (8%)	8 (17%)	9 (18%)
Adverse Experience	6 (13%)	4 (8%)	9 (18%)
Lost-to-Followup	5 (10%)	0 (0%)	1 (2%)
Other	5 (10%)	3 (6%)	3 (6%)

Results

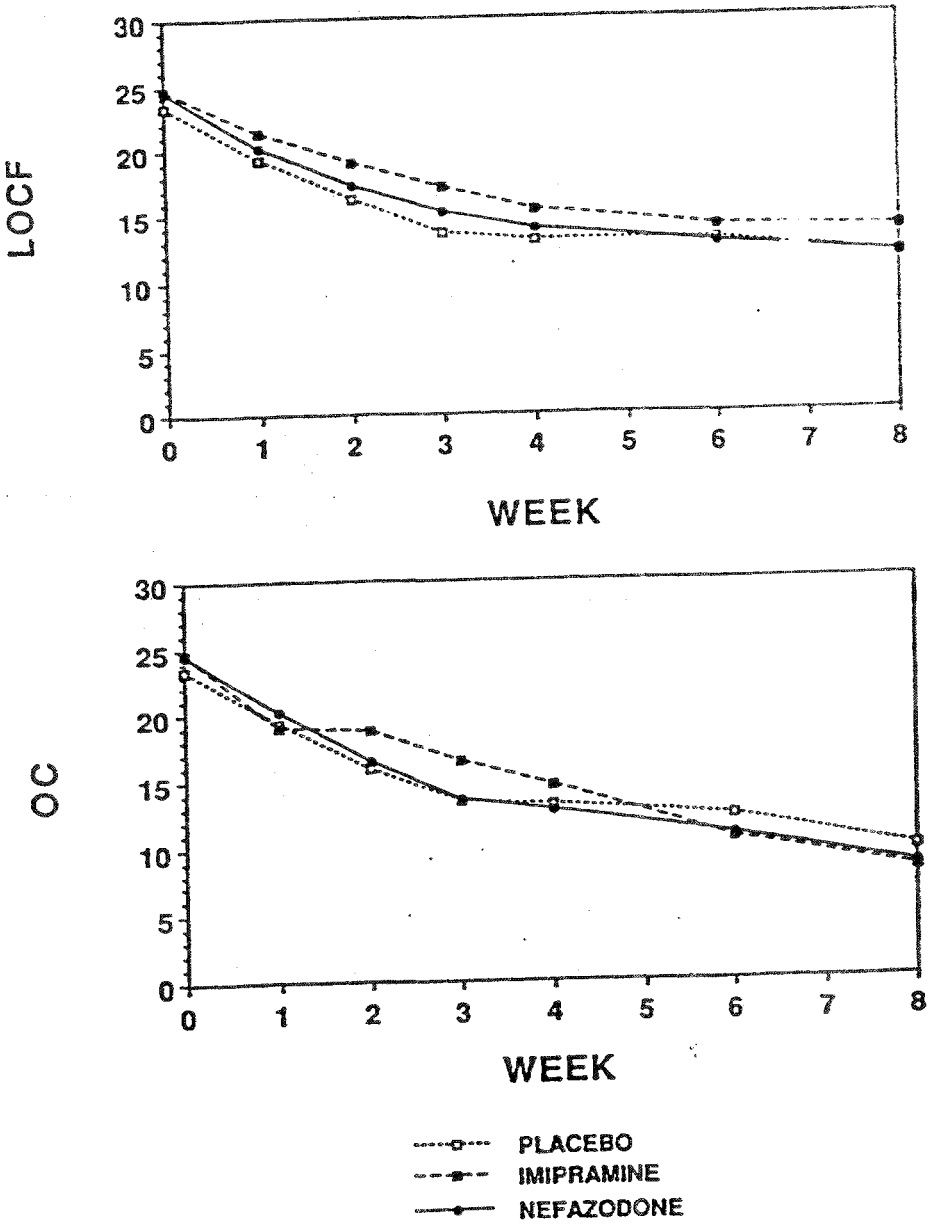
The Week 8 LOCF results below clearly show no differences between nefazodone and placebo. The observed cases results agreed with these LOCF results. At Week 8, the treatment difference between nefazodone and placebo on the HAM-D 17 Total for the completers was 2.5 (see Figure 9 on the following page). This difference was not significant with a p-value of .15. Also, the Week 6 results were consistent with the Week 8 results (Figure 9).

Table 20. Study CN104-105
Center 1 - Psychiatric Practices
Sponsor's Results

	NEF	PLA	IMP	P-VALUE vs PLA	
	Mean	Mean	Mean	NEF	IMP
HAM-D 17 Total					
Baseline	24.5	23.3	24.6	.10	.05
Week 8 LOCF	-12.8	-11.6	-10.9	.81	.12
HAM-D Item 1					
Baseline	3.1	3.0	3.1	.11	.44
Week 8 LOCF	-1.6	-1.3	-1.4	.26	.86
CGI Severity of Illness					
Baseline	4.6	4.4	4.7	.10	.03
Week 8 LOCF	-1.7	-1.5	-1.4	.55	.72
CGI Global Improvement					
Week 8 LOCF	2.1	2.4	2.6	.22	.57

Due to the baseline differences observed for each drug group compared to the placebo group, this reviewer requested that the sponsor perform analyses of covariance. The results of these analyses for both the nefazodone/placebo comparison and the imipramine/placebo comparison showed no significant treatment effects with p-values greater than the ones produced without adjustment for baseline.

Figure 9. Study CN 104-005
Center 1
HAM-D 17 Total by Week
Means



Center 2

The treatment groups were comparable with regard to age and race. There was an imbalance with regard to gender; the placebo group was 53% women, the nefazodone group was 75% women and the imipramine group was 60% women. About half the patients in all the groups were diagnosed with recurrent depression. In the placebo group, 45% of the patients had previously used antidepressants while in the two drug groups only about 28% of the patients reported prior use.

Patient Disposition

There were notably more completers in the nefazodone group (71%) compared to the placebo group (55%) and the imipramine group (49%). The chief reason for withdrawal in the placebo group was lack of efficacy while no patients in the nefazodone group or the imipramine group dropped for this reason. Of the 14 dropouts in the nefazodone group, 4 dropped due to adverse events compared to 11 in the imipramine group. Most of the dropouts in the imipramine group occurred during the first 3 weeks of the study.

Table 21. Study CN104-005
Center 2
Patients on Study

WEEK	NEFAZODONE	PLACEBO	IMIPRAMINE
Randomized	48	47	43
1	43 (90%)	40 (85%)	32 (74%)
2	41 (85%)	38 (81%)	27 (63%)
3	38 (79%)	36 (77%)	25 (58%)
4	38 (79%)	33 (70%)	25 (58%)
6	36 (75%)	26 (55%)	22 (51%)
8	34 (71%)	26 (55%)	21 (49%)

Table 22. Study CN104-005
Center 2
Reasons for Dropouts

Reason for Dropout	NEFAZODONE	PLACEBO	IMIPRAMINE
Lack of Efficacy	0 (0%)	9 (19%)	0 (0%)
Adverse Experience	4 (8%)	4 (9%)	11 (26%)
Lost-to-Followup	5 (10%)	1 (2%)	4 (9%)
Other	5 (10%)	7 (15%)	7 (16%)

Results

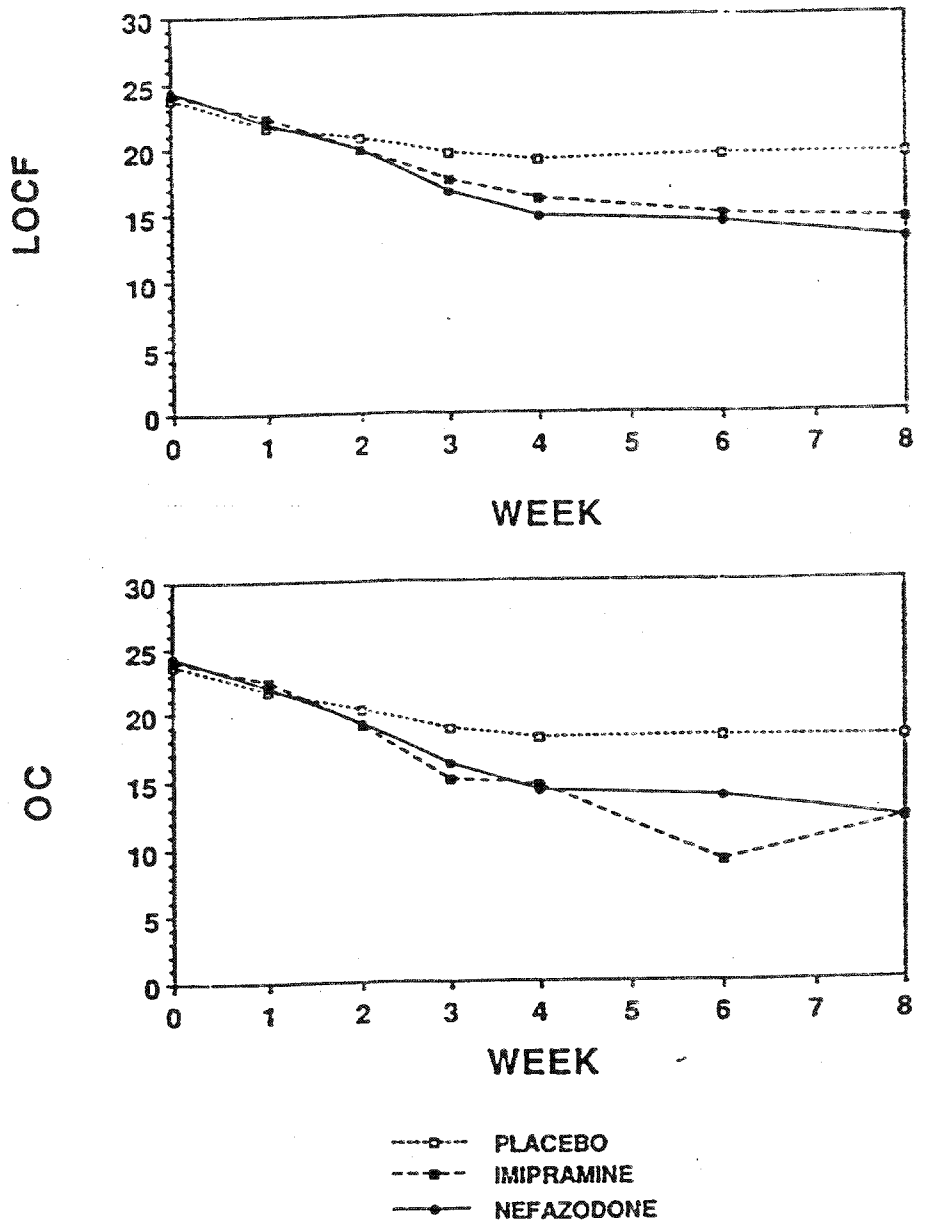
The nefazodone group was significantly different ($p < .001$) from placebo on the 4 efficacy measures (Table 23) with differences first apparent at Week 3. The LOCF results and OC results were consistent as can be seen clearly in Figure 10 on the following page.

Table 23. Study CN104-105
Center 2 - Family Practices
Sponsor's Results

	NEFAZODONE Mean	PLACEBO Mean	IMIPRAMINE Mean	P-VALUE[1] NEF vs PLA
HAM-D 17 Total				
Baseline	24.3	23.7	24.0	.38
Week 8 LOCF	-11.2	-4.3	-9.5	<.001
HAM-D Item 1				
Baseline	2.8	2.8	2.8	.96
Week 8 LOCF	-1.3	-0.4	-1.2	<.001
CGI Severity of Illness				
Baseline	4.4	4.3	4.3	.76
Week 8 LOCF	-1.4	-0.5	-1.2	<.001
CGI Global Improvement				
Week 8 LOCF	2.3	3.5	2.7	<.001

[1] P-values for the OC analyses were all less than .01.

Figure 10. Study CN 104-005
Center 2
HAM-D 17 Total by Week
Means



Reviewer's Comments on Study 104-005

It is clear that the differences between the centers lies predominately in the placebo groups (see Figures 9 and 10). Therefore, the lack of a significant treatment difference in Center 1 does not necessarily indicate a lack of efficacy for nefazodone, particularly since the imipramine group shows no difference from placebo in Center 1, as well.

The results for Center 2 clearly favor nefazodone over placebo. It should be noted that the placebo effect in this center is markedly smaller than the effects observed in the other studies of this submission (the placebo change from baseline for the other studies ranges from about -7 down to -9). This difference in magnitude of effect may be related to clinical factors such as the use of family practice physicians or the characteristics of the patients studied.

To further examine the differences between the centers, baseline data for the centers is summarized below. These values seem to indicate that the patients in Center 2 are less severely ill at baseline than the patients in Center 1.

Study 104-005
Baseline Values by Center

	Center 1			Center 2		
	NEF	PLA	IMP	NEF	PLA	IMP
HAM-D Item #1						
Moderate	88%	87%	80%	80%	66%	78%
Severe	12%	7%	13%	0%	7%	0%
CGI Severity						
Moderate	44%	57%	41%	67%	66%	70%
Marked	51%	38%	52%	31%	30%	27%
Severe	5%	2%	4%	2%	2%	3%
Recurrent	60%	62%	65%	49%	50%	49%
# Prior Depress. Episodes						
Mean	5.1	4.1	4.5	2.8	3.7	2.0
Median	1	1	1	1	1	0
Previous Antidepressant Use	58%	56%	57%	45%	29%	28%

To examine the relationship of prior depressive episodes to HAM-D 17 Total response, this reviewer performed an ANCOVA using number of prior episodes as the covariate. This analysis was done for the centers combined and separately for each center. Adjusting for the number of prior depressive episodes had no effect on the HAM-D 17 Total treatment differences.

To determine if the treatment effect differences between the centers were related to antidepressant use, this reviewer performed a 3-way ANOVA with treatment, center and previous antidepressant use as factors. The analysis revealed a highly significant 3-way interaction effect (center by treatment by previous antidepressant use) with p=.01. Next 2-way ANOVA's with treatment and previous antidepressant use as factors were performed. For Center 1 (psychiatric sites), the interaction term for treatment by previous antidepressant use was not significant (p=.30) whereas for Center 2 (family practice sites) the interaction term was borderline significant (p=.15). The latter suggests that the treatment effects for previous users versus nonusers differed within Center 2. Further examination of the Center 2 data revealed that the interaction was due to quantitative differences; that is, the magnitude of the treatment differences varied with previous use or nonuse of antidepressants. Differences in percentages of patients with previous antidepressant use does not help to explain the differences between the centers.

From the sponsor's tables of HAM-D responses by gender, this reviewer noted a large difference between the placebo change from baseline for males compared to females for Center 1 (see table below). No gender differences were seen in Center 2.

Study CN104-005 Center 1
HAM-D 17 Total Change from Baseline by Gender

	NEF HIGH	PLACEBO	IMP
MALES			
Week 8 LOCF	-10.5 (n=19)	-8.3 (n=16)	-11.2 (n=16)
OC	-14.1 (n=11)	-8.8 (n=13)	-15.1 (n=10)
FEMALES			
Week 8 LOCF	-14.8 (n=22)	-13.4 (n=30)	-10.8 (n=30)
OC	-17.4 (n=18)	-16.6 (n=22)	-17.3 (n=16)

The small numbers and the post hoc nature of this examination precludes drawing any conclusions from this difference; however it does suggest that further inspection of gender differences may be worthwhile.

For Study CN104-005, the results for Center 1 (psychiatric sites) show no difference between the drug groups (high dose nefazodone and imipramine) and the placebo group. However, the results for Center 2 provide convincing statistical evidence for the efficacy of nefazodone compared to placebo.

7.2.2.3 **Study Conduct/Outcome** (see appendix for related tables)

Patient Disposition: 240 patients at two study centers were randomized to treatment. 231 patients were evaluable for efficacy.

Demographics: Of the 240 patients, 148 (62%) were women and 92 (38%) men. Patient age ranged from 18 to 79 years. 239 met the diagnostic criteria for Major Depression (DSM-III) and one met the criteria for Bipolar Disorder, Depressed; melancholia was diagnosed in 109 (45%) patients; 150 (62%) patients had recurrent episodes of depression; and 149 (62%) patients had their current episode of depression for at least 6 months.

Dosing Information: Oral capsules administered BID. Recommended dosage ranges: low-dose nefazodone, 150 to 300 mg/day (50-mg capsule), beginning at 100 mg/day; high-dose nefazodone, 300 to 600 mg/day (100-mg capsule), beginning at 200 mg/day; placebo 2-6 capsules per day. The mean modal dose at Week 6 was 246.6 mg/day for the low-dose nefazodone group, 396.8 mg/day for the high-dose nefazodone group, and 5.1 capsules/day for the placebo group.

Concomitant Medications: The protocol permitted the use of chloral hydrate for sleep and this was the most frequently used concomitant psychotropic medication. Fifteen patients took prohibited concomitant psychotropic medications (alprazolam, amitriptyline, caffeine, diazepam, fluoxetine HCl, imipramine, Librax, lorazepam, nortriptyline HCl, temazepam, chlormezanone, and unspecified sleeping pill); these patients were not excluded from the analyses.

Efficacy Results: Patients were considered evaluable for efficacy if they were randomized to treatment, received a dose of study medication, and had an efficacy evaluation during treatment. Of the 231 patients meeting these criteria, 75 received placebo, 78 received low-dose nefazodone; and 78 received high-dose nefazodone.

Low dose effects are not different from placebo. The high dose group was not significantly deferent from placebo on the HAM-D depressed mood item, but was on three other variables.

7.2.2.4 Conclusions:
Study 07A0A-004B does provide statistical evidence that the high dose of Nefazodone is effective compared to placebo for three of the four efficacy variables.

7.2.3 Study CN104-006 A Double-Blind Trial of Nefazodone, Imipramine, and Placebo in the Treatment of Depressed Outpatients (Protocol CN104-006).

7.2.3.1 Investigator\Locations: Louis Fabre, Jr., M.D., Ph.D, Research Testing Inc., Houston, Texas, and Dallas, Texas, USA; Cal K. Cohn, M.D., The Hauser Clinic and Associates, Houston, Texas, USA.

7.2.3.2 Study Plan:

Objectives: To determine the safety and efficacy of nefazodone, imipramine, and placebo in the treatment of moderately to severely

depressed outpatients meeting DSM-III-R criteria for Major Depression, Single Episode or Recurrent, or Bipolar Disorder, Depressed, and to provide data on the effective dose range.

Population to be Studied: Outpatients of either sex, 18 years of age or older, with a diagnosis of Major Depression (Single Episode or Recurrent) or Bipolar Disorder, Depressed (DSM-III-R).

Study Design: Multicenter, randomized, double-blind, parallel-group, eight-week comparison of the safety and efficacy of nefazodone, imipramine, and placebo. The trial was preceded by a one- to four-week baseline evaluation phase designed to ensure that all eligibility criteria were fulfilled and all relevant baseline data were recorded. Rating scales included: 28-Item Hamilton Rating Scale for Depression (HAM-D-28), Hamilton Rating Scale for Anxiety (HAM-A), Symptom Checklist-87 (SCL-87), Clinical Global Impressions (CGI) Scale, and Patient's Global Assessments (PGA) Scale.

Plan for Analysis: The statistical analyses included a two-way analysis of variance (ANOVA) model with study center, treatment, and study center by treatment interaction effects. This model was used to test for baseline comparability as well as differences between treatments for the change from Baseline in HAM-D and CGI Severity scores. Categorical data such as CGI and PGA Improvement scores were analyzed within the framework of the generalized Cochran-Mantel-Haenszel (CMH) procedure, using study center as the stratification variable. Both the two-way ANOVA and CMH models tested the differences between treatments averaged across the study centers. The planned sample size of 240 patients had a power of ≥ 80% to detect an average pairwise difference of four points in the HAM-D-17 Total Score between placebo and the other treatments (nefazodone, imipramine), within the range of variability projected for this study.

7.2.3.3 **Study Conduct/Outcome** (see related appendix tables)

Patient Disposition: 263 patients were randomized to three treatment groups. 237 patients were evaluable for efficacy.

Demographics: Of the 263 patients, 176 (67%) were women and 87 (33%) were men. Patient age ranged from 18 to 70 years. 259 (99%) patients met DSM-III-R criteria for moderate to severe Major Depression (Single or Recurrent Episode) and 3 (1%) met the diagnostic criteria for Bipolar Disorder, Depressed, and the diagnosis of one patient was unrecorded; 149 (58%) patients experienced a previous depressive episode.

Dosing Information: Oral capsules administered QD or BID. Recommended dosage ranges: nefazodone (100-mg capsule), recommended titration range 100 to 600 mg/day); imipramine (50-mg capsule), recommended titration range 50 to 300 mg/day; or placebo, recommended titration range one to six capsules/day. The mean modal dose at Week 8 was 363.6 mg/day for the nefazodone group and 160.5 mg/day for the imipramine group.

Concomitant Medications: The protocol permitted the use of chloral hydrate for sleep and this was the most frequently used concomitant psychotropic medication. Four patients took prohibited concomitant psychotropic medications (diazepam, fluoxetine HCl, Synalgos, and triazolam); however, these patients were not excluded from the analyses.

Efficacy Results: Patients were considered evaluable for efficacy (i.e., included in the Intent-to-Treat Sample) if they were randomized to treatment, received a dose of study medication, and had an efficacy

evaluation during treatment. Of 237 patients evaluable for efficacy, 78 received placebo, 79 received imipramine, and 80 received nefazodone.

The HAM-D results at week 8 for center 2 are borderline but the other 3 variables are strongly supportive with both LOCF and OC in agreement. For center one no efficacy variable is significantly different at any time.

Appendix results are presented for the combined analysis.

7.2.3.4 **Conclusions:**
This study shows that results from the two centers do not agree. Center one does not distinguish Nefazodone from placebo, however, Imipramine was not significantly different either. Center two is positive for both Nefazodone and Imipramine but the combined analysis for both centers is not positive.

006

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003

7.2.4 **Study 03A0A-003 (Conducted 11/86 to 6/90)**
A Multicenter, Double-Blind Comparison of Nefazodone, Imipramine, and Placebo in Patients with Moderate to Severe Depression (Protocol 03A0A-003).

7.2.4.1 **Investigators\Locations:** Neelakanta Nair, M.D., John Pecknold, M.D. and Syed Jamal Mirmiran, M.D., Verdun, Quebec and Pointe Claire, Quebec; Ronald A. Remick, M.D., Vancouver, British Columbia; Bishan Saxena, Ph.D. and Paul Grof, M.D., Hamilton, Ontario; Rejean Fontaine, M.D., Montreal, Quebec; Manuel Matas, M.D., Winnipeg, Manitoba.

7.2.4.2 **Study Plan:**

Objectives: To establish the safety and efficacy of nefazodone as compared to imipramine and placebo in the treatment of patients diagnosed with Major Depressive Disorder.

Population to be Studied: Outpatients of either sex, aged 18-65, with a diagnosis of Major Depressive Disorder (Research Diagnostic Criteria - that had been modified to require that dysphoric features be present for at least four weeks).

Study Design: Multicenter, randomized, double-blind, parallel group 6-week comparison of a high- and a low-dose of nefazodone, imipramine, and placebo. Ratings scales included: 25-Item Hamilton Rating Scale for Depression (HAM-D-25), Clinical Global Impressions (CGI) Scale, Patient's Global Assessments (PGA) Scale, Hamilton Rating Scale for Anxiety (HAM-A), and Symptom Checklist-90 (SCL-90).

Plan for Analysis: A two-way analysis of variance (ANOVA) model with study-center stratum, treatment, and study-center stratum by treatment interaction effects was used to test for Baseline comparability as well as differences between treatments for the change from Baseline in HAM-D and CGI Severity scores. Categorical data such as CGI and PGA Improvement Scores were analyzed within the framework of the generalized Cochran-Mantel-Haenszel (CMH) procedure, using study-center stratum as the stratification variable. Both the two-way ANOVA and CMH models were used to test the differences between treatments averaged across the study-center strata. The two-way ANOVA model also was used to test differences between treatments within each study-center stratum for the change from Baseline in HAM-D scores. A Fisher's Exact Permutation test was used to compare treatments within each study-center stratum for CGI and PGA. The

TABLE A
Protocol: CN104-006
Demographic Characteristics for Total Patient Sample

Treatment Groups	N	Age (years)		Sex [N (%)]		Race [N (%)]	
		Mean	Range	Male	Female	White	Non-White
Nefazodone	88	37.3		21 (24)	67 (76)	63 (72)	25 (28)
Imipramine	88	37.6		33 (37)	55 (62)	67 (76)	21 (24)
Placebo	87	38.1		33 (38)	54 (62)	59 (68)	28 (32)

TABLE B
Protocol: CN104-006
Patient Completion Rates

Treatment Groups	Number Randomized	Intent-to-Treat Sample	Completers [N (%)]					
			Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8
Nefazodone	88	80	71 (89)	68 (85)	57 (71)	47 (59)	48 (60)	44 (55)
Imipramine	88	79	73 (92)	67 (85)	58 (73)	45 (57)	45 (57)	43 (54)
Placebo	87	78	73 (94)	70 (90)	65 (83)	56 (72)	48 (62)	50 (64)

TABLE C
Protocol: CN104-006
Dosing Information

Treatment Groups	Mean Modal Dose (mg/day) for Completers in Active Drug Groups					
	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8
Nefazodone	281.7	320.6	321.1	344.7	354.2	363.6
Imipramine	121.2	137.3	140.5	151.1	163.3	160.5

TABLE D
Protocol: CN104-006
Mean (Least Squares) Change from Baseline in HAM-D-17 Total Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8	
	N	X	N	X	N	X	N	X	N	X	N	X	N	X
Nefazodone	80	23.5	79	-4.6	79	-5.9	79	-8.0	79	-8.8	80	-9.5	80	-10.0
Imipramine	79	23.7	79	-3.9	79	-7.1	79	-8.7	79	-9.8	79	-10.2	79	-11.0
Placebo	78	23.8	77	-4.0	77	-5.6	78	-7.1	78	-7.9	78	-8.6	78	-8.9
2-sided p-values for pairwise comparisons														
Nefazodone vs Placebo	0.59		0.40		0.74		0.37		0.41		0.43		0.35	
Imipramine vs Placebo	0.78		0.93		0.09		0.12		0.09		0.19		0.10	

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8	
	N	X	N	X	N	X	N	X	N	X	N	X	N	X
Nefazodone	80	23.5	71	-4.8	68	-5.7	57	-8.8	47	-10.4	47	-11.5	44	-13.3
Imipramine	79	23.7	73	-4.1	66	-7.9	57	-10.2	45	-12.5	45	-13.4	42	-14.8
Placebo	78	23.8	73	-4.1	70	-6.0	65	-8.0	56	-9.1	48	-11.4	50	-12.5
2-sided p-values for pairwise comparisons														
Nefazodone vs Placebo	0.59		0.34		0.79		0.51		0.30		0.92		0.55	
Imipramine vs Placebo	0.78		0.97		0.05		0.06		0.01		0.15		0.10	

TABLE F
Protocol: CN104-006
Mean (Least Squares) Change from Baseline in HAM-D Depressed Mood (Item 1) Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8	
	N	X	N	X	N	X	N	X	N	X	N	X	N	X
Nefazodone	80	3.0	79	-0.3	79	-0.6	79	-0.8	79	-0.9	80	-1.1	80	-1.2
Imipramine	79	3.0	79	-0.4	79	-0.8	79	-1.0	79	-1.1	79	-1.2	79	-1.3
Placebo	78	3.0	77	-0.2	77	-0.6	78	-0.7	78	-0.8	78	-0.9	78	-0.9
2-sided p-values for pairwise comparisons														
Nefazodone vs Placebo	0.26		0.58		0.81		0.44		0.60		0.40		0.15	
Imipramine vs Placebo	0.53		0.04		0.07		0.08		0.12		0.13		0.04	

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk		Wk 4		Wk 6		Wk 8	
	N	X	N	X	N	X	N	X	N	X	N	X	N	X
Nefazodone	80	3.0	71	-0.3	68	-0.6	57	-1.0	47	-1.1	47	-1.4	44	-1.8
Imipramine	79	3.0	73	-0.5	66	-1.0	57	-1.2	45	-1.4	45	-1.7	42	-1.8
Placebo	78	3.0	73	-0.3	70	-0.6	65	-0.8	56	-0.9	48	-1.2	50	-1.3
2-sided p-values for pairwise comparisons														
Nefazodone vs Placebo	0.26		0.63		0.89		0.15		0.28		0.37		0.01	
Imipramine vs Placebo	0.53		0.03		0.01		0.01		0.01		0.01		0.00	

TABLE H
Protocol: CN104-006
Mean (Least Squares) Change from Baseline in CGI: Doctor's Opinion of Severity

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8	
	N	X	N	X	N	X	N	X	N	X	N	X	N	X
Nefazodone	80	4.6	79	-0.5	79	-0.7	79	-1.0	79	-1.2	80	-1.4	80	-1.6
Imipramine	79	4.6	79	-0.4	79	-0.9	79	-1.2	79	-1.3	79	-1.5	79	-1.6
Placebo	78	4.6	77	-0.4	77	-0.7	78	-0.9	78	-1.0	78	-1.1	78	-1.2
2-sided p-values for pairwise comparisons														
Nefazodone vs Placebo	0.88		0.58		0.97		0.61		0.31		0.12		0.11	
Imipramine vs Placebo	0.98		0.83		0.08		0.20		0.11		0.07		0.12	

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8	
	N	X	N	X	N	X	N	X	N	X	N	X	N	X
Nefazodone	80	4.6	71	-0.5	68	-0.7	57	-1.1	47	-1.6	47	-1.8	44	-2.2
Imipramine	79	4.6	73	-0.5	67	-1.1	58	-1.4	45	-1.7	46	-2.1	43	-2.3
Placebo	78	4.6	73	-0.4	70	-0.7	64	-1.1	55	-1.2	49	-1.5	50	-1.8
2-sided p-values for pairwise comparisons														
Nefazodone vs Placebo	0.88		0.41		0.97		0.89		0.05		0.15		0.06	
Imipramine vs Placebo	0.98		0.65		0.03		0.17		0.01		0.01		0.03	

Appendix CN104-005

TABLE I
Protocol: CN104-006
Mean (Least Squares) Score in CGI Scale: Doctor's Opinion of Improvement

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week											
	Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Nefazodone	71	3.1	79	2.9	79	2.7	79	2.5	80	2.4	80	2.3
Imipramine	73	3.3	79	2.8	79	2.5	79	2.4	79	2.3	79	2.3
Placebo	73	3.2	77	3.1	78	2.9	78	2.7	78	2.7	78	2.6
2-sided p-values for pairwise comparisons												
Nefazodone vs Placebo	0.35		0.30		0.24		0.18		0.12		0.09	
Imipramine vs Placebo	0.74		0.05		0.05		0.05		0.10		0.08	

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week											
	Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Nefazodone	71	3.1	68	2.9	57	2.6	47	2.0	47	1.9	44	1.6
Imipramine	73	3.3	67	2.6	58	2.3	45	1.8	45	1.8	43	1.6
Placebo	73	3.2	70	3.1	64	2.7	55	2.6	48	2.3	50	2.1
2-sided p-values for pairwise comparisons												
Nefazodone vs Placebo	0.35		0.49		0.39		0.01		0.07		0.02	
Imipramine vs Placebo	0.74		0.02		0.02		<0.01		0.01		0.02	

Study CN104-006 (Conducted 1/89 to 7/90)

Study CN104-006 was an 8-week dose-titration study designed to compare 3 treatment arms; nefazodone (600 mg/day peak allowable dose), imipramine (300 mg/day peak allowable dose) and placebo. A total of 240 patients were randomized at 2 centers in Texas; investigator Fabre in Dallas and investigator Cohn in Houston.

The results for the 2 centers differed appreciably with respect to patient dropout patterns, demographics, and efficacy responses. In Center 1 (Fabre), only 39% of the patients completed the study compared to 65% in Center 2 (Cohn). (See Tables 20 and 22.) Sixty-five percent of the patients in Center 1 were female, 61% were white and 30% were hispanic; in Center 2, 72% were female and the majority were white (84%). Neither nefazodone nor imipramine beat placebo in Center 1 on any efficacy variable whereas in Center 2 both treatment groups were statistically significantly superior to placebo on all 4 efficacy variables. An ANOVA revealed a nonsignificant treatment by center effect; excluding the imipramine group, the interaction was significant with a p-value of .15.

In addition to these disparities, it is questionable whether Center 1 was well-conducted. One investigator within Center 1 (Dr. Leal) was reprimanded for allegedly falsifying BP and pulse data. One must assume that internal audits checked for further problems with Dr. Leal's data. For comparison purposes, the HAM-D data for Dr. Leal's patients is summarized below (3 patients had no data).

PATIENTS TREATED BY DR. LEAL
CHANGE FROM BASELINE HAM-D 17 TOTAL

	NEFAZODONE MEAN (N)	PLACEBO MEAN (N)	IMIPRAMINE MEAN (N)
WEEK 8 LOCF	-11.8 (n = 5)	-9.8 (n = 6)	-4.7 (n = 6)
WEEK 8 OC	-16.7 (n = 3)	-14 (n = 4)	-12 (n = 1)

Due to these center differences, the results are presented in this review by center. Note, however, that the efficacy results were not significant for the HAM-D total comparisons when the studies were combined.

Center 1 (Fabre)

There was an imbalance with regard to gender among the treatment groups; placebo group was 59% women, the imipramine group was 52% women and the nefazodone group was 76% women. This center had the largest number of hispanic patients of any center in the submission; 34% of the placebo patients, 17% of the imipramine patients and 38% of the nefazodone patients were hispanic. The groups were comparable with regard to psychiatric history. Seventy-one percent had experienced prior depressive episodes (mean of 5.5 prior episodes). Only 24% of the patients had taken antidepressants previously.

Patient Disposition

Fewer patients completed this study than in any of the other studies in this submission (39%). Also, unlike the other studies, the nefazodone group lost the highest number of patients of the 3 groups. A total of 30 patients out of 45 randomized dropped out of the nefazodone group. The 2 major reasons for nefazodone dropouts were lack of efficacy during Week 3 and adverse experiences during Weeks 1 and 2. In the placebo group, 10 patients withdrew consent and were discontinued (7 during Week 1). The leading reason for dropouts in the imipramine group was adverse experience during week 1.

Table 19. Study CN104-006
Center 1
Patients on Study

WEEK	NEFAZODONE	PLACEBO	IMIPRAMINE
Randomized	45	44	46
1	39 (87%)	34 (77%)	36 (78%)
2	34 (76%)	29 (66%)	32 (70%)
3	24 (53%)	27 (61%)	26 (57%)
4	20 (44%)	24 (55%)	24 (52%)
6	16 (36%)	20 (45%)	20 (43%)
8	15 (35%)	18 (41%)	19 (41%)

Table 20. Study CN104-006
Center 1
Reasons for Dropouts

Reason for Dropout	NEFAZODONE	PLACEBO	IMIPRAMINE
Lack of Efficacy	10 (22%)	8 (18%)	4 (9%)
Adverse Experience	9 (20%)	3 (7%)	10 (22%)
Lost-to-Followup	5 (11%)	1 (2%)	5 (11%)
Patient Withdrew Consent	2 (4%)	10 (23%)	5 (11%)
Other	4 (9%)	4 (9%)	3 (6%)

Results

Only the Week 8 data is summarized below. A graphical depiction of the HAM-D data by week is provided on the following page (Figure 7). No statistically significant differences were noted for either nefazodone or imipramine on any efficacy variable at any timepoint.

Table 21. Study CN104-006
Center 1
Sponsor's Results

	NEF	PLA	IMP	P-VALUE vs PLA	
	Mean	Mean	Mean	NEF	IMP
HAM-D 17 Total					
Baseline	24.2	24.2	23.8	.97	.53
Week 8 LOCF	-8.0	-8.6	-8.9	.72	.85
OC	-12.4	-13.8	-13.4	.53	.85
HAM-D Item 1					
Baseline	2.9	2.9	3.0	.55	.66
Week 8 LOCF	-0.8	-0.8	-1.0	.93	.34
OC	-1.5	-1.2	-1.6	.28	.16
CGI Severity of Illness					
Baseline	5.1	5.0	5.1	.37	.26
Week 8 LOCF	-1.5	-1.4	-1.5	.68	.62
OC	-2.4	-2.2	-2.6	.56	.33
CGI Global Improvement					
Week 8 LOCF	2.2	2.4	2.3	.87	.57
OC	1.5	1.6	1.5	.62	.74

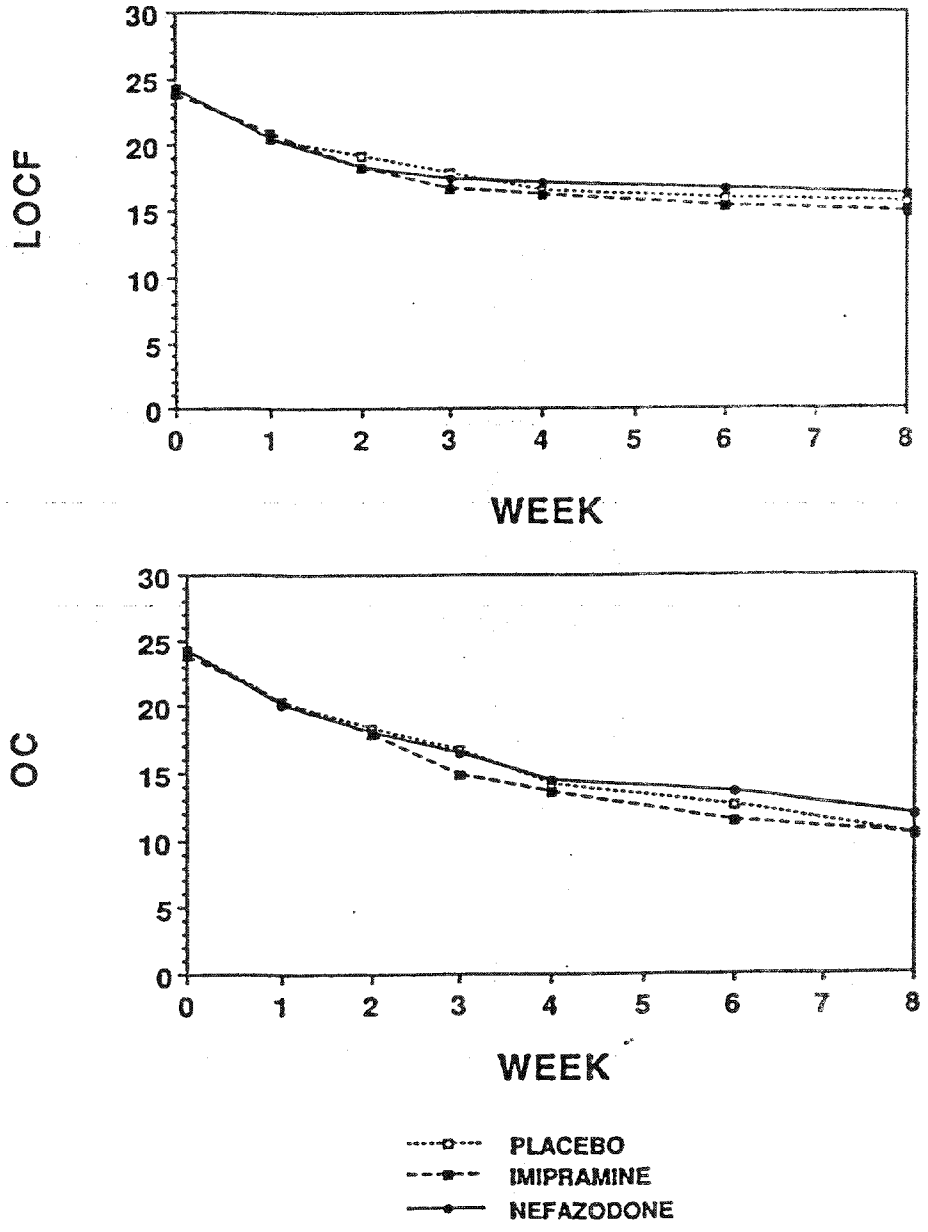
This reviewer requested HAM-D 17 Total results by race from the sponsor. Only the Week 8 OC data for whites and hispanics are summarized below; data for blacks is not included since there were only a total of 7 black patients with data. The results for hispanics favor nefazodone while the results for whites do not. However, due to the small numbers in these subgroups, no conclusions can be drawn from the data.

HAM-D 17 Total OC Means at Week 8

	NEFAZODONE MEAN (N)	PLACEBO MEAN (N)	IMIPRAMINE MEAN (N)
WHITES	-10.4 (n=7)	-14.8 (n=12)	-12.6 (n=14)
HISPANICS	-15.0 (n=8)	-13.5 (n=6)	-15.3 (n=3)

The standard error for each mean was about 2.0.

Figure 7. Study CN 104-006
Center 1
HAM-D 17 Total by Week
Means



Center 2 (Cohn)

The treatment groups were comparable with respect to demographics and psychiatric history. More than 80% of the patients were white and about three-fourths were women. Less than half the patients in this center had recurrent depression; the mean number of prior depressive episodes for all patients was 1.5. Twenty-seven percent of the patients had previously used antidepressants.

Patient Disposition

About 65% of the patients in Center 2 completed the study. The primary reason for dropout in all 3 treatment groups was adverse experience; most occurring during the first 2 weeks of the study. An unusually small number of patients dropped due to lack of efficacy.

Table 22. Study CN104-006
Center 2
Patients on Study

WEEK	NEFAZODONE	PLACEBO	IMIPRAMINE
Randomized	43	43	42
1	35 (81%)	42 (98%)	32 (76%)
2	34 (79%)	40 (93%)	30 (71%)
3	32 (74%)	38 (88%)	27 (64%)
4	30 (70%)	33 (77%)	25 (60%)
6	29 (67%)	31 (72%)	24 (57%)
8	28 (65%)	31 (72%)	24 (57%)

Table 23. Study CN104-006
Center 2
Reasons for Dropouts

Reason for Dropout	NEFAZODONE	PLACEBO	IMIPRAMINE
Lack of Efficacy	1 (2%)	4 (9%)	1 (2%)
Adverse Experience	7 (16%)	5 (12%)	10 (24%)
Lost-to-Followup	5 (12%)	0 (0%)	6 (14%)
Patient Withdrew Consent	0 (0%)	1 (2%)	0 (0%)
Other	4 (9%)	2 (5%)	1 (2%)

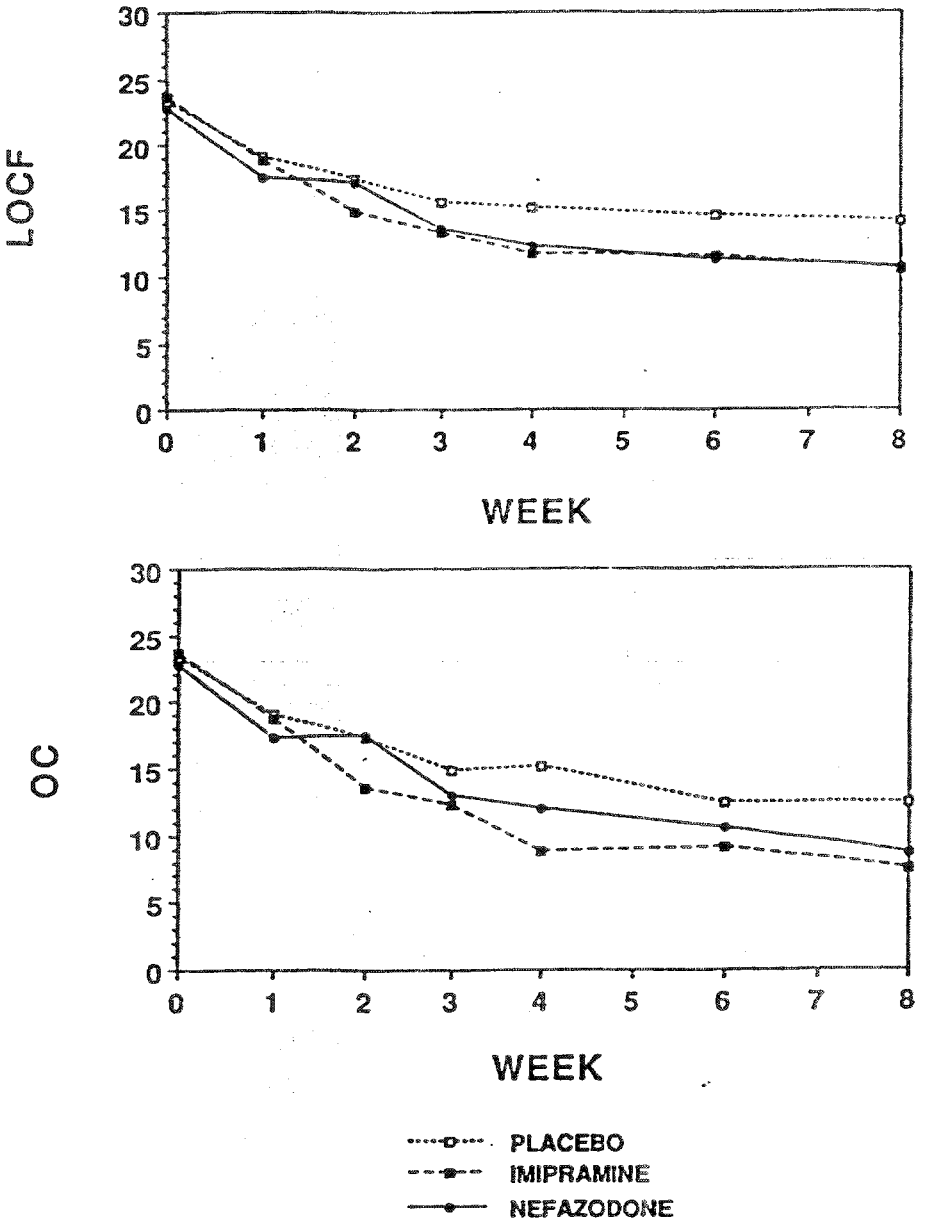
Results

Only the Week 8 results are summarized below; the Week 6 results were not positive for any nefazodone/placebo comparison. The HAM-D 17 Total results for nefazodone are nearly significant with p-values of .09 and .07 for LOCF and OC, respectively. (For the HAM-D 25, the p-values for nefazodone versus placebo were .13 [LOCF] and .10 [OC].) For the other 3 primary efficacy variables, nefazodone is statistically significantly superior to placebo.

Table 24. Study CN104-006
Center 2
Sponsor's Results

	NEF	PLA	IMP	P-VALUE vs PLA	
	Mean	Mean	Mean	NEF	IMP
HAM-D 17 Total					
Baseline	22.8	23.4	23.6	.46	.81
Week 8 LOCF	-12.1	-9.2	-13.0	.09	.09
OC	-14.2	-11.1	-16.1	.07	.01
HAM-D Item 1					
Baseline	3.1	3.1	3.0	.32	.18
Week 8 LOCF	-1.6	-1.1	-1.6	.04	.05
OC	-2.0	-1.4	-2.1	.01	<.001
CGI Severity of Illness					
Baseline	4.1	4.2	4.1	.26	.27
Week 8 LOCF	-1.6	-1.1	-1.6	.06	.08
OC	-2.0	-1.3	-2.0	.02	.03
CGI Global Improvement					
Week 8 LOCF	2.2	2.8	2.2	.02	.03
OC	1.7	2.9	1.8	<.001	.01

Figu 3. Study CN 104-006
Center 2
HAM-D 17 Total by Week
Means



Reviewer's Comments on Study CN104-006

The results from the 2 centers in Study CN104-006 do not agree. The results for Center 1 clearly do not distinguish nefazodone from placebo, however since imipramine also was not significantly different from placebo, this center could be considered as inadequate and incapable of producing positive results. The large number of dropouts offers a plausible reason for the failure of the study at Center 1.

The Week 8 results for Center 2 are positive for both nefazodone and imipramine. Even though the HAM-D total results for nefazodone are borderline ($p<.09$), the other 3 efficacy variables provide strong supportive evidence in favor of nefazodone with both the LOCF and OC results in agreement. Since most of the studies in this submission were 6 week studies it is worth noting that at Week 6 the nefazodone response was not statistically significantly different from placebo on any variable.

evaluation during treatment. Of 237 patients evaluable for efficacy, 78 received placebo, 79 received imipramine, and 80 received nefazodone.

The HAM-D results at week 8 for center 2 are borderline but the other 3 variables are strongly supportive with both LOCF and OC in agreement. For center one no efficacy variable is significantly different at any time.

Appendix results are presented for the combined analysis.

7.2.3.4 **Conclusions:**
This study shows that results from the two centers do not agree. Center one does not distinguish Nefazodone from placebo, however, Imipramine was not significantly different either. Center two is positive for both Nefazodone and Imipramine but the combined analysis for both centers is not positive.

7.2.4 **Study 03A0A-003 (conducted 11/86 to 6/90)**
A Multicenter, Double-Blind Comparison of Nefazodone, Imipramine, and Placebo in Patients with Moderate to Severe Depression (Protocol 03A0A-003).

7.2.4.1 **Investigators\Locations:** Neelakanta Nair, M.D., John Pecknold, M.D. and Syed Jamal Mirmiran, M.D., Verdun, Quebec and Pointe Claire, Quebec; Ronald A. Remick, M.D., Vancouver, British Columbia; Bishan Saxena, Ph.D. and Paul Grof, M.D., Hamilton, Ontario; Rejean Fontaine, M.D., Montreal, Quebec; Manuel Matas, M.D., Winnipeg, Manitoba.

7.2.4.2 **Study Plan:**

Objectives: To establish the safety and efficacy of nefazodone as compared to imipramine and placebo in the treatment of patients diagnosed with Major Depressive Disorder.

Population to be Studied: Outpatients of either sex, aged 18-65, with a diagnosis of Major Depressive Disorder (Research Diagnostic Criteria - that had been modified to require that dysphoric features be present for at least four weeks).

Study Design: Multicenter, randomized, double-blind, parallel group 6-week comparison of a high- and a low-dose of nefazodone, imipramine, and placebo. Ratings scales included: 25-Item Hamilton Rating Scale for Depression (HAM-D-25), Clinical Global Impressions (CGI) Scale, Patient's Global Assessments (PGA) Scale, Hamilton Rating Scale for Anxiety (HAM-A), and Symptom Checklist-90 (SCL-90).

Plan for Analysis: A two-way analysis of variance (ANOVA) model with study-center stratum, treatment, and study-center stratum by treatment interaction effects was used to test for Baseline comparability as well as differences between treatments for the change from Baseline in HAM-D and CGI Severity scores. Categorical data such as CGI and PGA Improvement Scores were analyzed within the framework of the generalized Cochran-Mantel-Haenszel (CMH) procedure, using study-center stratum as the stratification variable. Both the two-way ANOVA and CMH models were used to test the differences between treatments averaged across the study-center strata. The two-way ANOVA model also was used to test differences between treatments within each study-center stratum for the change from Baseline in HAM-D scores. A Fisher's Exact Permutation test was used to compare treatments within each study-center stratum for CGI and PGA. The

planned sample size of 240 patients had a power of ≥ 80% to detect an average difference of approximately 5 points in the HAM-D-17 Total Score between placebo and each of the other treatments (high- or low-dose nefazodone and imipramine), within the range of variability projected for this study.

7.2.4.3 **Study Conduct/Outcome** (see appendix for related tables)

Patient Disposition: 204 patients at five study centers received study medication. All 180 patients at Study Center 2191 were evaluable for efficacy and 23 of 24 patients were evaluable for efficacy at the four discontinued centers.

Demographics: Of the 180 patients Study Center 2191, 112 (62%) were women and 68 (38%) men. They ranged in age from 20 to 65 and 124 (69%) met DSM-III diagnostic criteria for Major Depression, Melancholic Subtype; of the patients whose status was known, 86 (54%) experienced a previous depressive episode.

Dosing Information: Oral capsules given BID or TID. Recommended dosage ranges: low-dose nefazodone, 50 to 250 mg/day; high-dose nefazodone, 100 to 500 mg/day; imipramine, 50 to 250 mg/day; placebo, two to 10 capsules/day. For patients at Center 2191 who had an efficacy evaluation at Week 6 the mean of the Modal Daily Dose at Week 6 was 245.6 mg/day for low-dose nefazodone, 462.1 mg/day for high-dose nefazodone, 215.7 mg/day for imipramine, and 9.9 capsules/day for placebo.

Concomitant Medications: The protocol permitted the use of chloral hydrate for sleep and this was the most frequently used concomitant psychotropic medication. Seventeen patients (14 in Center 2191) took prohibited concomitant psychotropic medications (diazepam, flurazepam, hydroxyzine, loctopam, lorazepam, maprotiline, oxazepam, thiopental, triazolam), but these patients were not excluded from the analysis.

Efficacy Results: Patients were considered evaluable for efficacy (i.e., included in the Intent-to-Treat Sample) if they were randomized to treatment, received a dose of study medication, and had an efficacy evaluation during treatment. One hundred eighty patients at Center 2191 were evaluable for efficacy; 44 received high-dose nefazodone, 46 received low-dose nefazodone, 45 received imipramine, and 45 received placebo.

There were no significant differences for the nefazodone low dose group at any time. The HAM-D 17 total LOCF was significant in the high nefazodone group at weeks 5 and 6. The OC effects were not significant for any variable.

Appendix data is provided only for center 2191.

7.2.4.4 **Conclusions:**

In this study, the low dose Nefazodone group was not effective. The high dose Nefazodone group beat placebo on all four efficacy variables when looking at the LOCF results. The OC results do not agree with the LOCF results. The combined analysis fails to distinguish nefazodone from placebo.

7.2.5 Study CN104-002 (conducted 7/88 to 11/90)
A Double-Blind Trial of Nefazodone, Imipramine, and Placebo in the Treatment of Depressed Outpatients (Protocol CN104-002).

7.2.5.1 Investigator\Location: John P. Feighner, M.D., Feighner Research Institute, Poway, California.

MEMORANDUM

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

DATE: July 2, 1993

FROM: Masahiro Takeuchi, Sc.D. (HFD - 713)

SUBJECT: Supplemental Analyses of Study 03A0A-003 Data (NDA 20-152)

TO: Joy Mele and S. Edward Nevius, Ph.D. (HFD-713)

INTRODUCTION

(Note: This consult is in response to a request from Ms. Joy Mele, mathematical statistician, Division of Biometrics, for additional analyses on Study 03A0A-003.)

Study 03A0A-003 was designed to investigate the efficacy and safety of nefazodone for the treatment of depression. This trial was randomized, 6 - week, placebo-controlled, double-blind study. The outcome measurements were taken at baseline, week 1, week 2, week 3, week 4, week 5, and week 6. In this supplemental analysis we focus our attention on the HAM-D 17 Total variable for Center 2191 patients in the placebo, high dose Nefazodone, and Imipramine treatment groups. This report includes results from an application of longitudinal analysis and an investigation of the effects of dropouts on results from this study.

The initial randomized sample size and completers for each group were as follows:

	PLACEBO	NEF HIGH	IMIPRAMINE
Randomized	45	44	45
Completers	24	33	26
	(53%)	(75%)	(58%)

The sponsor, employing ANOVA, reported the following results describing the significance of tested week 6, treatment group differences in HAM-D 17 Total change from baseline:

P-VALUES FOR PLACEBO COMPARISONS AT WEEK 6

	NEF HIGH	IMIPRAMINE
LOCF*	0.03	0.04
OC*	0.50	0.07

*LOCF -- last observation carried forward; and OC -- observed cases.

Note: For a more detailed description of the results from this study, please refer to the attached excerpt from Ms. Mele's statistical review .

In comparing the results for the NEF HIGH treatment group, there is a large and somewhat puzzling difference in results employing LOCF and OC analyses. In contrast, the results describing the IMIPRAMINE treatment group were consistent.

In the LOCF analysis the last observed value for each noncompleter is substituted for missing data. For example, in this study a large number of dropouts were recorded in week 3 for each of the treatment groups; under the LOCF assumption the week 6 analysis is based on a number of values recorded at week 3. It is likely that this LOCF assumption becomes less realistic as the time interval between the last observation and the time of the analysis increases.

LONGITUDINAL ANALYSIS

As an alternative, a longitudinal analysis uses all of the repeated data recorded for each subject to describe time trends for each group and to compare trends between groups. Linear

mixed effects models (Laird and Ware, 1982) and the generalized estimating equation (GEE) approach (Liang and Zeger, 1986) are well established statistical methodologies appropriate for the longitudinal analysis of correlated data . In the linear case with the GEE approach we can relax the normal assumption by introducing a 'sandwich' estimator.

However, these methods do not directly address potential problems with missing data. Application of these methodologies should be preceded by an analysis aimed at determining the nature of the missing values. For example, linear mixed-effects models and the normal case of the GEE approach will only be valid when missing data are due to the so-called 'ignorable missing mechanism,' while other applications of the GEE approach will require a more restrictive assumption: 'missing completely at random.'

(I) DEFINITION OF MISSING MECHANISM

Since we face a missing data problem, we have to consider a missing data generating mechanism to decide whether we can apply the longitudinal method to the observed data in a regular fashion or we have to consider alternatives.

In general we have two types of missing mechanisms, (i) ignorable missing mechanism and (ii) nonignorable missing mechanism. If missing data are generated by the ignorable missing mechanism, we can apply the longitudinal methods in a usual fashion, but if the missing data are generated by the nonignorable missing mechanism, we can not apply those methods directly to the observed data.

The ignorable missing mechanism can be categorized into two types of the mechanisms, missing completely at random (MCAR) and missing at random (MAR). MCAR can be defined as a missing mechanism that a probability of missing data occurrence does not depend on the past observed values nor on the future values we cannot observe. In this sense the missing values will occur at random, not depending on any factors. On the other hand, MAR can be defined as a

missing mechanism that a probability of missingness can depend on the past observed values, but not on the future values. One possible example is that a subject drops out of a study because he or she entered the study with a high initial value, although the effect of the treatment was the same as the effect on subjects with a low initial value.

With the nonignorable missing mechanism, the probability of missing values depend on the past observed values and the future unobservable values: in this case, potentially, probabilities can be modeled using observed values and other factors. For example, the probability can be modeled by the subjects' initial values and the rate of change of the efficacy variable over time. Wu and Carroll (1988) employ a probit regression model with initial value, rate of change, and duration of a subject in the trial. These concepts were introduced by Dempster, Laird, and Rubin. Mathematical details can be referred to their paper and monograph (Little and Rubin, 1987). The effect of missing data on longitudinal analysis, especially for linear models, was investigated by Laird, 1988.

(2) DEFINITION OF THE RIGHT INFORMATIVE CENSORING PROCESS

In a clinical trial, noncompleters pose a problem that is similar to the right censoring problems with the analysis of survival data. Since we are interested in the time trends of treatment effect over the course of the trial, the right censoring process can be defined to be "noninformative" if the process does not depend on the individual rates of change of the efficacy variable during the trial, and to be "informative" if the process does depend on the rate of the change (Wu and Carroll, 1988).

If the right censoring process is noninformative, this process can be characterized as an ignorable missing mechanism. That means that we can directly apply longitudinal analyses to the observed data. If the right censoring process is informative, the missing process might be due to a nonignorable missing mechanism. In this case, if we apply longitudinal procedures to the observed data in a routine fashion, the estimators will be biased.

APPLICATION OF LONGITUDINAL ANALYSIS AND ITS RESULTS

In employing the GEE approach, we began by restricting the analysis to completers and investigated the time trend in each treatment. In each treatment, linear models are chosen as parsimonious models, because the quadratic term in each group was statistically significant. To adjust for the quadratic term in a linear model, the first-order autocorrelation (AR-1) was used as a 'working' correlation in the generalized estimating equations. Graph 1 shows the time trend for each treatment. The next table shows the significance of comparisons of results (slopes) with placebo.

PLACEBO COMPARISONS
P-VALUES

	NEF-HIGH	IMIPRAMINE
COMPLETERS	0.42	0.02

Secondly we restricted the analysis to noncompleters and investigated the time trends in each treatment group. We then compared the time trends between completers and noncompleters in each treatment group to see whether the right censoring was informative or noninformative. Dropouts were due to lack of efficacy, adverse experiences, patient refusal, etc. The next table shows the frequency of the dropouts for all reasons and for lack of efficacy in each treatment by week:

FREQUENCY OF DROPOUTS

	PLACEBO		NEF-HIGH		IMIPRAMINE	
WEEK	ALL	LACK OF EFF	ALL	LACK OF EFF	ALL	LACK OF EFF
1	3	1	0	0	0	0
2	0	0	2	0	3	1
3	11	9	5	4	9	6
4	2	2	2	1	6	4
5	5	3	2	1	1	0

Graph 2, Graph 3, and Graph 4 show the time trends for completers, noncompleters for "all reasons," and noncompleters due to "lack of efficacy" for each treatment. In a comparison of these figures, the time trends for noncompleters due to "lack of efficacy" varied noticeably from the trends observed for noncompleters for "all reasons." The frequency table shows that most dropouts are due to the lack of efficacy. Therefore the time trend in noncompleters for reasons other than lack of efficacy should be very similar to that for completers. The next table displays the results of statistical tests comparing the time trends for completers with those for noncompleters for "all reasons" and for "lack of efficacy":

COMPLETERS VS NONCOMPLETERS

	PLACEBO	NEF-HIGH	IMIPRAMINE
COMPLETERS VS NON WITH ALL	$P < 0.01$	$P = 0.1$	$P < 0.01$
COMPLETERS VS NON WITH LACK	$P << 0.01$	$P << 0.01$	$P << 0.01$

It is apparent that the right censoring (due to dropouts) was most likely to be "informative," i.e., due to a nonignorable missing mechanism. The next table summarizes the results:

MISSING MECHANISM

	PLACEBO	NEF-HIGH	IMIPRAMINE
Noninformative Right Censoring			
Informative Right Censoring	Yes	Yes	Yes

With results indicating the existence of informative right censoring, we could not directly employ the GEE approach with the observed data. Wu and Carroll (1988) have proposed an approach to the analysis of data with informative right censoring, that appears to be applicable to this circumstance. In their approach, they assume that the repeated measurements of the primary variable follow a linear function of time, and that the right censoring mechanism depends on a subject's initial value and slope. They assume that the right censoring mechanism can be described by probit regression. It is known that these estimates are sensitive to a model misspecification of the right censoring mechanism (Wu and Carroll, 1988, and Laird, 1988). Therefore we applied their method in the least efficient manner, i.e., using 'unweighted least squares' (UWLE). This approach has been shown to be robust with respect to censoring mechanism. The next table displays the results of comparisons of treatment group time trends with the placebo trend following application of this methodology.

PLACEBO COMPARISON
P-VALUES

NEF-HIGH	**IMIPRAMINE**
P = 0.02	P = 0.002

Note: these results assume β_i *is normally distributed with mean* B_K *and covariance* $\Sigma_{\beta K}$ *(Equation 2.1, Wu and Carroll, 1988)*

DISCUSSION:

Since we are dealing with a missing data problem, we need to investigate whether the missing mechanism is an ignorable mechanism or nonignorable mechanism. Using the informative right censoring definition, the missing mechanism is more likely due to informative right censoring, i.e., due to nonignorable missing mechanism. The next table summarizes all the comparison of all the results from these analyses:

PLACEBO COMPARISON
P-VALUES

	COMP	NONINFO	INFO	OC	LOCF
NEF-HIGH	P=0.42	P=0.16	P=0.02	P=0.50	P=0.03
IMIPRAMINE	P=0.02	P=0.002	P=0.002	P=0.07	P=0.04

Notes: ***COMP*** *stands for* ***completers,*** ***NONINFO*** *stands for noninformative right censoring,* ***INFO*** *stands for informative right censoring, OC stands for observed case, and* ***LOCF*** *stands for last observation carried forward.*

*In the analysis of data for completers (**COMP**), as explained above, the data set was restricted to the subjects who completed the trial.*

*For **NONINFO**, all possible data sets were used to estimate the linear coefficients. This analysis would be valid if the missing mechanism came from noninformative right censoring, i.e., ignorable missing mechanism.*

*For **INFO**, Wu and Carroll's approach was employed. This approach assumes that the informative right censoring mechanism is a function of initial values, the slope , and the time of dropout. In general, if the missing mechanism is nonignorable, then we need to model the missing mechanism. If we treat the right censoring as noninformative and use the entire data set, the estimators will be biased. Here, we used the unweighted least squares estimates. Since the estimators are not weighted, this estimator will be a roobust to the selection of a model for the informative censoring, e.g. logistic regression model or probit regression model, but with unweighted least squares, we lose efficiency of the estimators.*

*For **OC**, the analysis was done at week 6 with the observed data set at week 6.*

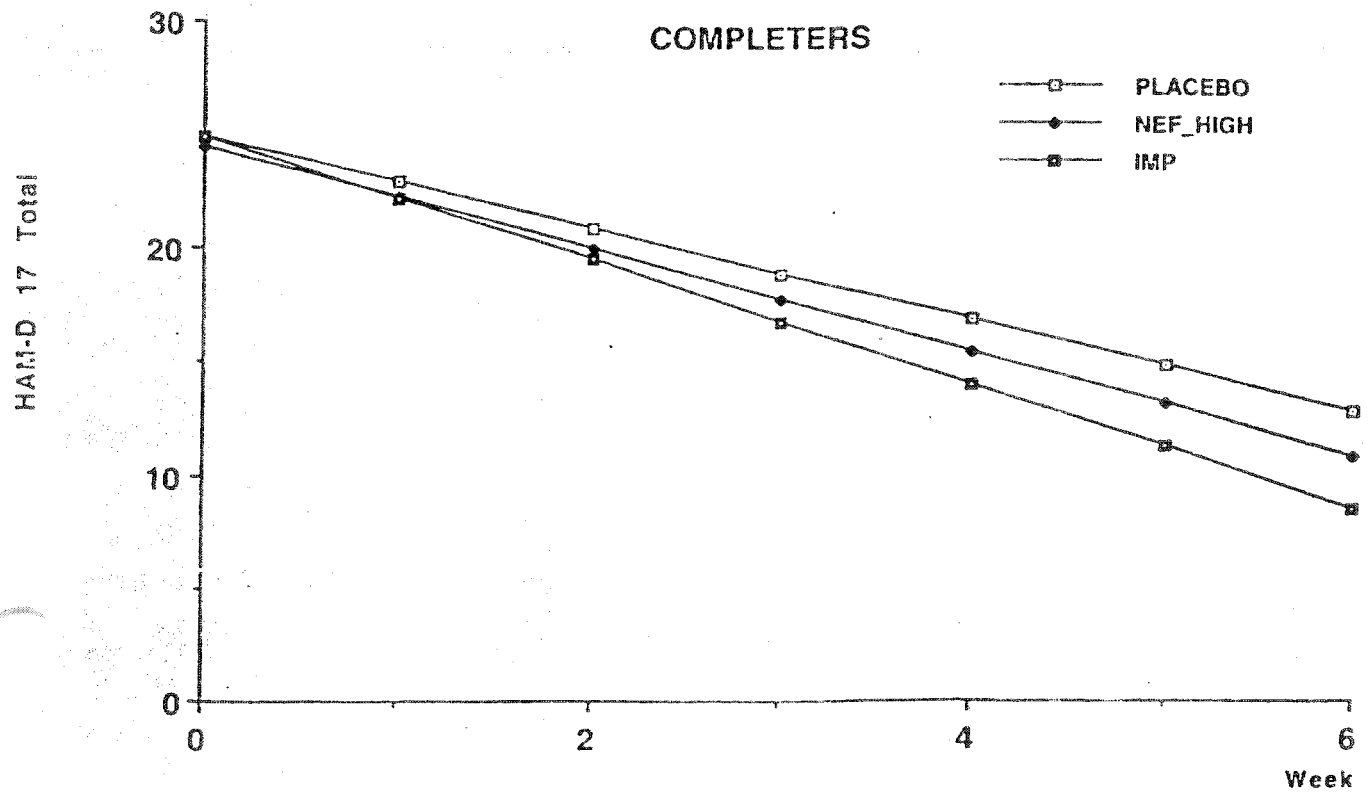
*For **LOCF**, the missing data were carried forward to week 6. As mentioned above, in this analysis, the assumption is made that the last observed data remains constant throughout the study.*

In this analysis, the completers in the 3 treatment groups behaved in a similar fashion, but the dropouts due to the lack of efficacy were noticeably different, i.e., in the placebo group, the HAM-D 17 scores increased over time, while, in contrast, in NEF-HIGH and IMIPRAMINE groups, scores decreased over time. These factors contribute to the observed difference in OC and LOCF analyses, and in the COMP and INFO analyses. This approach is discussed for repeated categorical data by Park and Davis, 1993.

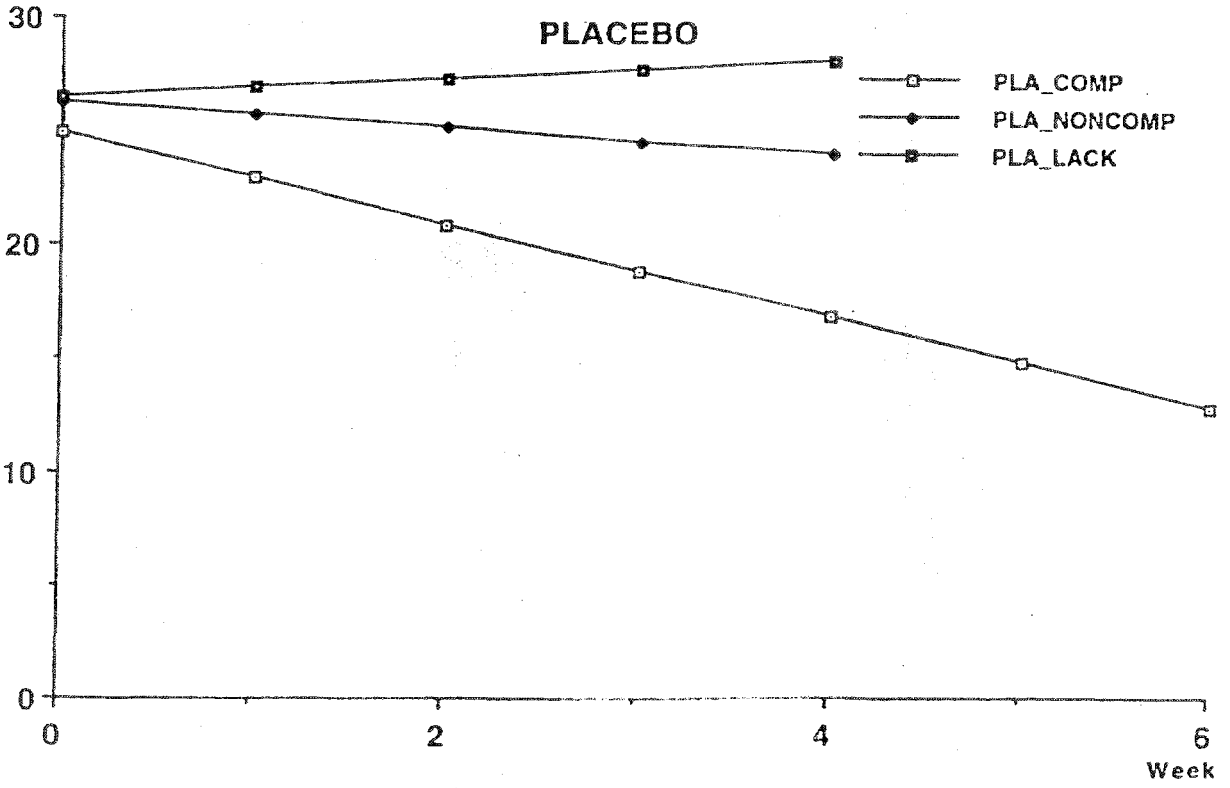
Masahiro Takeuchi Sc.D.

cc: HFD-713/Dr. Dubey
HFD-713/Dr. Wilson

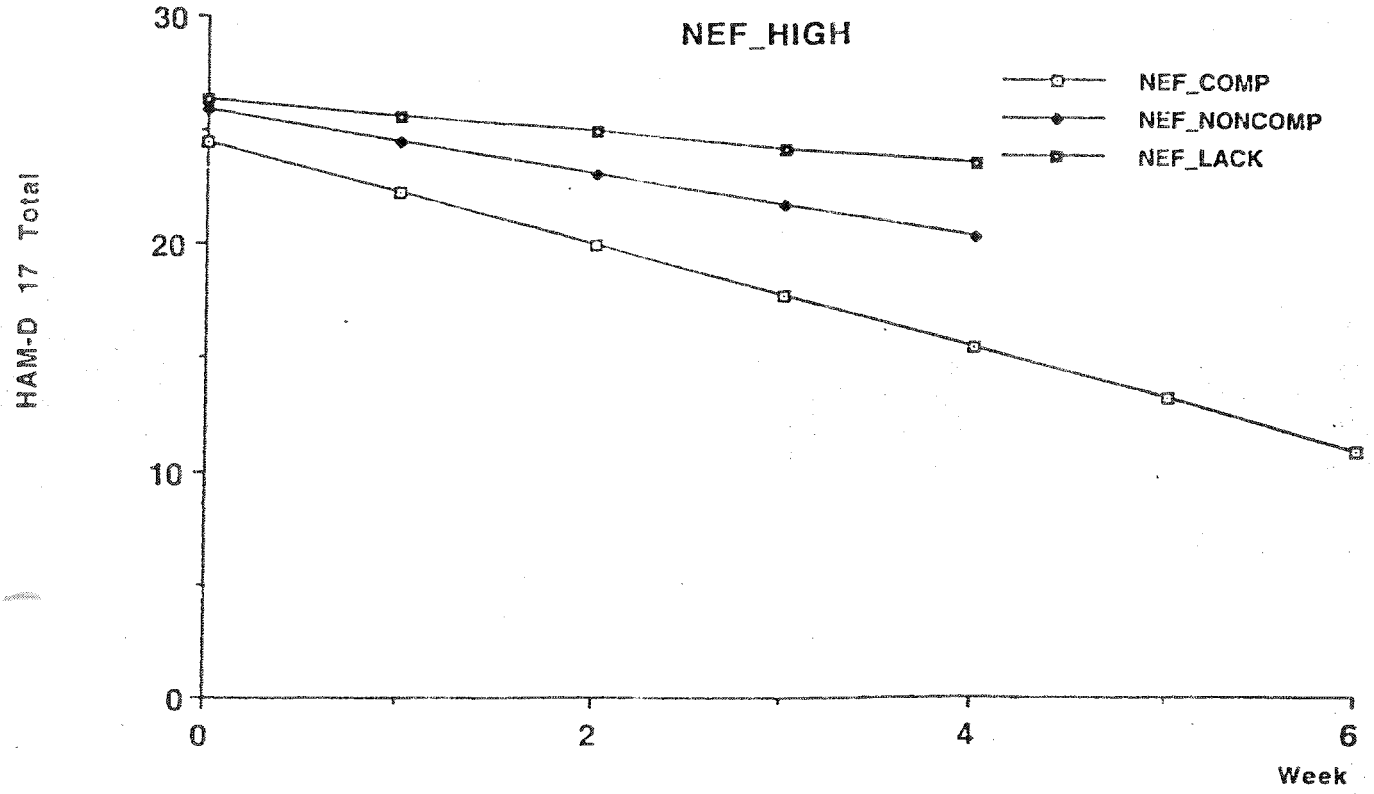
GRAPH 1


COMPLETERS
PLACEBO
NEF_HIGH
IMP
HAM-D 17 Total
30
20
10
0
0
2
4
6
Week

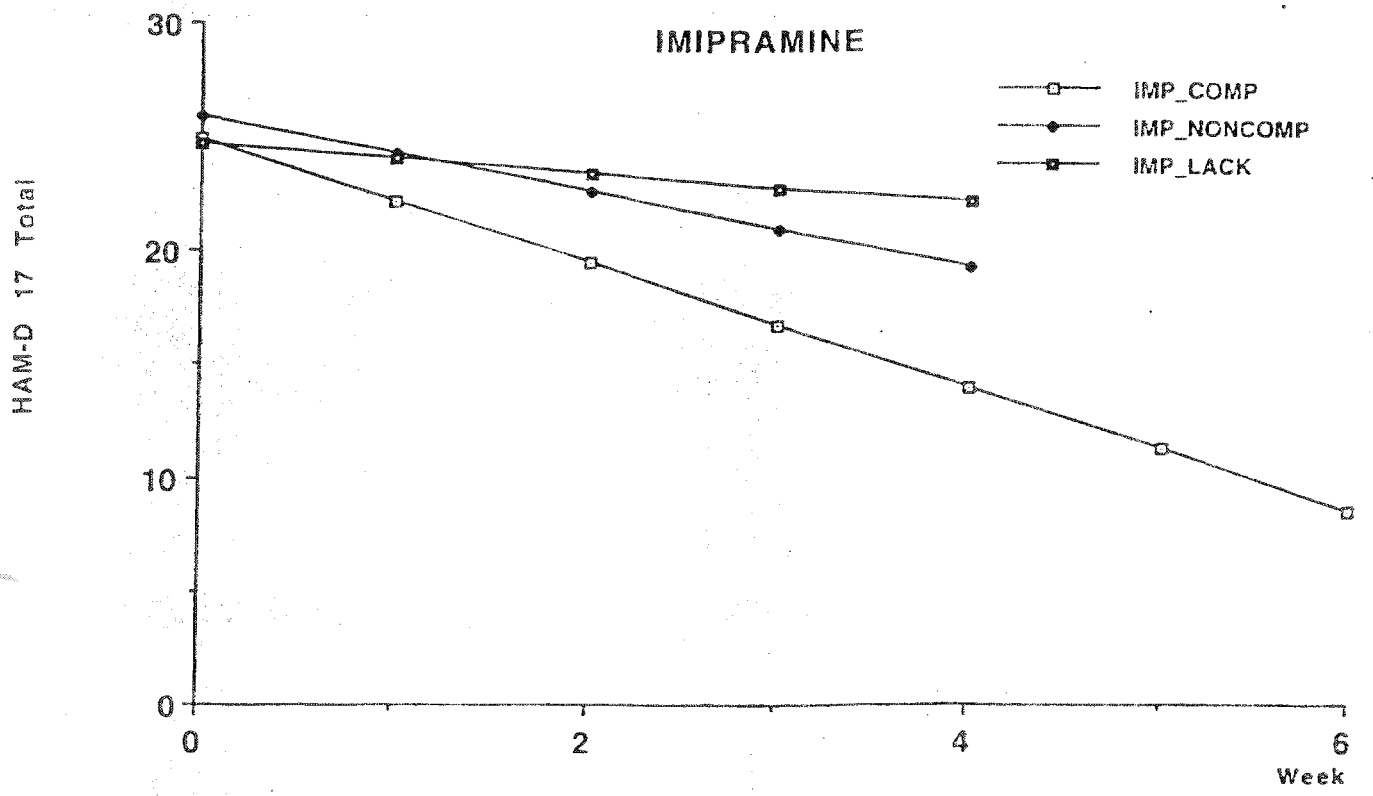
GRAPH 2


PLACEBO
30
20
10
0
HAM-D 17 Total
0
2
4
6
Week
PLA_COMP
PLA_NONCOMP
PLA_LACK

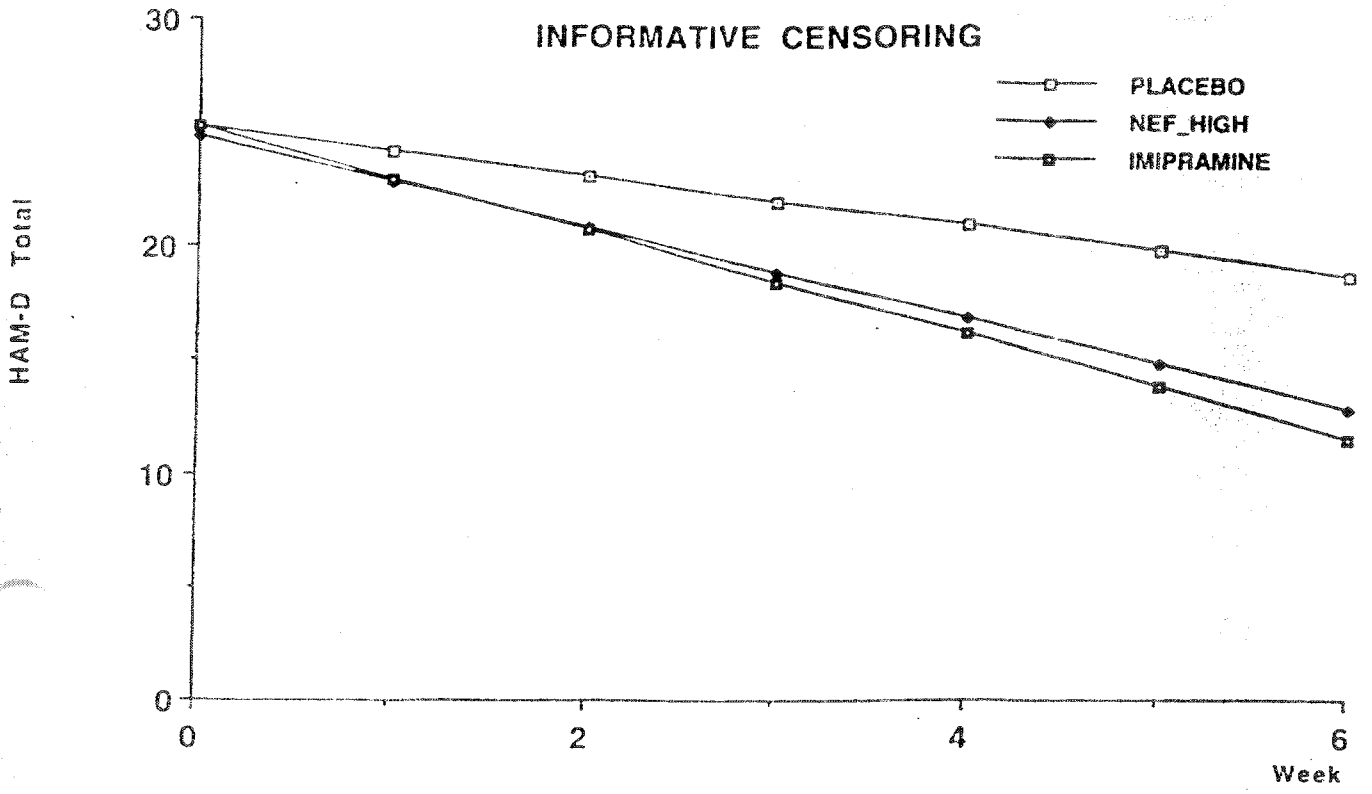
GRAPH 3

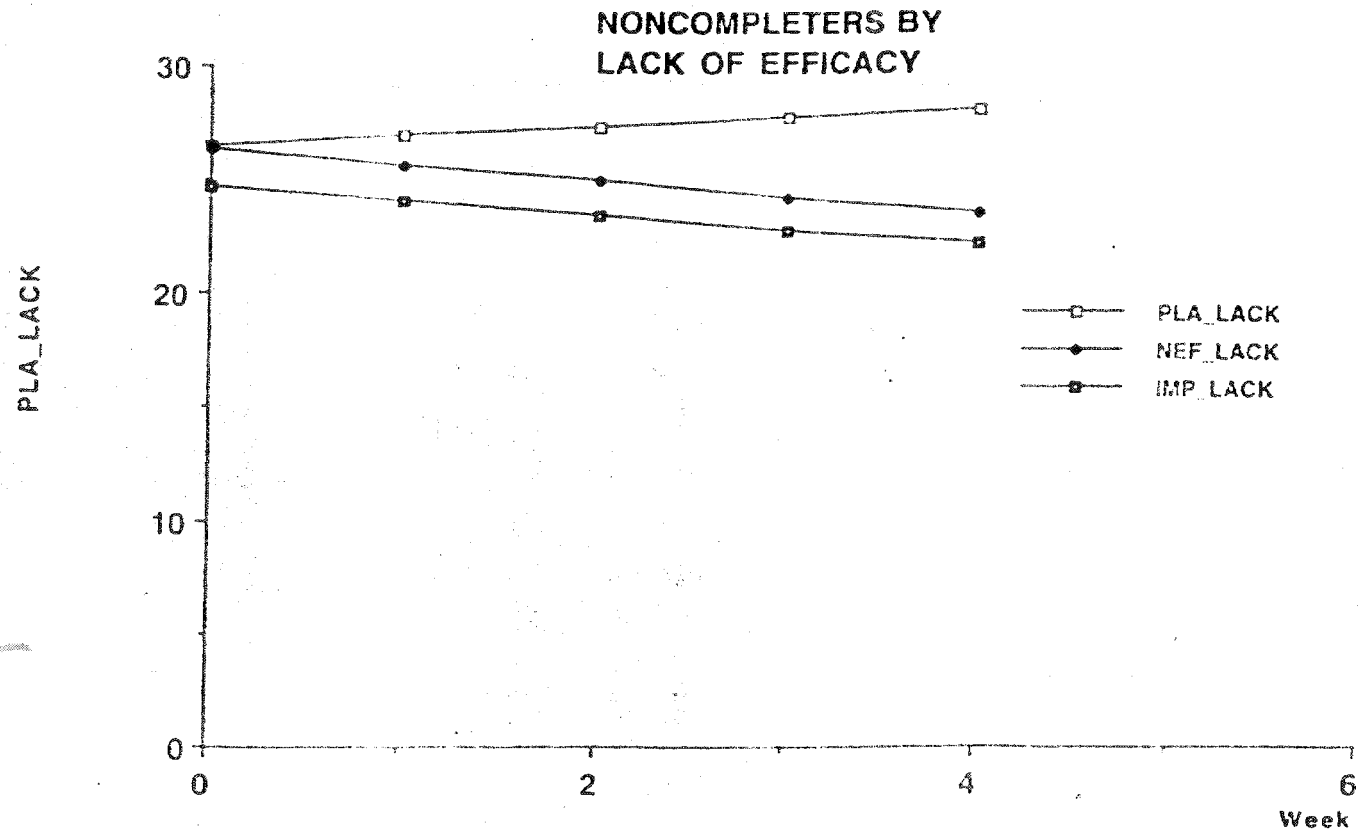

NEF_HIGH
NEF_COMP
NEF_NONCOMP
NEF_LACK
HAM-D 17 Total
30
20
10
0
0
2
4
6
Week

GRAPH 4


IMIPRAMINE
IMP_COMP
IMP_NONCOMP
IMP_LACK
HAM-D 17 Total
30
20
10
0
0
2
4
6
Week

GRAPH 5


INFORMATIVE CENSORING
PLACEBO
NEF_HIGH
IMIPRAMINE
HAM-D Total
30
20
10
0
0
2
4
6
Week


NONCOMPLETERS BY
LACK OF EFFICACY
PLA_LACK
30
20
10
0
0
2
4
6
Week
PLA_LACK
NEF_LACK
IMP_LACK

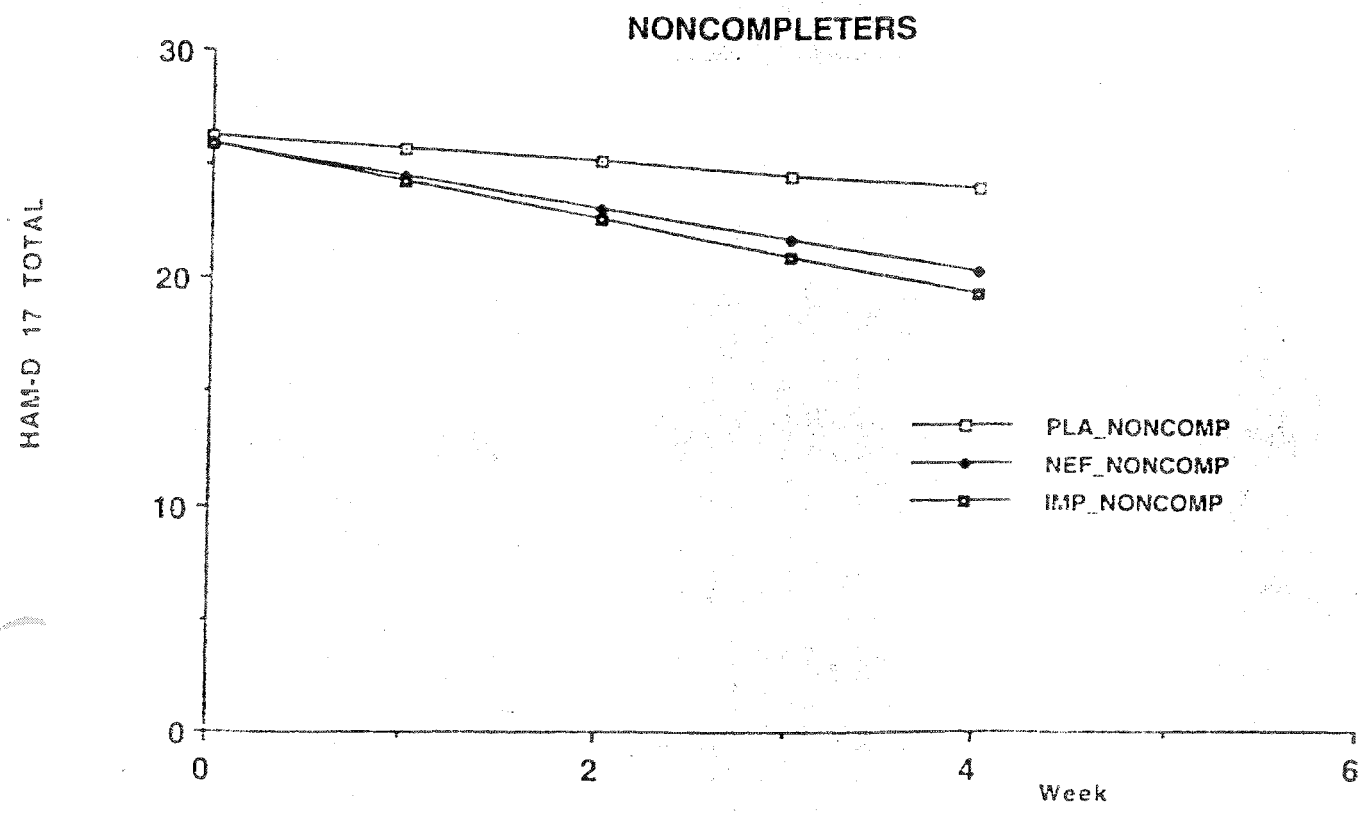

NONCOMPLETERS
HAM-D 17 TOTAL
30
20
10
0
0
2
4
6
Week
PLA_NONCOMP
NEF_NONCOMP
IMP_NONCOMP

TABLE A
Protocol: 03A0A-003, Stratum: 2191
Demographic Characteristics for Total Patient Sample

Treatment Groups	n	Age (years)		Sex [n(%)]		Race [n(%)]	
		Mean	Range	Male	Female	White	Non-White
Nefazodone-Low	46	39.9		18 (39)	28 (61)	46 (100)	0
Nefazodone-High	44	43.3		12 (27)	32 (73)	44 (100)	0
Imipramine	45	43.9		23 (51)	22 (49)	45 (100)	0
Placebo	45	42.2		15 (33)	30 (67)	45 (100)	0

TABLE B
Protocol: 03A0A-003, Stratum: 2191
Patient Completion Rates

Treatment Groups	Number Randomized	Intent-to-Treat Sample	Completers [n(%)]					
			Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6
Nefazodone-Low	46	46	46 (100)	44 (96)	45 (98)	43 (93)	38 (83)	34 (74)
Nefazodone-High	44	44	44 (100)	44 (100)	42 (95)	37 (84)	34 (77)	33 (75)
Imipramine	45	45	45 (100)	45 (100)	42 (93)	35 (78)	29 (64)	27 (60)
Placebo	45	45	45 (100)	42 (93)	42 (93)	31 (69)	29 (64)	24 (53)

TABLE C
Protocol: 03A0A-003, Stratum: 2191
Dosing Information

Treatment Groups	Mean Modal Dose (mg/day) for Completers in Active Drug Groups					
	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6
Nefazodone-Low	102.2	204.0	242.2	245.3	246.1	245.6
Nefazodone-High	206.8	410.2	473.8	475.7	473.5	462.1
Imipramine	102.2	200.0	225.6	226.4	222.4	215.7

TABLE D
Protocol: 03A0A-003, Stratum: 2191
Mean (Least Squares) Change from Baseline in HAM-D-17 Total Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone-Low	46	25.2	46	-2.1	46	-4.8	46	-7.0	46	-8.1	46	- 7.8	46	- 8.2
Nefazodone-High	44	25.6	44	-2.4	44	-6.4	44	-7.5	44	-9.2	44	-10.1	44	-11.0
Imipramine	45	25.8	45	-1.2	45	-7.0	45	-8.6	45	-9.6	45	-10.8	45	-10.8
Placebo	45	25.9	45	-1.4	45	-3.0	45	-5.9	45	-6.4	45	- 6.1	45	- 6.8
2-sided p-values for pairwise comparisons														
Nefazodone-Low vs Placebo	0.28		0.41		0.15		0.45		0.29		0.32		0.45	
Nefazodone-High vs Placebo	0.59		0.23		0.01		0.29		0.09		0.03		0.03	
Imipramine vs Placebo	0.86		0.79		0.00		0.07		0.05		0.01		0.04	

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone-Low	46	25.2	46	-2.1	44	-5.0	45	-7.2	43	- 8.9	38	- 9.8	34	-10.7
Nefazodone-High	44	25.6	44	-2.4	44	-6.4	41	-8.0	37	-10.2	34	-11.9	33	-13.2
Imipramine	45	25.8	45	-1.2	45	-7.0	41	-9.3	34	-11.8	29	-15.0	27	-15.7
Placebo	45	25.9	45	-1.4	42	-3.4	42	-6.4	31	- 9.3	29	- 9.6	24	-11.9
2-sided p-values for pairwise comparisons														
Nefazodone-Low vs Placebo	0.28		0.41		0.20		0.62		0.80		0.93		0.55	
Nefazodone-High vs Placebo	0.59		0.23		0.02		0.33		0.60		0.23		0.50	
Imipramine vs Placebo	0.86		0.79		0.00		0.06		0.16		0.01		0.07	

TABLE F
Protocol: 03A0A-003, Stratum: 2191
Mean (Least Squares) Change from Baseline in HAM-D Depressed Mood (Item 1) Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone-Low	46	3.0	46	-0.3	46	-0.5	46	-0.8	46	-0.9	46	-1.0	46	-1.0
Nefazodone-High	44	2.8	44	-0.2	44	-0.5	44	-0.7	44	-0.9	44	-0.8	44	-1.0
Imipramine	45	3.0	45	-0.2	45	-0.7	45	-0.9	45	-1.1	45	-1.1	45	-1.2
Placebo	45	3.0	45	-0.1	45	-0.3	45	-0.7	45	-0.6	45	-0.6	45	-0.6
2-sided p-values for pairwise comparisons														
Nefazodone-Low vs Placebo	0.55		0.09		0.22		0.32		0.15		0.06		0.12	
Nefazodone-High vs Placebo	0.03		0.67		0.13		0.97		0.23		0.32		0.15	
Imipramine vs Placebo	1.00		0.32		0.02		0.23		0.03		0.01		0.02	

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANCOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone-Low	46	3.0	46	-0.3	46	-0.4	46	-0.8	46	-0.9	46	-0.9	46	-0.9
Nefazodone-High	44	2.8	44	-0.2	44	-0.6	44	-0.9	44	-1.0	44	-0.9	44	-1.1
Imipramine	45	3.0	45	-0.2	45	-0.6	45	-0.9	45	-1.0	45	-1.1	45	-1.2
Placebo	45	3.0	45	-0.1	45	-0.3	45	-0.6	45	-0.6	45	-0.5	45	-0.6
2-sided p-values for pairwise comparisons														
Nefazodone-Low vs Placebo	0.55		0.11		0.28		0.4		[illegible]		[illegible]		[illegible]	
Nefazodone-High vs Placebo	0.03		0.26		0.01		[illegible]		[illegible]		[illegible]		[illegible]	
Imipramine vs Placebo	1.00		0.30		0.01		[illegible]		[illegible]		[illegible]		[illegible]	

TABLE 7

Protocol: 03A0A-003, Stratum: 2341

Mean (Least Squares) Change from Baseline in HAM-D Depressed Mood Item

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 4		Wk 6					
	n	X	n	X	n	X	n	X	n	X				
Nefazodone-Low	46	3.0	46	-0.3	44	-0.5	45	-0.9	43	-1.2				
Nefazodone-High	44	2.8	44	-0.2	44	-0.5	41	-0.7	37	-1.1				
Imipramine	45	3.0	45	-0.2	45	-0.7	41	-0.8	38	-1.2				
Placebo	45	3.0	45	-0.1	42	-0.3	42	-0.5	32	-0.7				
2-sided p-values for pairwise comparisons														
Nefazodone-Low vs Placebo	0.55		0.09		0.30		0.49		0.54					
Nefazodone-High vs Placebo	0.03		0.67		0.23		0.51		0.74					
Imipramine vs Placebo	1.00		0.32		0.04		0.32		0.15					

TABLE H
Protocol: 03A0A-003, Stratum: 2191
Mean (Least Squares) Change from Baseline in CGI Scale: Doctor's Opinion of Severity

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone-Low	46	5.4	46	-0.4	46	-0.7	46	-1.0	46	-1.3	46	-1.4	46	-1.5
Nefazodone-High	44	5.5	44	-0.5	44	-1.0	44	-1.3	44	-1.6	44	-1.7	44	-1.9
Imipramine	45	5.6	45	-0.3	45	-1.1	45	-1.6	45	-1.5	45	-1.9	45	-1.9
Placebo	45	5.5	45	-0.2	45	-0.5	45	-1.0	45	-1.0	45	-1.0	45	-1.1
2-sided p-values for pairwise comparisons														
Nefazodone-Low vs Placebo	0.45		0.37		0.40		0.80		0.30		0.23		0.29	
Nefazodone-High vs Placebo	0.66		0.20		0.02		0.16		0.07		0.05		0.03	
Imipramine vs Placebo	0.30		0.68		0.01		0.02		0.08		0.01		0.02	

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone-Low	46	5.4	45	-0.4	43	-0.7	44	-1.0	43	-1.5	38	-1.8	34	-1.9
Nefazodone-High	44	5.5	44	-0.5	44	-1.0	42	-1.4	37	-1.8	34	-2.0	33	-2.2
Imipramine	45	5.6	45	-0.3	45	-1.1	42	-1.6	35	-1.8	29	-2.7	27	-2.9
Placebo	45	5.5	45	-0.2	42	-0.5	42	-1.1	31	-1.5	29	-1.7	24	-2.0
2-sided p-values for pairwise comparisons														
Nefazodone-Low vs Placebo	0.45		0.34		0.45		0.92		0.97		0.70		0.85	
Nefazodone-High vs Placebo	0.66		0.20		0.04		0.24		0.35		0.33		0.52	
Imipramine vs Placebo	0.30		0.68		0.01		0.04		0.33		0.01		0.03	

TABLE I
Protocol: 03AOA-003, Stratum: 2191
Mean Score in CGI Scale: Doctor's Opinion of Improvement

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week											
	Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Nefazodone-Low	45	3.6	46	3.3	46	2.9	46	2.7	46	2.8	46	2.7
Nefazodone-High	44	3.5	44	3.0	44	2.8	44	2.7	44	2.5	44	2.3
Imipramine	45	3.8	45	3.0	45	2.6	45	2.6	45	2.5	45	2.5
Placebo	45	3.9	45	3.7	45	3.2	45	3.2	45	3.2	45	3.0
2-sided p-values for pairwise comparisons												
Nefazodone-Low vs Placebo	0.02		0.04		0.26		0.07		0.20		0.28	
Nefazodone-High vs Placebo	0.01		<0.01		0.13		0.05		0.01		0.02	
Imipramine vs Placebo	0.47		<0.01		0.02		0.03		0.01		0.06	

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week											
	Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Nefazodone-Low	45	3.6	43	3.2	44	2.9	43	2.5	38	2.5	34	2.3
Nefazodone-High	44	3.5	44	3.0	42	2.8	37	2.4	34	2.1	33	1.9
Imipramine	45	3.8	45	3.0	42	2.5	35	2.3	29	1.8	27	1.7
Placebo	45	3.9	42	3.6	42	3.1	31	2.7	29	2.6	24	2.1
2-sided p-values for pairwise comparisons												
Nefazodone-Low vs Placebo	0.02		0.06		0.48		0.50		0.71		0.44	
Nefazodone-High vs Placebo	0.01		<0.01		0.26		0.30		0.07		0.47	
Imipramine vs Placebo	0.47		<0.01		0.02		0.12		<0.01		0.16	

Study 03A0A-003 (Conducted 11/86 to 6/90)

In Study 03A0A-003, patients were randomized to 4 treatment arms: low dose nefazodone; high dose nefazodone; imipramine and placebo. The first three groups could be titrated to peak doses (mg/day) of 250, 500 and 250, respectively. The duration of treatment was 6 weeks.

Study 03A0A-003 was originally planned as a multicenter study with 5 centers (all in Canada). Enrollment was initiated 11/86 at Center 2191 (Fontaine); about 6 months later the other 4 center began enrollment. One investigator withdrew from the study and the other 3 centers ended recruitment of patients after 1 to 8 months due to slow enrollment, change in personnel or change in priorities. The protocol was amended 7/11/88 to change the proposed sample size allocation from 240 patients at 4 centers to 240 patients at Center 2191.

The number of patients randomized and the number of completers for the 3 small centers and Center 2191 are shown in the table below. Of the 204 patients randomized, 180 (88%) were in Center 2191 while only 24 patients were enrolled in the other 3 centers.

Table 4. Study 03A0A-003
Sample Sizes

	NEF LOW	NEF HIGH	PLACEBO	IMIPRAMINE
All Patients				
Randomized	51	50	52	51
Completers	36 (71%)	37 (74%)	29 (56%)	30 (59%)
Center 2191				
Randomized	46	44	45	45
Completers	33 (72%)	33 (75%)	24 (53%)	26 (58%)
3 Small Centers				
Randomized	5	6	7	6
Completers	3 (60%)	4 (67%)	5 (71%)	4 (67%)

For the "all patients" dataset, the sponsor performed a 2-way ANOVA including the treatment-by-center interaction term in the model (the 3 small centers were combined to form 1 center). effects were assessed using the Type III/IV sum of squares. For the by center analyses, a 1-way ANOVA was performed. The results are presented on the following page.

It should be noted that in the sponsor's study report, only the results for Center 2191 were presented without providing the rationale for the exclusion of the 24 patients in the small centers. However information regarding the combined sample and the small centers was provided in appendices.

From the table of HAM-D 17 Total results below, it can be seen that the low dose clearly does not beat placebo for any dataset. The placebo comparisons for the high dose nefazodone group and the imipramine group show a significant treatment effect for patients in Center 2191 but not for all patients combined. (The pattern of response seen for the HAM-D 17 Total was repeated for each of the other 3 efficacy variables.)

Table 5. Study 03A0A-003
Sponsor's HAM-D 17 Total Change from Baseline Results

	TREATMENT GROUP				PLACEBO COMPARISON P-VALUES		
	LOW	HIGH	PLA	IMP	LOW	HIGH	IMP
All Patients	*LEAST SQUARES MEANS*						
Baseline	26.4	25.4	26.5	25.2	.96	.23	.18
Week 6							
LOCF	-7.4	-11.6	-11.3	-11.1	.17p[1]	.90	.95p
OC	-11.8	-13.5	-16.5	-16.0	.11p	.26p	.84p
Center 2191	*MEANS*						
Baseline	25.2	25.6	25.9	25.8	.28	.59	.86
Week 6							
LOCF	-8.2	-11.0	-6.8	-10.8	.45	.03	.04
OC	-10.7	-13.2	-11.9	-15.7	.55	.50	.07
3 Small Centers	*MEANS*						
Baseline	27.6	25.2	27.0	24.6	.74	.28	.18
Week 6							
LOCF	-6.6	-12.2	-15.7	-11.4	.08p	.47p	.41p
OC	-13.0	-13.8	-21.2	-16.3	.13p	.14p	.32p

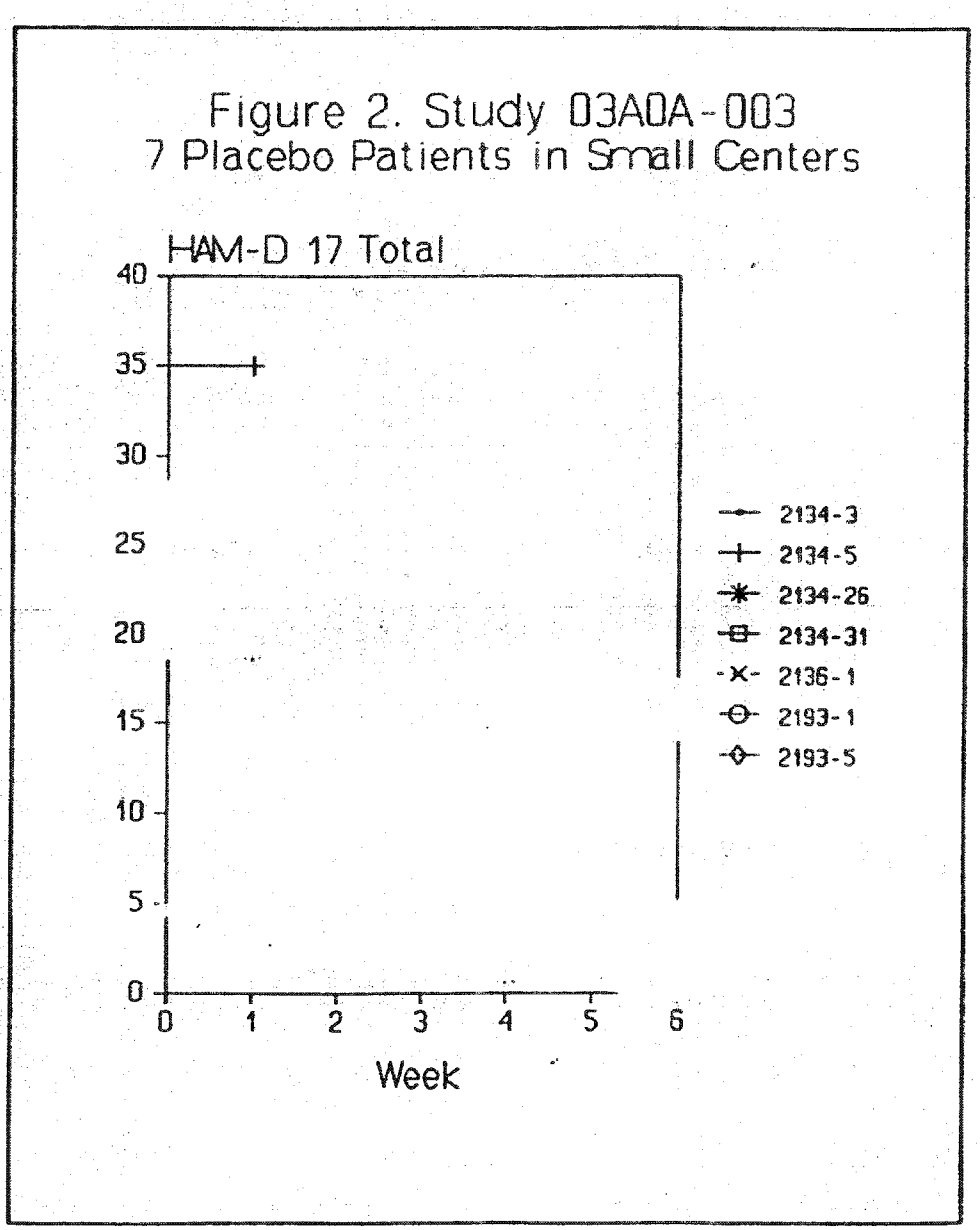
Reviewer's Comments on "All Patients" Analyses

In this section, I will discuss the "all patients" analyses and how the results compare to the Center 2191 results. In the section that follows, the sponsor's analysis of Center 2191 will be presented and discussed.

From the table above it can be seen that the high nefazodone response is consistent across the 3 samples while the placebo response is not. The inconsistency of the combined results with the Center 2191 results appears then to be due to the large positive response seen for the placebo patients in the small centers.

[1] A "p" indicates that the results favor placebo.

There were only 7 patients in the placebo groups of the 3 small centers. Four of the 7 patients had HAM-D values of less than 5 at the completion of the study (see figure below); only 10% of the placebo patients in Center 2191 had values less than 5 at endpoint (the mean and median HAM-D LOCF for the placebo group was 18). (Note that the 3 different line types in Figure 2 represent patients in the 3 different small centers.)



The inclusion of these placebo patients with unusually large responses in a Type III SS analysis which gives equal weight to each center (the one performed by the sponsor) produces nonsignificant treatment differences. Regardless of the aberrant placebo effect, equal weighting of centers of grossly different sample sizes does not seem reasonable to this reviewer. Two alternate approaches would be to analyze all the data excluding the interaction term but including the center term (giving equal weight to each patient) or analyze only the data from Center 2191. This reviewer did the former and the sponsor did the latter (which is discussed in full on the following pages). The "all patients" results for ANOVA at Week 6 and for a repeated measures analysis using data from Weeks 1 to 6 showed borderline significant differences between high dose nefazodone and placebo (HAM-D 17 Total LOCF, $p = .07$); for ANCOVA, using baseline as a covariate, the comparison was statistically significant (HAM-D 17 Total LOCF, $p = .05$).

One drawback of the "all patients" analysis is that we must assume that the interaction term is truly nonsignificant. This does not seem to be a reasonable assumption for 3 reasons; 1) the test for interaction is underpowered due to the grossly different sample sizes of the 2 centers, 2) one "center" is a combination of 3 small centers so true center effects cannot be measured, and 3) the large placebo response in the small centers raises questions about the results of this pseudo center. Therefore the sponsor's approach of looking primarily at Center 2191 seems to be acceptable. Also since randomization is blocked on center, it is not unreasonable to focus on a single large center.

Center 2191

Patient Disposition

With respect to demographics and psychiatric history, the treatment groups in Center 2191 were similar. Slightly more than half of the patients had experienced a previous depressive episode for which antidepressants were prescribed.

The primary reason for dropout for all groups was lack of efficacy (see tables below). These dropouts occurred during Weeks 3 and 4.

Table 6. Study 03A0A-003
Center 2191
Patients on Study

	NEFAZODONE			
WEEK	LOW	HIGH	PLACEBO	IMIPRAMINE
Randomized	46	44	45	45
1	45 (98%)	44 (100%)	43 (96%)	45 (100%)
2	45 (98%)	42 (95%)	42 (93%)	42 (93%)
3	43 (94%)	36 (82%)	31 (69%)	33 (73%)
4	38 (83%)	35 (80%)	29 (64%)	28 (62%)
5	34 (74%)	33 (75%)	24 (53%)	27 (60%)
6	33 (72%)	33 (75%)	24 (53%)	26 (58%)

Table 7. Study 03A0A-003
Center 2191
Reasons for Dropouts

	NEFAZODONE			
Reason for Dropout	LOW	HIGH	PLACEBO	IMIPRAMINE
Lack of Efficacy	7 (15%)	6 (14%)	15 (33%)	11 (24%)
Adverse Experience	1 (2%)	0 (0%)	1 (2%)	3 (7%)
Lost-to-Followup	1 (2%)	0 (0%)	0 (C%)	0 (0%)
Patient Refusal	1 (2%)	2 (5%)	3 (7%)	1 (2%)
Other	3 (7%)	3 (7%)	2 (4%)	4 (9%)

Results

The low dose (peak allowable dose of 250 mg/day) of nefazodone was not statistically significantly different from placebo for any variable at any timepoint. In fact, for the observed cases results, the magnitude of the placebo effect is sometimes larger than the magnitude of the low dose effect. (See Figure 3 on the following page.)

The high dose (peak allowable dose of 500 mg/day) of nefazodone was significantly better than placebo at Weeks 5 and 6 ($p = .03$) according to the HAM-D 17 Total LOCF (see Figure 3). The observed cases treatment effects were not significant at any single week; however, a repeated measures analysis performed by this reviewer on data from Weeks 1 to 6 revealed a statistically significant difference between the high dose group and the placebo group with a p-value of .03.

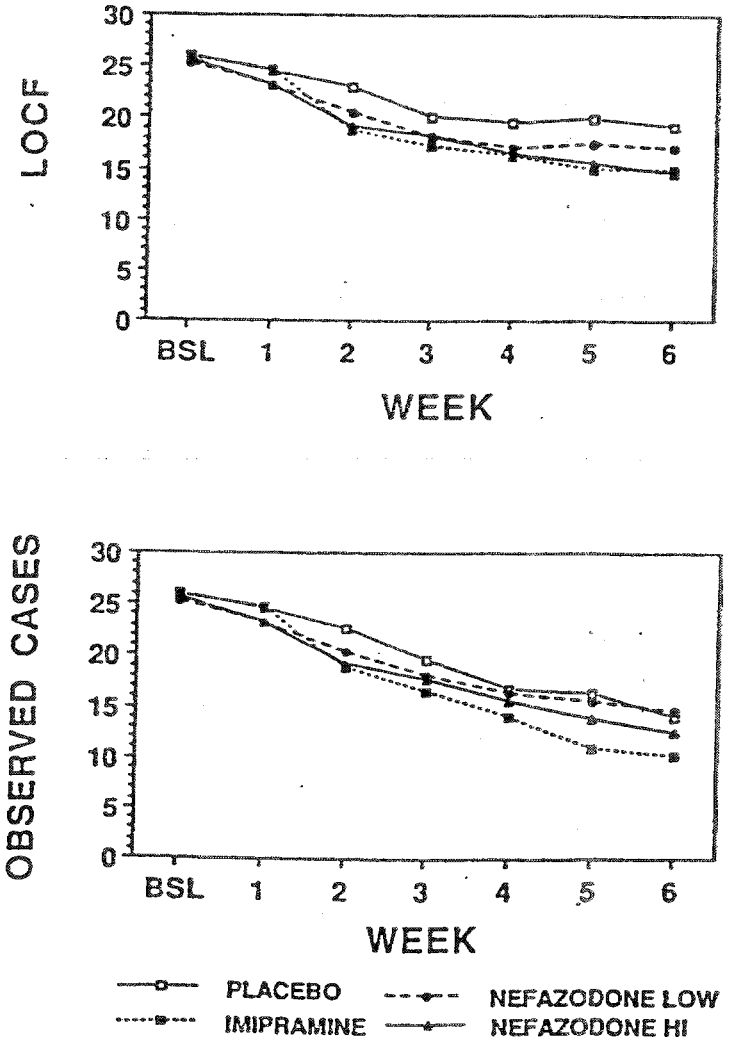
The nefazodone and placebo baselines for HAM-D Item #1 were significantly different ($p = .03$); 91% of the placebo patients had a baseline score of 3 while 80% of the nefazodone patients had a score of 3 and 20% had a score of 2 at baseline. The sponsor performed an ANCOVA on the LOCF data to adjust for baseline and found a significant treatment difference with $p = .02$. The results at Weeks 4 and 5 were consistent with the week 6 results.

Table 8. Study 03A0A-003
Center 2191
Sponsor's Results

	NEF LOW Mean	NEF HIGH Mean	PLA Mean	IMP Mean	PLACEBO COMPARISON P-VALUES	
					HIGH	IMP
HAM-D 17 Total						
Baseline	25.2	25.6	25.9	25.8	.59	.86
Week 6						
LOCF	-8.2	-11.0	-6.8	-10.8	.03	.04
OC	-10.7	-13.2	-11.9	-15.7	.50	.07
HAM-D Item 1						
Baseline	3.0	2.8	3.0	3.0	.03	1.0
Week 6						
LOCF	-1.0	-1.1	-0.6	-1.2	.02[1]	.01
OC	-1.1	-1.4	-1.0	-1.7	.23[1]	.01
CGI Severity of Illness						
Baseline	5.4	5.5	5.5	5.6	.66	.30
Week 6						
LOCF	-1.5	-1.9	-1.1	-1.9	.03	.02
OC	-1.9	-2.2	-2.0	-2.9	.52	.03
CGI Global Improvement						
Week 6						
LOCF	2.7	2.3	3.0	2.5	.02	.08
OC	2.3	1.9	2.1	1.7	.49	.12

[1] ANCOVA results with baseline as the covariate.

Figure 3. Study 03AOA - 003
Center 2191
HAM-D 17 Total by Week
Means



Reviewer's Comments on Center 2191 Results

It is clear in this study that the low dose of nefazodone (peak allowable dose of 250 mg/day) was not effective.

The high dose of nefazodone beat placebo on all 4 efficacy variables when looking at the LOCF results. The OC results did not agree with the LOCF results. (See figure on previous page.) The percentage of dropouts for high dose nefazodone (25%) compared to placebo (47%) suggests that the lack of agreement for the LOCF and OC results may be due to the dropouts in the placebo group. That is, the dropouts in the placebo group may bias the LOCF results for the drug since those patients were not given the opportunity to improve. However, for imipramine, the LOCF and the OC comparisons agree suggesting that it may not be the dropouts in the placebo group that contribute to the lack of agreement of the results for the nefazodone group. Nevertheless, the effect of the dropouts on treatment effect should be examined further.

The dropout patterns for the drug groups in Center 2191 were unusual compared to what was observed in the other studies in this submission and compared to what is typically seen for imipramine. Usually, in the high dose nefazodone group and the imipramine group, 2 to 3 times more patients drop due to adverse events than due to lack of efficacy. In this study, for all groups, only 5 patients dropped due to an adverse event while the majority of dropouts discontinued due to lack of efficacy (Table 6). These results, also are surprising since the protocol does not list "lack of efficacy" as a criterion for removal from the study (with the exception of this study and Study 104-002, all the protocols in this submission specifically list "lack of efficacy" as a criterion for removal). However, the Doctor's Disposition form does list "patient feels worse or no change" as a potential reason for withdrawal.

This reviewer performed a series of Week 6 LOCF analyses on the HAM-D 17 Total to study the contribution of dropouts to the treatment effect. To study the effect of very early dropouts, a Week 6 LOCF analysis excluding patients with only Week 1 data (1 high dose nefazodone patient and 3 placebo patients) was performed. This analysis produced a p-value of .05 for the nefazodone/placebo comparison. Repeating the analysis excluding patients with only Week 1 and Week 2 data again yielded a significant p-value (.02). So the early dropouts do not seem to contribute noticeably to the positive LOCF results observed. For a third analysis, all patients with only Week 1, 2 or 3 data were excluded. The analysis produced a p-value of .21 for the high dose nefazodone/placebo comparison and a p-value of .09 for the imipramine/placebo comparison suggesting that the dropouts at Week 3 do contribute to the positive LOCF results. The mean change from baseline for those dropouts was about -4 for the 7 nefazodone dropouts and about +0.1 for the 14 placebo dropouts. Patients who dropped after Week 2 primarily discontinued due to lack of efficacy so it seems reasonable to include these patients in assessments of treatment effect (the LOCF analysis). However, one must be willing to assume that the responses for these patients would not have improved appreciably during the remainder of the trial.

In addition, longitudinal data analyses were performed by Dr. Masahiro Takeuchi (HFD-713) to examine the LOCF/OC differences and the contribution of dropouts to the treatment effects. His analyses, which are provided in a separate document, showed a significant difference between high dose nefazodone and placebo with p=.02.

CN104-002 ~~H88 11/20 PF Feighner~~

medication. 223 patients were evaluable for efficacy.

Demographics: Of the 234 patients, 134 (57%) were women and 100 (43%) men. They ranged in age from 18 to 69 and 168 (72%) met DSM-III diagnostic criteria for Major Depression, Melancholic Subtype; 138 (59%) experienced a previous depress e episode.

Dosing Information: 2 oral capsules given BID. Dosages: nefazodone 50 mg/day (one 25-mg capsule, one placebo capsule); nefazodone 100 mg/day, (two 25-mg capsules); nefazodone 200 mg/day, (two 50-mg capsules); nefazodone 300 mg/day, (one 100-mg capsule, one 50-mg capsule).

Concomitant Medications: The protocol permitted the use of chloral hydrate for sleep and this was the most frequently used concomitant psychotropic medication. Six patients, four on placebo and two on 50 mg/day nefazodone, took prohibited concomitant psychotropic medication (alprazolam, hydroxyzine, diazepam, and triazolam), but these patients were not excluded from the analyses.

Efficacy Results: (see appendix) Patients were considered evaluable for efficacy (i.e., included in the Intent-to-Treat Sample) if they were randomized to treatment, received a dose of study medication, and had an efficacy evaluation during treatment. Two hundred twenty-three patients were evaluable for efficacy; 47 received placebo, 43 received nefazodone 50 mg/day, 46 received nefazodone 100 mg/day, 46 received nefazodone 200 mg/day, 41 received nefazodone 300 mg/day and 11 patients were lost to follow-up.

The week 6 results (LOCF and OC) for the CGI and the HAM-D Mood Item 1 were not significant at any dose level. In this study the treatment effects seen for the 200 mg/day dose are greater than the effects seen for the 300 mg/day.

7.2.6.4 **Conclusions:** This trial failed to show statistically that Nefazodone is more effective than placebo for the treatment of depression.

7.2.7 **03A0A-004A** A Double-Blind Trial of Two Daily Dose Ranges of Nefazodone ~~and Placebo~~ in the Treatment of Depressed Outpatients

7.2.7.1 **Investigator\Locations:** James Claghorn, M.D., Clinical Research Associates, Houston, Texas, USA (Study 2407); A. John Rush, M.D., University of Texas, Health Science Center at Dallas, Dallas, Texas, USA (Study 2410).

7.2.7.2 Study Plan:

Objectives: To determine the safety and efficacy of nefazodone titrated in two dose ranges (recommended low-dose range 150-300 mg/day and recommended high-dose range 300-600 mg/day) as compared to placebo in the treatment of patients with moderate to severe depression.

Population to be Studied: Outpatients of either sex, 18 years of age or older, with a diagnosis of Major Depressive Episode or Bipolar Disorder, Depressed (DSM-III).

Study Design: Multicenter, randomized, double-blind, parallel-group, 6-week comparison of the safety and efficacy of two dose ranges of nefazodone and placebo. Rating scales included: 17-Item Hamilton Rating Scale for Depression (HAM-D-17); Clinical Global Impressions (CGI) Scale;

Inventory for Depressive Symptomatology - Clinician (IDS-C); and Inventory for Depressive Symptomatology -Self Report (IDS-SR). A narrative of the physician's overall assessment was collected on the End-of-Study Evaluation Form.

Plan for Analysis: A two-way analysis of variance (ANOVA) model with study center, treatment, and study center by treatment interaction effects was used to test for baseline comparability as well as differences between treatments for the change from Baseline in HAM-D and CGI Severity scores. Categorical data such as CGI Improvement scores were analyzed within the framework of the generalized Cochran-Mantel-Haenszel (CMH) procedure, using study center as the stratification variable. Both the two-way ANOVA and CMH models tested the differences between treatments averaged across the study centers. The planned sample size of 240 patients had a power of ≥ 80% to detect an average difference of four points in the HAM-D-17 Total score between nefazodone and placebo.

7.2.7.3 **Study Conduct/Outcome** (see related appendix table)

Patient Disposition: 240 patients at two study centers were randomized to treatment. 230 patients were evaluable for efficacy.

Demographics: Of the 240 patients, 144 (60%) were women and 96 (40%) men. Patient age ranged from years. 227 met the DSM-III criteria for Major Depression and 13 met the criteria for Bipolar Disorder, Depressed; melancholia was diagnosed in 26 (11%) patients; 158 (66%) patients had recurrent episodes of depression; and 151 (63%) patients had their current episode of depression for at least 6 months.

Dosing Information: Oral capsules administered BID. Recommended dosage ranges: low-dose nefazodone, 150 to 300 mg/day (50-mg capsule), beginning at 100 mg/day; high-dose nefazodone, 300 to 600 mg/day (100-mg capsule), beginning at 200 mg/day; placebo 2-6 capsules/day. The mean modal dose at Week 6 was 276.0 mg/day for the low-dose nefazodone group, 513.5 mg/day for the high-dose nefazodone group, and 5.5 capsules/day for the placebo group.

Concomitant Medications: The protocol permitted the use of chloral hydrate for sleep and this was the most frequently used concomitant psychotropic medication. Fifteen patients took prohibited concomitant psychotropic medications (alprazolam, amitriptyline, diazepam, hydroxyzine HCl, Librax, lorazepam, L-tryptophan, nortriptyline HCl, oxazepam, promethazine, Synalgos, and unspecified tranquilizer); these patients were not excluded from the analyses.

Efficacy Results: Patients were considered evaluable for efficacy if they were randomized to treatment, received a dose of study medication, and had an efficacy evaluation during treatment. Of the 230 patients meeting these criteria, 77 received placebo, 77 received low-dose nefazodone; and 76 received high-dose nefazodone.
In 004A the low dose and high dose effects are not different from placebo effects.

7.2.7.4 **Conclusions** In 04A neither the low or high dose group is superior to placebo in any efficacy variable. The lack of a active control group make interpretation difficult and OC results favor placebo.

Appendix 03A0A-004A

TABLE A
Protocol: 03A0A-004A
Demographic Characteristics for Total Patient Sample

Treatment Groups	N	Age (years)		Sex [N (%)]		Race [N (%)]	
		Mean	Range	Male	Female	White	Non-White
Nefazodone-Low	80	40.1		37 (46)	43 (54)	65 (81)	15 (19)
Nefazodone-High	80	39.6		30 (38)	50 (63)	71 (89)	9 (11)
Placebo	80	36.8		29 (36)	51 (64)	69 (86)	11 (14)

TABLE B
Protocol: 03A0A-004A
Patient Completion Rates

Treatment Groups	Number Randomized	Intent-to-Treat Sample	Completers [N (%)]					
			Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6
Nefazodone-Low	80	77	72 (94)	66 (86)	60 (78)	55 (71)	50 (65)	48 (62)
Nefazodone-High	80	76	70 (92)	64 (84)	57 (75)	56 (74)	48 (63)	52 (68)
Placebo	80	77	72 (94)	68 (88)	66 (86)	58 (75)	54 (70)	49 (64)

TABLE C
Protocol: 03A0A-004A
Dosing Information

Treatment Groups	Mean Modal Dose (mg/day) for Completers in Active Drug Groups					
	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6
Nefazodone-Low	166.0	256.1	274.2	267.3	271.0	276.0
Nefazodone-High	334.3	478.1	519.3	517.9	537.5	513.5

TABLE D
Protocol: 03AOA-C04A
Mean (Least Squares) Change from Baseline in HAM-D-17 Total Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	N	X	N	X	N	X	N	X	N	X	N	X	N	X
Nefazodone-Low	77	23.2	77	-3.6	77	-5.5	77	-6.7	77	-7.8	77	-7.8	77	-8.3
Nefazodone-High	76	23.6	76	-3.7	76	-6.1	76	-7.6	76	-8.7	76	-9.0	76	-9.5
Placebo	77	23.5	77	-3.1	77	-4.2	77	-6.1	77	-7.8	77	-8.5	77	-8.9
2-sided p-values for pairwise comparisons														
Nefazodone-Low vs Placebo	0.46		0.48		0.11		0.55		0.98		0.54		0.62	
Nefazodone-High vs Placebo	0.88		0.39		0.02		0.11		0.37		0.66		0.66	

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	N	X	N	X	N	X	N	X	N	X	N	X	N	X
Nefazodone-Low	77	23.2	72	-3.5	64	-5.8	60	-7.3	53	- 9.1	50	- 8.8	48	-11.3
Nefazodone-High	76	23.6	70	-3.7	63	-6.8	55	-8.7	56	-10.2	48	-10.4	50	-12.1
Placebo	77	23.5	72	-3.2	68	-4.5	65	-6.6	56	- 9.3	54	-10.8	49	-13.0
2-sided p-values for pairwise comparisons														
Nefazodone-Low vs Placebo	0.46		0.72		0.13		0.51		0.88		0.14		0.19	
Nefazodone-High vs Placebo	0.88		0.47		0.01		0.05		0.45		0.78		0.45	

TABLE D
Protocol: 03A0A-004A
Mean (Least Squares) Change from Baseline in HAM-D-17 Total Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	N	X	N	X	N	X	N	X	N	X	N	X	N	X
Nefazodone-Low	77	23.2	77	-3.6	77	-5.5	77	-6.7	77	-7.8	77	-7.8	77	-8.3
Nefazodone-High	76	23.6	76	-3.7	76	-6.1	76	-7.6	76	-8.7	76	-9.0	76	-9.5
Placebo	77	23.5	77	-3.1	77	-4.2	77	-6.1	77	-7.8	77	-8.5	77	-8.9
2-sided p-values for pairwise comparisons														
Nefazodone-Low vs Placebo	0.46		0.48		0.11		0.55		0.98		0.54		0.62	
Nefazodone-High vs Placebo	0.88		0.39		0.02		0.11		0.37		0.66		0.66	

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	N	X	N	X	N	X	N	X	N	X	N	X	N	X
Nefazodone-Low	77	23.2	72	-3.5	64	-5.8	60	-7.3	53	- 9.1	50	- 8.8	48	-11.3
Nefazodone-High	76	23.6	70	-3.7	63	-6.8	55	-8.7	56	-10.2	48	-10.4	50	-12.1
Placebo	77	23.5	72	-3.2	68	-4.5	65	-6.6	56	- 9.3	54	-10.8	49	-13.0
2-sided p-values for pairwise comparisons														
Nefazodone-Low vs Placebo	0.46		0.72		0.13		0.51		0.88		0.14		0.19	
Nefazodone-High vs Placebo	0.88		0.47		0.01		0.05		0.45		0.78		0.45	

TABLE F
Protocol: 03A0A-004A
Mean (Least Squares) Change from Baseline in HAM-D Depressed Mood (Item 1) Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	N	X	N	X	N	X	N	X	N	X	N	X	N	X
Nefazodone-Low	76	2.8	76	-0.3	76	-0.5	76	-0.6	76	-0.8	76	-0.8	76	-0.8
Nefazodone-High	76	2.8	76	-0.4	76	-0.6	76	-0.8	76	-0.9	76	-1.0	76	-1.0
Placebo	77	2.7	77	-0.4	77	-0.4	77	-0.6	77	-0.8	77	-0.9	77	-1.1
2-sided p-values for pairwise comparisons														
Nefazodone-Low vs Placebo	0.44		0.53		0.33		0.96		0.92		0.33		0.10	
Nefazodone-High vs Placebo	0.45		0.80		0.07		0.16		0.42		0.82		0.79	

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	N	X	N	X	N	X	N	X	N	X	N	X	N	X
Nefazodone-Low	76	2.8	71	-0.3	64	-0.5	60	-0.6	53	-1.0	50	-0.9	48	-1.1
Nefazodone-High	76	2.8	70	-0.4	63	-0.7	55	-0.9	56	-1.0	48	-1.1	50	-1.3
Placebo	77	2.7	72	-0.4	68	-0.4	65	-0.7	56	-1.0	54	-1.1	49	-1.6
2-sided p-values for pairwise comparisons														
Nefazodone-Low vs Placebo	0.44		0.36		0.31		0.74		0.99		0.20		0.01	
Nefazodone-High vs Placebo	0.45		0.85		0.06		0.19		0.72		0.99		0.15	

TABLE H
Protocol: 03A0A-004A
Mean (Least Squares) Change from Baseline in CGI: Doctor's Opinion of Severity

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	N	X	N	X	N	X	N	X	N	X	N	X	N	X
Nefazodone-Low	77	4.5	77	-0.3	77	-0.5	77	-0.8	77	-0.9	77	-1.1	77	-1.2
Nefazodone-High	76	4.4	76	-0.2	76	-0.5	76	-0.9	76	-1.2	76	-1.3	76	-1.4
Placebo	77	4.4	77	-0.2	77	-0.4	77	-0.7	77	-1.0	77	-1.1	77	-1.3
2-sided p-values for pairwise comparisons														
Nefazodone-Low vs Placebo	0.20		0.41		0.42		0.89		0.79		0.95		0.60	
Nefazodone-High vs Placebo	0.88		0.51		0.49		0.42		0.25		0.23		0.45	

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	N	X	N	X	N	X	N	X	N	X	N	X	N	X
Nefazodone-Low	77	4.5	71	-0.3	66	-0.6	60	-0.9	54	-1.1	50	-1.2	48	-1.6
Nefazodone-High	76	4.4	70	-0.3	64	-0.5	56	-1.0	56	-1.3	47	-1.3	52	-1.7
Placebo	77	4.4	72	-0.2	68	-0.5	66	-0.9	58	-1.2	54	-1.4	49	-1.9
2-sided p-values for pairwise comparisons														
Nefazodone-Low vs Placebo	0.20		0.64		0.33		0.96		0.61		0.41		0.11	
Nefazodone-High vs Placebo	0.88		0.56		0.84		0.55		0.55		0.51		0.25	

TABLE I
Protocol: 03A0A-004A
Mean (Least Squares) Score in CGI Scale: Doctor's Opinion of Improvement

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week											
	Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Nefazodone-Low	75	3.5	77	3.2	77	3.0	77	2.9	77	2.8	77	2.7
Nefazodone-High	75	3.5	76	3.1	76	2.9	76	2.6	76	2.5	76	2.5
Placebo	77	3.6	77	3.4	77	3.0	77	2.8	77	2.7	77	2.7
2-sided p-values for pairwise comparisons												
Nefazodone-Low vs Placebo	0.35		0.41		0.97		0.49		0.91		0.68	
Nefazodone-High vs Placebo	0.66		0.13		0.33		0.29		0.20		0.40	

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week											
	Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Nefazodone-Low	70	3.4	66	3.2	60	2.9	54	2.7	50	2.5	48	2.2
Nefazodone-High	70	3.5	64	3.0	56	2.6	56	2.3	47	2.3	52	2.1
Placebo	72	3.5	68	3.3	66	2.9	58	2.4	54	2.3	49	1.9
2-sided p-values for pairwise comparisons												
Nefazodone-Low vs Placebo	0.43		0.61		0.79		0.16		0.33		0.21	
Nefazodone-High vs Placebo	0.74		0.14		0.18		0.45		0.93		0.31	

Study 03A0A-004A (Conducted 4/87 to 5/90)
Study 03A0A-004B (Conducted 8/87 to 5/89)

Studies 03A0A-004A and 004B were both conducted under the same protocol. Both studies were originally designed as single center studies. Under an amendment to the protocol a second center was added to each study.

Each study is a 6-week trial of 3 treatment arms; low dose nefazodone (peak allowable dose of 300 mg/day), high dose nefazodone (peak allowable dose of 600 mg/day) and placebo. Therapy could be extended to 46 weeks for responders. No active control was used in these studies.

The results for these studies are presented in the next 2 sections of this review followed by reviewer's comments on both studies.

Study 03A0A-004A

The center results for this study were essentially the same, therefore only the combined results will be discussed here.

About 66% of the patients had experienced at least one previous episode of depression; the mean number of prior depressive episodes in the placebo and high dose groups was 6 and in the low dose group was 4.

Patient Disposition

One-hundred and twenty patients were enrolled in each of the 2 centers (Claghorn and Rush) for a total of 240 patients, 80 patients in each treatment group. About 60% of the patients completed the study.

The pattern of dropouts in this study followed what is generally seen in anti-depressant trials; the low dose and placebo patients dropped predominately due to lack of efficacy during Weeks 3, 4 and 5 while the major reason for dropout in the high dose patients was adverse events during Weeks 1 and 2.

Table 9. Study 03A0A-004A
Patients on Study

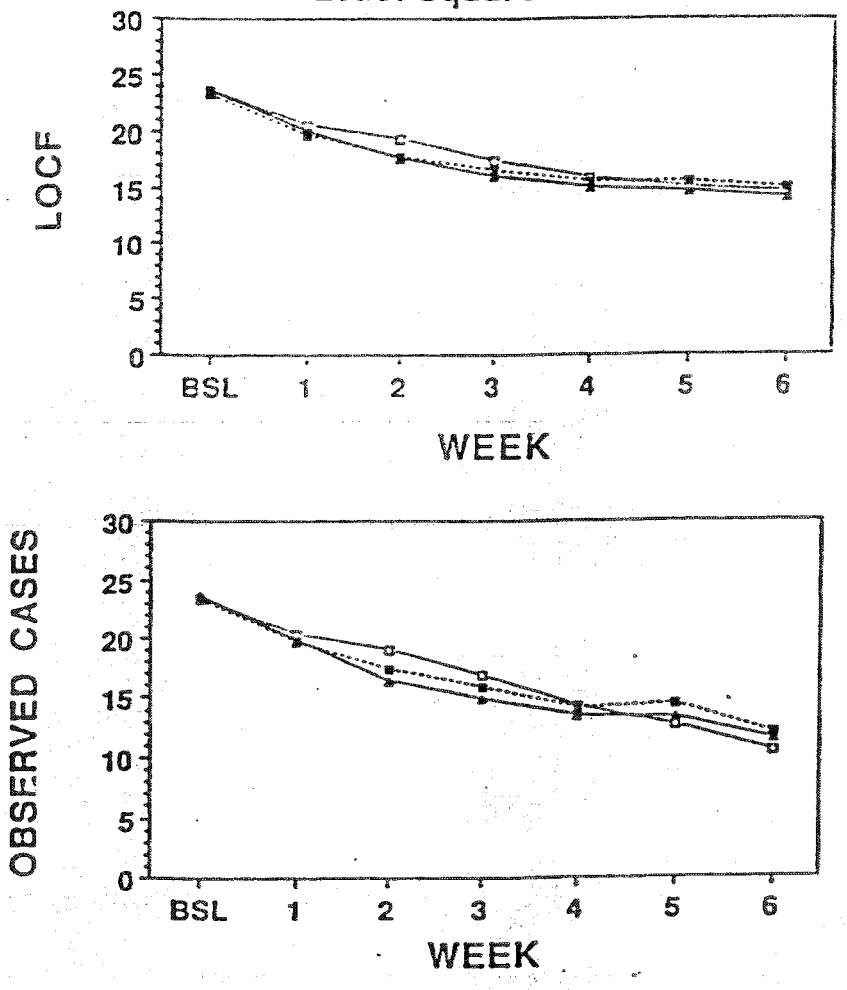
	NEFAZODONE		
WEEK	LOW	HIGH	PLACEBO
Randomized	80	80	80
1	72 (90%)	70 (88%)	73 (91%)
2	66 (83%)	65 (81%)	70 (88%)
3	61 (76%)	64 (80%)	63 (79%)
4	55 (69%)	57 (71%)	56 (70%)
5	48 (60%)	51 (64%)	49 (61%)
6	47 (59%)	51 (64%)	48 (60%)

Table 10. Study 03A0A-004A
Reasons for Dropouts

	NEFAZODONE		
Reason for Dropout	LOW	HIGH	PLACEBO
Lack of Efficacy	14 (18%)	3 (4%)	14 (18%)
Adverse Experience	10 (13%)	14 (18%)	5 (6%)
Lost-to-Followup	4 (5%)	5 (6%)	4 (5%)
Other	5 (6%)	7 (9%)	9 (11%)

The graph of the least squares means for HAM-D 17 Total by week shows that the groups did not differ at any timepoint for both LOCF and OC.

Figure 4. Study 03AOA - 004A
HAM-D 17 Total by Week
Least Square Means



Reviewer Comments on Studies 03A0A-004A and 03A0A-004B

Both studies were conducted under the same protocol however the treatment comparisons for the 2 studies differ appreciably. For Study 03A0A-004A, all high dose nefazodone/placebo comparisons at Week 6 (LOCF and OC) were nonsignificant and, in fact, the placebo responses for the observed cases data were larger than the high dose nefazodone responses; whereas, for Study 03A0A-004B, the HAM-D Total and the CGI results clearly favor high dose nefazodone over placebo.

The 2 studies differed in 2 ways; the percentage of completers was greater in Study 03A0A-004B than in 03A0A-004A (75% versus 61%) and dosing for the high dose groups was different (see Figure 11 on page 46). The large number of dropouts may have contributed to a lack of effect in 004A, however the agreement between the OC results and the LOCF results suggests that the dropouts are not the major reason for the lack of a significant treatment effect. Furthermore, from Figure 4 on page 19, it can be seen that at Week 4 (when about 70% of the patients remained on study) the LOCF and OC means for the HAM-D 17 total are not different. The dosing in 004A was higher than in 004B with mean modal doses of 513.5 mg/day and 397 mg/day at Week 6, respectively. One might suppose that the higher dose could result in more dropouts due to ADE and contribute to a nonsignificant effect, that is, the LOCF results could be biased against the drug due to early dropouts in drug group. However the ADE's in 004A compared to 004B for the high dose do not suggest that the higher dose used in 004A resulted in more dropouts due to toxicity (compare Tables 10 and 13).

The studies were similar in that 1) data for both studies satisfied the assumptions for ANOVA so the analyses performed appeared to be the appropriate ones for both studies and 2) the patient populations in both studies were comparable; there were no notable differences in the baseline parameters.

This reviewer could not discern any clear reasons why the results for these 2 studies differed. The inclusion of an active control arm may have provided some explanation for the lack of efficacy observed in the 004A study.

The discrepancy between the HAM-D 17 Total results and the HAM-D Depressed Mood Item results in Study 03A0A-004B deserves further examination. Below are summarized the data for the items of the HAM-D 17 that showed large placebo differences including Item 1 for comparison. About 25% of the treatment difference observed on the HAM-D Total was due to Items 3 and 7. (In studies in this submission which showed significant differences on Item 1, the magnitude of the treatment difference was 0.5 or greater.)

HAM-D ITEM	NEFAZODONE HIGH Mean Change	PLACEBO Mean Change	MEAN TREATMENT DIFFERENCE
1. Depressed Mood	-1.3	-1.1	0.2
2. Guilty Feelings	-1.1	-0.8	0.3
3. Suicide	-0.9	-0.5	0.4 *
7. Work and Interest	-1.5	-1.0	0.5 *
10. Psychic Anxiety	-1.1	-0.9	0.2
11. Somatic Anxiety	-1.1	-0.9	0.2
13. Anergia	-0.9	-0.7	0.2

* = $p<.05$

In summary, the results from Study 03A0A-004A do not provide statistical evidence of the efficacy of nefazodone over placebo. Study 03A0A-004B provides statistical evidence that the high dose of nefazodone is effective compared to placebo for 3 of the 4 efficacy variables.

treatment, received a dose of study medication, and had an efficacy evaluation during treatment. Of the 260 patients evaluable for efficacy, 91 received placebo, 83 received imipramine, and 86 received nefazodone. Sixteen patients were lost to follow up.

There are no differences in the week 8 LOCF nefazodone and placebo results for center one. In Center 2 the nefazodone group was significantly different ($p<.001$) from placebo on the 4 efficacy measures. These differences are first apparent at week 3. The LOCF and OC results are also consistent.

Data is provided for the combined analysis in the appendix.

7.2.1.4 Conclusion: Center one, in this study, did not differentiate Nefazodone or Imipramine from placebo. Center two clearly does differentiate Nefazodone from placebo and the combined analysis isalso postive.

CN 114-005

7.2.2 Study 03A0A-004B (8/87 to 5/89) A Double-Blind Trial of Two Daily Dose Ranges of Nefazodone and Placebo in the Treatment of Depressed Outpatients

OK

7.2.2.1 Investigator/Locations: Joseph Mendels, M.D., Philadelphia Medical Institute, Philadelphia, PA (Study 2408); Frederick Reimherr, M.D., University of Utah, College of Medicine, Salt Lake City, UT (Study 2531).

7.2.2.2 Study Plan:

Objectives: To determine the safety and efficacy of nefazodone titrated in two dose ranges (recommended low-dose range 150-300 mg/day and recommended high-dose range 300-600 mg/day) as compared to placebo in the treatment of outpatients with moderate to severe depression.

Population to be Studied: Outpatients of either sex, 18 years of age or older, with a diagnosis of Major Depressive Episode or Bipolar Disorder, Depressed (DSM-III).

Study Design: Multicenter, randomized, double-blind, parallel group, 6-week comparison of the safety and efficacy of two dose ranges of nefazodone and placebo. Rating scales included: 17-Item Hamilton Rating Scale for Depression (HAM-D-17); Clinical Global Impressions (CGI) Scale; Inventory for Depressive Symptomatology - Clinician (IDS-C); and Inventory for Depressive Symptomatology -Self Report (IDS-SR). A narrative of the physician's overall assessment was collected on the End-of-Study Evaluation Form.

Plan for Analysis: A two-way analysis of variance (ANOVA) model with study center, treatment, and study center by treatment interaction effects was used to test for baseline comparability as well as differences between treatments for the change from Baseline in HAM-D and CGI Severity scores. Categorical data such as CGI Improvement scores were analyzed within the framework of the generalized Cochran-Mantel-Haenszel (CMH) procedure, using study center as the stratification variable. Both the two-way ANOVA and CMH models tested the differences between treatments averaged across the study centers. The planned sample size of 240 patients had a power of $\geq 80\%$ to detect an average difference of four points in the HAM-D-17 Total score between nefazodone and placebo.

7.2.2.3 **Study Conduct/Outcome** (see appendix for related tables)

Patient Disposition: 240 patients at two study centers were randomized to treatment. 231 patients were evaluable for efficacy.

Demographics: Of the 240 patients, 148 (62%) were women and 92 (38%) men. Patient age ranged from 18 to 79 years. 239 met the diagnostic criteria for Major Depression (DSM-III) and one met the criteria for Bipolar Disorder, Depressed; melancholia was diagnosed in 109 (45%) patients; 150 (62%) patients had recurrent episodes of depression; and 149 (62%) patients had their current episode of depression for at least 6 months.

Dosing Information: Oral capsules administered BID. Recommended dosage ranges: low-dose nefazodone, 150 to 300 mg/day (50-mg capsule), beginning at 100 mg/day; high-dose nefazodone, 300 to 600 mg/day (100-mg capsule), beginning at 200 mg/day; placebo 2-6 capsules per day. The mean modal dose at Week 6 was 246.6 mg/day for the low-dose nefazodone group, 396.8 mg/day for the high-dose nefazodone group, and 5.1 capsules/day for the placebo group.

Concomitant Medications: The protocol permitted the use of chloral hydrate for sleep and this was the most frequently used concomitant psychotropic medication. Fifteen patients took prohibited concomitant psychotropic medications (alprazolam, amitriptyline, caffeine, diazepam, fluoxetine HCl, imipramine, Librax, lorazepam, nortriptyline HCl, temazepam, chlormezanone, and unspecified sleeping pill); these patients were not excluded from the analyses.

Efficacy Results: Patients were considered evaluable for efficacy if they were randomized to treatment, received a dose of study medication, and had an efficacy evaluation during treatment. Of the 231 patients meeting these criteria, 75 received placebo, 78 received low-dose nefazodone; and 78 received high-dose nefazodone.

Low dose effects are not different from placebo. The high dose group was not significantly deferent from placebo on the HAM-D depressed mood item, but was on three other variables.

7.2.2.4 Conclusions:
Study 03A0A-004B does provide statistical evidence that the high dose of Nefazodone is effective compared to placebo for three of the four efficacy variables.

7.2.3 Study CN104-006 A Double-Blind Trial of Nefazodone, Imipramine, and Placebo in the Treatment of Depressed Outpatients (Protocol CN104-006).

7.2.3.1 Investigator\Locations: Louis Fabre, Jr., M.D., Ph.D, Research Testing Inc., Houston, Texas, and Dallas, Texas, USA; Cal K. Cohn, M.D., The Hauser Clinic and Associates, Houston, Texas, USA.

7.2.3.2 Study Plan:

Objectives: To determine the safety and efficacy of nefazodone, imipramine, and placebo in the treatment of moderately to severely

Appendix 03A0A-004B

TABLE A
Protocol: 03A0A-004B
Demographic Characteristics for Total Patient Sample

Treatment Groups	n	Age (years)		Sex [n(%)]		Race [n(%)]	
		Mean	Range	Male	Female	White	Non-White
Nefazodone-Low	80	38.4		29 (36)	51 (64)	72 (90)	8 (10)
Nefazodone-High	80	39.1		32 (40)	48 (60)	71 (89)	9 (11)
Placebo	80	40.1		31 (39)	49 (61)	71 (89)	9 (11)

TABLE B
Protocol: 03A0A-004B
Patient Completion Rates

Treatment Groups	Number Randomized	Intent-to-Treat Sample	Completers [n(%)]					
			Wk 1	Wk 2	Wk 3	Wk 4	WK 5	Wk 6
Nefazodone-Low	80	78	72 (92)	68 (87)	68 (87)	62 (79)	59 (76)	59 (76)
Nefazodone-High	80	78	70 (90)	72 (92)	67 (86)	60 (77)	56 (72)	62 (79)
Placebo	80	79	78 (99)	58 (73)	64 (85)	52 (69)	54 (72)	58 (77)

TABLE C
Protocol: 03A0A-004B
Dosing Information

Treatment Groups	Mean Modal Dose (mg/day) for Completers on Nefazodone					
	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6
Nefazodone-Low	161.1	247.8	256.6	262.9	266.1	246.6
Nefazodone-High	321.4	440.3	449.3	415.0	428.8	396.8

TABLE D
Protocol: 03A0A-004B
Mean (Least Squares) Change from Baseline in HAM-D-17 Total Score *

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone-Low	78	25.1	78	-4.1	78	-6.0	78	- 8.0	78	- 8.9	78	- 9.2	78	-10.1
Nefazodone-High	78	25.4	78	-5.6	78	-9.1	78	-10.4	78	-11.3	78	-12.4	78	-12.7
Placebo	75	25.0	75	-4.8	75	-6.6	75	- 7.5	75	- 8.4	75	- 9.4	75	- 9.5
2-sided p-values for pairwise comparisons														
Nefazodone-Low vs Placebo	0.91		0.44		0.58		0.62		0.67		0.86		0.69	
Nefazodone-High vs Placebo	0.43		0.30		0.01		0.01		0.01		0.02		0.02	

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone-Low	78	25.1	71	-4.1	67	-6.4	68	- 8.0	61	- 9.3	59	-10.6	59	-11.8
Nefazodone-High	78	25.4	70	-5.9	72	-9.7	67	-11.0	59	-11.5	56	-13.7	62	-14.2
Placebo	75	25.0	73	-4.8	57	-7.5	64	- 8.3	52	-10.1	54	-11.1	58	-11.7
2-sided p-values for pairwise comparisons														
Nefazodone-Low vs Placebo	0.91		0.40		0.33		0.81		0.59		0.72		0.95	
Nefazodone-High vs Placebo	0.43		0.20		0.03		0.02		0.30		0.07		0.08	

TABLE F
Protocol: 03A0A-0048
Mean (Least Squares) Change from Baseline in HAM-D Depressed Mood (Item 1) Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		WK 5		Wk 6	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone-Low	78	2.9	78	-0.4	78	-0.7	78	-0.8	78	-0.9	78	-0.9	78	-1.2
Nefazodone-High	78	2.8	78	-0.4	78	-0.7	78	-1.0	78	-1.1	78	-1.2	78	-1.3
Placebo	75	2.9	75	-0.4	75	-0.7	75	-0.7	75	-1.0	75	-1.0	75	-1.1
2-sided p-values for pairwise comparisons														
Nefazodone-Low vs Placebo	0.64		0.45		0.92		0.43		0.78		0.56		0.70	
Nefazodone-High vs Placebo	0.18		0.78		0.79		0.07		0.38		0.33		0.36	

ORSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone-Low	78	2.9	71	-0.3	67	-0.8	68	-0.9	61	-0.9	59	-1.1	59	-1.4
Nefazodone-High	78	2.8	70	-0.5	72	-0.8	67	-1.0	59	-1.1	56	-1.4	62	-1.4
Placebo	75	2.9	73	-0.5	57	-0.8	64	-0.7	52	-1.1	54	-1.2	58	-1.3
2-sided p-values for pairwise comparisons														
Nefazodone-Low vs Placebo	0.64		0.36		0.96		0.46		0.35		0.54		0.70	
Nefazodone-High vs Placebo	0.18		0.98		0.96		0.11		0.95		0.48		0.68	

TABLE H
Protocol: 03A0A-004B
Mean (Least Squares) Change from Baseline in CGI Scale: Doctor's Opinion of Severity

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		WK 5		Wk 6	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone-Low	78	4.2	78	-0.2	78	-0.3	78	-0.5	78	-0.7	78	-0.7	78	-0.9
Nefazodone-High	78	4.3	78	-0.4	78	-0.6	78	-0.9	78	-1.0	78	-1.2	78	-1.4
Placebo	74	4.3	74	-0.3	74	-0.4	74	-0.5	74	-0.6	74	-0.9	74	-0.9
2-sided p-values for pairwise comparisons														
Nefazodone-Low vs Placebo	0.75		0.31		0.26		0.78		0.85		0.46		0.87	
Nefazodone-High vs Placebo	0.51		0.30		0.19		0.01		0.02		0.09		0.02	

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone-Low	78	4.2	72	-0.2	68	-0.3	68	-0.6	62	-0.7	59	-0.9	58	-1.2
Nefazodone-High	78	4.3	70	-0.4	72	-0.7	67	-0.9	60	-1.0	56	-1.3	62	-1.6
Placebo	74	4.3	73	-0.3	57	-0.5	64	-0.6	52	-0.8	53	-1.0	57	-1.1
2-sided p-values for pairwise comparisons														
Nefazodone-Low vs Placebo	0.75		0.38		0.19		0.86		0.64		0.51		0.56	
Nefazodone-High vs Placebo	0.51		0.14		0.34		0.05		0.41		0.25		0.04	

TABLE I
Protocol: 03A0A-004B
Mean (Least Squares) Score in CGI Scale: Doctor's Opinion of Improvement

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week											
	Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Nefazodone-Low	71	3.6	77	3.4	77	3.1	77	3.0	77	2.9	77	2.7
Nefazodone-High	71	3.4	78	2.9	78	2.8	78	2.7	78	2.5	78	2.4
Placebo	73	3.6	74	3.4	74	3.4	74	3.2	74	3.0	74	2.9
2-sided p-values for pairwise comparisons												
Nefazodone-Low vs Placebo	0.80		0.82		0.08		0.29		0.38		0.28	
Nefazodone-High vs Placebo	0.24		<0.01		<0.01		<0.01		<0.01		0.03	

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week											
	Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Nefazodone-Low	71	3.6	68	3.4	68	3.1	62	2.9	59	2.6	58	2.4
Nefazodone-High	70	3.4	72	2.8	67	2.7	60	2.6	56	2.4	62	2.2
Placebo	73	3.6	57	3.3	64	3.2	52	2.8	53	2.8	57	2.5
2-sided p-values for pairwise comparisons												
Nefazodone-Low vs Placebo	0.80		0.86		0.43		0.57		0.51		0.52	
Nefazodone-High vs Placebo	0.22		<0.01		0.01		0.32		0.04		0.17	

Study 03A0A-004B

In Study 03A0A-004B, all patients but one placebo patient were diagnosed with major depression; 62% had recurrent depression. (No summary information on number of prior depressive episodes or previous antidepressant use was given in the study report.)

Patient Disposition

A total of 240 patients were enrolled in this 2-center study; 80 in each treatment group. The percentage of completers in this study was the highest among all 8 placebo-controlled trials. About 75% of the patients remained on study at Week 6.

The major reason for patient discontinuation in all 3 treatment groups was adverse experience (ADE). See Table 13. Of the 28 patients dropping due to ADE, 19 were in Center 2408 (Mendels). Nine patients dropped during Week 1 in the placebo group, 6 due to ADE. More low dose nefazodone patients than placebo patients dropped due to lack of efficacy.

Table 12. Study 03A0A-004B
Patients on Study

	NEFAZODONE		
WEEK	LOW	HIGH	PLACEBO
Randomized	80	80	80
1	74 (93%)	75 (94%)	71 (89%)
2	73 (91%)	72 (90%)	69 (86%)
3	67 (84%)	68 (85%)	66 (83%)
4	63 (79%)	65 (81%)	60 (75%)
5	61 (76%)	64 (80%)	59 (74%)
6	60 (75%)	63 (79%)	58 (73%)

Table 13. Study 03A0A-004B
Reasons for Dropouts

	NEFAZODONE		
Reason for Dropout	LOW	HIGH	PLACEBO
Lack of Efficacy	6 (8%)	2 (3%)	4 (5%)
Adverse Experience	6 (8%)	11 (14%)	11 (14%)
Lost-to-Followup	6 (8%)	4 (5%)	3 (4%)
Other	2 (3%)	0 (0%)	4 (5%)

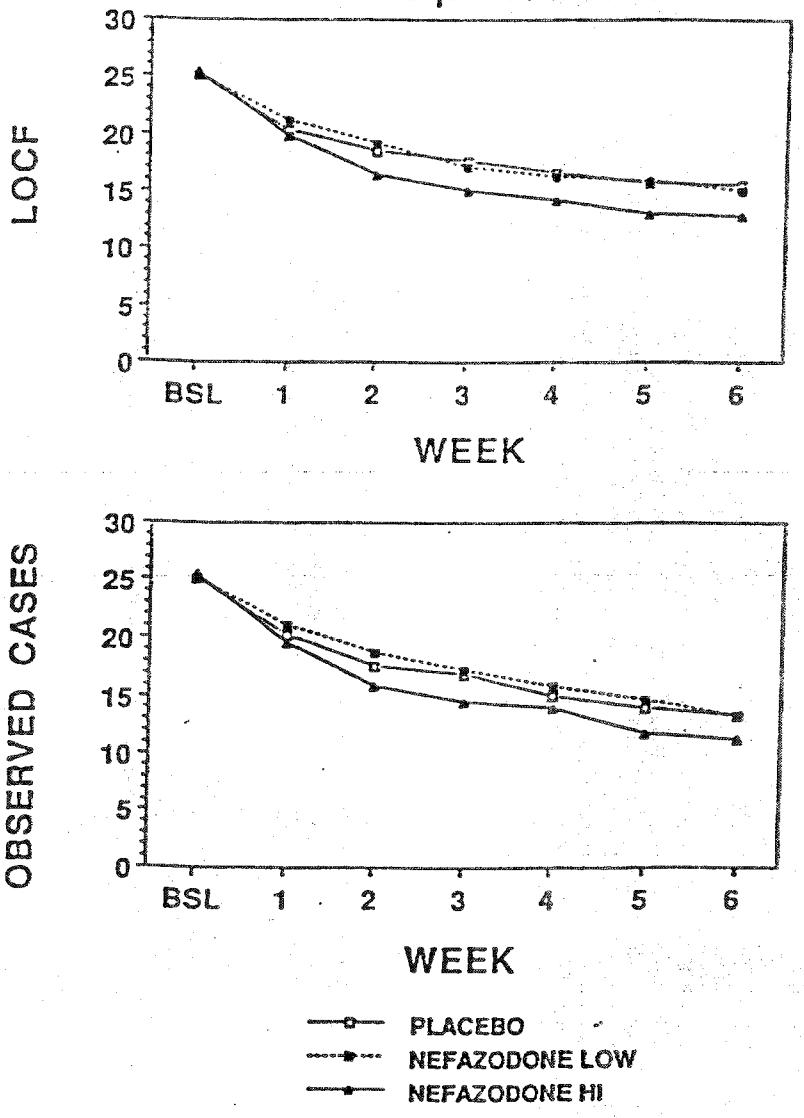
Results

The results for both centers combined are presented here. The treatment by center effect was nonsignificant with p = .70. From the table below and Figure 5 on the following page, it can be seen that the low dose effects are not different from the placebo effects (all p-values were greater than .30). The high dose of nefazodone is significantly more effective than placebo on the HAM-D 17 total and the CGI scores. The HAM-D 17 Total (LOCF) results were significant at every week after Week 1 ($p \leq .02$). The OC results for the HAM-D 17 Total were significant at Week 2 and 3 ($p \leq .03$) and borderline significant at Weeks 5 and 6 (p-values of .07 and .08, respectively).(See Figure 5 on the next page. The HAM-D Depressed Mood Item 1 shows no difference between the groups. Sixty-three percent of the placebo patients (47/75) showed an improvement on the HAM-D Item 1 versus 72% (56/78) of the high dose nefazodone patients (p = .07). The sponsor performed a CMH analysis of the HAM-D Depressed Mood Item stratifying for baseline, as requested by this reviewer, which yielded p-values of .14 (LOCF) and .29 (OC).

Table 6. Study 03A0A-004B
Sponsor's Results

	NEF LOW LS Mean	NEF HIGH LS Mean	PLA LS Mean	HIGH VS PLA p-value
HAM-D 17 Total				
Baseline	25.1	25.4	25.0	.43
Week 6				
LOCF	-10.1	-12.7	-9.5	.02
OC	-11.8	-14.2	-11.7	.08
HAM-D Item 1				
Baseline	2.9	2.8	2.9	.18
Week 6				
LOCF	-1.2	-1.3	-1.1	.36
OC	-1.4	-1.4	-1.3	.68
CGI Severity of Illness				
Baseline	4.3	4.3	4.3	.51
Week 6				
LOCF	-0.9	-1.4	-0.9	.02
OC	-1.2	-1.6	-1.1	.04
CGI Global Improvement				
Week 6				
LOCF	2.7	2.4	2.9	.03
OC	2.4	2.2	2.6	.15

Figure 5. Study 03AOA - 004B
HAM-D 17 Total by Week
Least Squares Means



7.2.8 030A2-004/005 Multi-Center, Double-Blind Comparison of Nefazodone, Imipramine, and Placebo in Patients with Moderate to Severe Depression (Protocols 030A2-0004 and 030A2-0005)

7.2.8.1 **Investigator, Locations:** Jambur Ananth, M.D., Harbor U.C.L.A. Medical Center, Torrance, California; John P. Feighner, M.D., Feighner Research Institute, Encinitas, California; David L. Dunner, M.D., University of Washington, Harborview Medical Center, Seattle, Washington; Joseph Mendels, M.D., Philadelphia Medical Institute, Philadelphia, Pennsylvania; Robert A. Riesenberg, M.D., Biobehavioral Associates, Decatur, Georgia; Carl Wellish, M.D., Arizona Psychiatric Associates, Ltd., Phoenix, Arizona.

7.2.8.2 **Study Plan:**

Objectives: To determine the safety and efficacy of nefazodone as compared to imipramine and placebo in the treatment of depressed patients, and to provide further data on the effective dose range of nefazodone.

Population to be Studied: Patients of either sex, 18 to 70 years of age, with a diagnosis of Major Depressive Episode with Melancholia (DSM-III) and Endogenous Major Depressive Disorder (RDC); dysphoric features must have been present for at least four weeks.

Study Design: Multicenter, randomized, double-blind, parallel-group, 6-week comparison of the safety and efficacy of nefazodone, imipramine, and placebo. Rating scales included: 25-Item Hamilton Rating Scale for Depression (HAM-D-25), Clinical Global Impressions (CGI) Scale, Patient's Global Assessments (PGA) Scale, Hamilton Rating Scale for Anxiety (HAM-A), and Symptom Checklist-90 (SCL-90).

Plan for Analysis: Sample means for Baseline values and weekly changes from Baseline for the HAM-D-17 Total score, the HAM-D Depressed Mood Item (Item 1) and the CGI: Doctor's Opinion of Severity. A responder/non-responder categorization was used to summarize data for the CGI: Doctor's Opinion of Improvement and the PGA: Patient's Opinion of Improvement.

7.2.8.3 **Study Conduct/Outcome** (see related appendix tables)

Patient Disposition: 226 patients at six study centers were randomized to treatment. 219 patients were evaluable for efficacy.

Demographics: Of the 240 patients, 109 (48%) were women and 117 (52%) men. Patient age ranged from years. All 226 patients met the DSM-III criteria for Major Depressive Episode with Melancholia Depressed and the RDC criteria for Endogenous Major Depressive Disorder. 122 (55%) patients had recurrent episodes of depression; and 103 (46%) patients had their current episode of depression for at least 12 months.

Dosing Information: Oral capsules administered BID or TID. Recommended dosage ranges: nefazodone, 50 to 250 mg/day (25-mg capsule); imipramine, 50 to 250 mg/day (25-mg capsule); placebo 2-10 capsules/day. The mean modal dose at Week 6 was 175.0 mg/day for the nefazodone group, 155.8 mg/day for the imipramine group, and 6.7 capsules/day for the placebo group.

Concomitant Medications: The protocol permitted the use of chloral hydrate for sleep and this was the most frequently used concomitant psychotropic medication. Four patients took prohibited concomitant

psychotropic medications (diazepam, lorazepam, and promethazine); these patients were not excluded from the analyses.

Efficacy Results: Patients were considered evaluable for efficacy if they were randomized to treatment, received a dose of study medication, and had an efficacy evaluation during treatment. Of the 219 patients meeting these criteria, 70 received placebo, 75 received imipramine; and 74 received nefazodone.

7.2.8.4 Conclusions
This was the first study and did not show significant results. The low nefazodone dose probably contributes to this finding.

7.3 Active Control Trials

Three studies that compared the activity of nefazodone to tricyclic antidepressants were conducted in Europe. Study 03A0A-006 in France, compared the activity of nefazodone to clomipramine in a sample of hospitalized, depressed patients. Study CN104-003, conducted in Belgium, compared the activity of nefazodone to that of imipramine in a sample of depressed outpatients. Study CN104-016, also conducted in Belgium, compared the activity of nefazodone to that of amitriptyline in a sample of depressed hospitalized patients.

All three studies employed a flexible dose-titration strategy whereby nefazodone was given in divided doses ranging from 100 to 400 mg/day in Studies CN104-003 and CN104-016, and from 100 to 600 mg/day in Study 03A0A-006. Study CN104-016 differed from CN104-003 and 03A0A-006 in that a much slower dose progression and suboptimal nefazodone dose was specified by protocol. This resulted in a markedly lower nefazodone dose (mean 243.5 mg/day) in CN104-016 compared to the other studies. The DSM-III or DSM-III-R diagnostic criteria were used for patient inclusion.

There are no between group differences which would be supportive of efficacy. The active-control trials do not offer any help with the question of efficacy over and above what can be learned from the results of the placebo-controlled trials.

7.4 Summary of Data Pertinent to Important Clinical Issues

7.4.1 Clinical Predictors of Response

The sponsor has examined pretreatment (Baseline) characteristics that might predict response to nefazodone therapy. Since no single study is large enough to permit an assessment of outcome in subgroups of patients, meta-analyses of the efficacy data for all patients enrolled in the eight placebo-controlled studies were performed. Four stratification criteria were used to establish different patient subgroups relating to severity of illness: 1) patients with severe depressive symptoms (Baseline Clinical Global Impressions (CGI) Severity of Psychopathology score of at least 5 (markedly ill); 2) Baseline 17-item Hamilton Depression (HAM-D-17) score $\geq$ 27); 3) patients meeting DSM-III or DSM-III-R criteria for Major Depression, Melancholic Subtype; and 4) patients with Recurrent Major Depression. An additional meta-analysis of patients stratified by pretreatment level of anxiety was done that included those placebo-controlled trials where HAM-A in addition to HAM-D ratings were carried out. Efficacy analyses utilized the Last Observation Carried Forward (LOCF) data set and were based on the Intent-to-Treat patient sample. The

TABLE A
Protocols: 030A2-0004/030A2-0005
Demographic Characteristics for Total Patient Sample

Treatment Groups	N	Age (years)		Sex [N (%)]		Race [N (%)]	
		Mean	Range	Male	Female	White	Non-White
Nefazodone	76	44.9		36 (47)	40 (53)	66 (87)	10 (1
Imipramine	76	42.1		45 (59)	31 (41)	68 (91)	(
Placebo	74	41.8		36 (49)	38 (51)	64 (88)	9 (12)*

* Race not recorded for one patient.

TABLE B
Protocols: 030A2-0004/030A2-0005
Patient Completion Rates

Treatment Groups	Number Randomized	Intent-to-Treat / Sample	Completers [N (%)]						
			Wk 0.5	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6
Nefazodone	76	74	67 (91)	66 (89)	67 (91)	60 (81)	60 (81)	54 (73)	52 (70)
Imipramine	76	75	65 (87)	66 (88)	61 (81)	56 (75)	50 (67)	46 (61)	43 (57)
Placebo	74	70	53 (76)	66 (94)	63 (90)	59 (84)	50 (71)	49 (70)	45 (64)

TABLE C
Protocols: 030A2-0004/030A2-0005
Dosing Information

Treatment Groups	Mean Modal Dose (mg/day) for Completers in Active Drug Groups						
	Wk 0.5	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6
Nefazodone	56.0	128.4	139.9	157.5	167.1	175.0	175.0
Imipramine	63.5	117.0	132.4	144.2	157.0	158.2	155.8

TABLE D
Protocol: 030A2-0007
Mean (Least Squares) Change from Baseline in HAM-D-17 Total Score

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone 50 mg/day	43	25.3	41	-5.6	40	-7.6	36	-10.7	37	-11.8	32	-14.0	29	-15.2
Nefazodone 100 mg/day	45	25.9	45	-6.2	41	-9.8	40	-10.8	38	-13.4	36	-15.0	34	-14.4
Nefazodone 200 mg/day	46	26.1	45	-7.0	44	-9.6	43	- 9.6	36	-13.3	32	-15.4	32	-16.4
Nefazodone 300 mg/day	41	25.4	39	-6.7	35	-8.5	36	-11.2	34	-11.4	35	-10.2	31	-12.7
Placebo	47	26.4	44	-5.4	45	-8.5	41	- 9.7	40	-10.5	31	- 9.9	34	-12.1
2-sided p-values for pairwise comparisons														
Nefazodone 50 vs Placebo	0.12		0.84		0.55		0.52		0.40		0.02		0.09	
Nefazodone 100 vs Placebo	0.44		0.49		0.33		0.48		0.06		0.00		0.19	
Nefazodone 200 vs Placebo	0.62		0.17		0.43		0.92		0.07		0.00		0.02	
Nefazodone 300 vs Placebo	0.16		0.28		0.99		0.33		0.59		0.84		0.74	

TABLE F
Protocol: 030A2-0007
Mean (Least Squares) Change from Baseline in HAM-D Depressed Mood (Item 1) Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone 50 mg/day	43	2.8	43	-0.7	43	-0.8	43	-1.1	43	-1.3	43	-1.2	43	-1.5
Nefazodone 100 mg/day	45	2.8	45	-0.6	45	-0.9	45	-1.1	45	-1.4	45	-1.7	45	-1.5
Nefazodone 200 mg/day	46	2.8	46	-0.7	46	-0.9	46	-0.9	46	-1.1	46	-1.5	46	-1.5
Nefazodone 300 mg/day	41	2.8	41	-0.4	41	-0.7	41	-1.1	41	-1.2	41	-1.1	41	-1.1
Placebo	47	2.9	47	-0.6	47	-0.9	47	-0.9	47	-1.0	47	-1.1	47	-1.2
2-sided p-values for pairwise comparisons														
Nefazodone 50 vs Placebo	0.53		0.49		0.61		0.38		0.21		0.77		0.33	
Nefazodone 100 vs Placebo	0.72		0.77		0.88		0.26		0.09		0.01		0.29	
Nefazodone 200 vs Placebo	0.31		0.63		0.91		0.84		0.81		0.15		0.31	
Nefazodone 300 vs Placebo	0.57		0.31		0.43		0.28		0.45		0.79		0.57	

TABLE F
Protocol: 030A2-0007
Mean (Least Squares) Change from Baseline in HAM-D Depressed Mood (Item 1) Score

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone 50 mg/day	43	2.8	41	-0.7	40	-0.8	36	-1.2	37	-1.4	32	-1.4	29	-1.9
Nefazodone 100 mg/day	45	2.8	45	-0.6	41	-1.0	40	-1.1	38	-1.5	36	-1.9	34	-1.6
Nefazodone 200 mg/day	46	2.8	45	-0.7	44	-0.9	43	-0.8	36	-1.2	32	-1.8	32	-1.8
Nefazodone 300 mg/day	41	2.8	39	-0.4	35	-0.8	36	-1.2	34	-1.2	35	-1.2	31	-1.3
Placebo	47	2.9	44	-0.6	45	-0.9	41	-1.0	40	-1.1	31	-1.3	34	-1.6
2-sided p-values for pairwise comparisons														
Nefazodone 50 vs Placebo	0.53		0.59		0.58		0.53		0.20		0.65		0.30	
Nefazodone 100 vs Placebo	0.72		0.87		0.77		0.67		0.16		0.02		0.93	
Nefazodone 200 vs Placebo	0.31		0.72		0.90		0.34		0.86		0.08		0.54	
Nefazodone 300 vs Placebo	0.57		0.32		0.70		0.36		0.65		0.64		0.36	

TABLE H
Protocol: 030A2-0007
Mean (Least Squares) Change from Baseline in CGI: Doctor's Opinion of Severity

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone 50 mg/day	43	4.6	43	-0.6	43	-0.8	43	-1.2	43	-1.4	43	-1.5	43	-1.6
Nefazodone 100 mg/day	46	4.6	46	-0.7	46	-1.1	46	-1.2	46	-1.6	46	-1.9	46	-1.7
Nefazodone 200 mg/day	46	4.5	46	-0.7	46	-0.9	46	-0.9	46	-1.2	46	-1.4	46	-1.6
Nefazodone 300 mg/day	41	4.6	41	-0.6	41	-0.9	41	-1.3	41	-1.3	41	-1.3	41	-1.6
Placebo	47	4.6	47	-0.5	47	-1.0	47	-1.1	47	-1.0	47	-1.1	47	-1.3
2-sided p-values for pairwise comparisons														
Nefazodone 50 vs Placebo	0.71		0.63		0.28		0.54		0.09		0.19		0.26	
Nefazodone 100 vs Placebo	0.75		0.24		0.63		0.44		0.01		0.01		0.14	
Nefazodone 200 vs Placebo	0.54		0.33		0.48		0.42		0.51		0.31		0.26	
Nefazodone 300 vs Placebo	0.90		0.54		0.64		0.25		0.26		0.42		0.32	

TABLE H
Protocol: 030A2-0007
Mean (Least Squares) Change from Baseline in CGI: Doctor's Opinion of Severity

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Nefazodone 50 mg/day	43	4.6	41	-0.6	40	-0.8	35	-1.2	37	-1.5	32	-1.8	29	-2.1
Nefazodone 100 mg/day	46	4.6	46	-0.7	41	-1.2	39	-1.3	38	-1.8	35	-2.1	34	-1.9
Nefazodone 200 mg/day	46	4.5	45	-0.7	44	-0.9	44	-0.9	36	-1.5	31	-1.9	32	-2.1
Nefazodone 300 mg/day	41	4.6	39	-0.6	34	-1.0	37	-1.4	33	-1.4	35	-1.5	31	-1.9
Placebo	47	4.6	44	-0.5	45	-1.0	41	-1.2	40	-1.1	30	-1.3	34	-1.6
2-sided p-values for pairwise comparisons														
Nefazodone 50 vs Placebo	0.71		0.63		0.35		0.96		0.12		0.12		0.17	
Nefazodone 100 vs Placebo	0.75		0.28		0.44		0.61		0.01		0.01		0.37	
Nefazodone 200 vs Placebo	0.54		0.36		0.47		0.22		0.19		0.05		0.16	
Nefazodone 300 vs Placebo	0.90		0.55		0.75		0.37		0.38		0.54		0.37	

TABLE I
Protocol: 030A2-0007
Mean (Least Squares) Score in CGI Scale: Doctor's Opinion of Improvement

LAST OBSERVATION CARRIED FORWARD ANALYSIS - ANOVA

Treatment Groups	Treatment Week											
	Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Nefazodone 50 mg/day	41	3.2	43	3.2	43	2.8	43	2.6	43	2.6	43	2.4
Nefazodone 100 mg/day	46	3.2	46	2.9	46	2.6	46	2.4	46	2.3	46	2.4
Nefazodone 200 mg/day	45	2.9	46	2.9	46	2.8	46	2.7	46	2.5	46	2.4
Nefazodone 300 mg/day	39	3.2	41	3.0	41	2.6	41	2.6	41	2.7	41	2.5
Placebo	44	3.3	47	3.0	47	2.9	47	3.0	47	2.9	47	2.8
2-sided p-values for pairwise comparisons												
Nefazodone 50 vs Placebo	0.64		0.46		0.63		0.08		0.15		0.09	
Nefazodone 100 vs Placebo	0.55		0.37		0.14		0.01		0.01		0.13	
Nefazodone 200 vs Placebo	0.07		0.38		0.76		0.15		0.10		0.11	
Nefazodone 300 vs Placebo	0.64		0.71		0.13		0.07		0.35		0.32	

TABLE I
Protocol: 030A2-0007
Mean (Least Squares) Score in CGI Scale: Doctor's Opinion of Improvement

OBSERVED CASES ANALYSIS - ANOVA

Treatment Groups	Treatment Week											
	Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Nefazodone 50 mg/day	41	3.2	40	3.1	35	2.7	36	2.4	32	2.2	29	1.8
Nefazodone 100 mg/day	46	3.2	41	2.8	38	2.5	38	2.3	35	2.1	34	2.2
Nefazodone 200 mg/day	45	2.9	44	2.8	44	2.8	36	2.4	31	2.0	32	1.9
Nefazodone 300 mg/day	39	3.2	34	2.9	37	2.5	33	2.6	35	2.6	31	2.3
Placebo	44	3.3	45	3.0	41	2.8	39	2.9	30	2.8	34	2.4
2-sided p-values for pairwise comparisons												
Nefazodone 50 vs Placebo	0.64		0.55		0.66		0.03		0.04		0.03	
Nefazodone 100 vs Placebo	0.55		0.39		0.24		0.01		0.01		0.47	
Nefazodone 200 vs Placebo	0.07		0.43		0.91		0.04		0.01		0.08	
Nefazodone 300 vs Placebo	0.64		0.74		0.28		0.19		0.56		0.68	

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Study 030A2-0007 (Conducted 12/85 to 4/89)

Study 030A2-0007 was a fixed dose study of 4 dose levels of nefazodone (50, 100, 200 and 300 mg/day) versus placebo. Patients were followed for 6 weeks and were given the option to continue for an additional 18 weeks.

A total of 194 patients were enrolled at 5 centers; 2 Canadian and 3 USA.

Patient Disposition

More than 60% of the patients completed the study in each treatment group (Table 1). Patients in the 300 mg/day group dropped earlier than patients in the other groups. During the first week on study, 8 patients in the 300 mg nefazodone group dropped due to toxicity. Two of those 8 patients had efficacy data and were included in the ITT sample. The other major reason for dropouts in the highest dose group was lack of efficacy with 5 out of the 7 dropping during Week 5. Lack of efficacy, also, was the major reason for dropouts in all the other treatment groups (Table 2).

Higher retention rates were observed in the Canadian centers than in the USA centers; in the USA centers only about 40% of the 300 mg patients completed while in the Canadian centers 65% completed.

Table 1. Study 030A2-0007
Patients on Study

	NEFAZODONE				
WEEK	50 mg	100 mg	200 mg	300 mg	Placebo
Randomized	46	47	47	47	47
1	41 (89%)	46 (98%)	44 (94%)	39 (83%)	46 (98%)
2	39 (85%)	42 (89%)	43 (91%)	37 (79%)	44 (94%)
3	37 (80%)	40 (85%)	38 (81%)	36 (77%)	41 (87%)
4	34 (74%)	37 (79%)	33 (70%)	35 (75%)	36 (77%)
5	29 (63%)	34 (72%)	32 (68%)	30 (64%)	34 (72%)
6	28 (61%)	33 (70%)	31 (66%)	29 (62%)	32 (68%)

Table 2. Study 030A2-0007
Reasons for Dropouts

	NEFAZODONE				
Reason for Dropout	50 mg	100 mg	200 mg	300 mg	Placebo
Lack of Efficacy	11 (24%)	7 (15%)	5 (11%)	7 (15%)	8 (17%)
Adverse Experience	3 (7%)	1 (2%)	5 (11%)	9 (19%)	3 (6%)
Lost-to-Followup	2 (4%)	3 (6%)	3 (6%)	1 (2%)	2 (4%)
Other	2 (4%)	3 (6%)	3 (6%)	1 (2%)	2 (4%)

Results

The results across the 5 centers were generally consistent and therefore no by-center results are presented here.

Baseline and Week 6 least squares means for each of the primary efficacy variables are presented in the table below. Only the placebo comparisons for the 2 highest doses are included in the table. In general, these results were consistent with the Week 4 and Week 5 results.

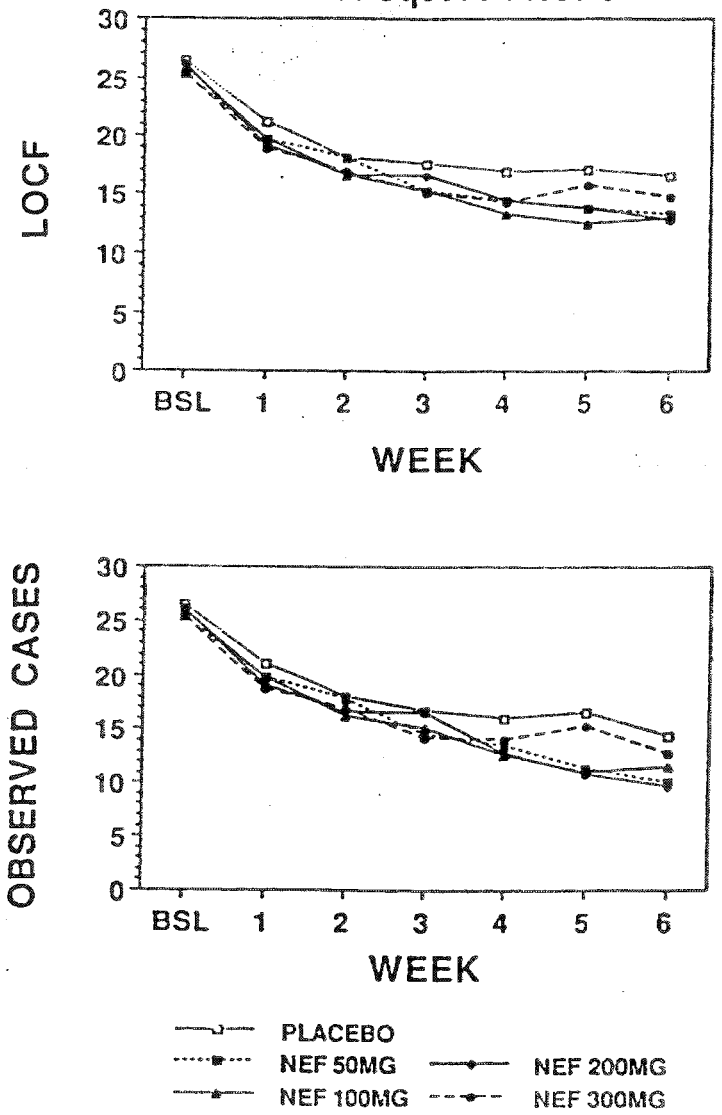
The Week 6 results (LOCF and OC) for the HAM-D Mood Item #1 and both CGI scores did not distinguish nefazodone from placebo at any dose level (all p-values > .10).

Table 3. Study 030A2-0007
Sponsor's Efficacy Results

	TREATMENT GROUP Least Squares Means					PLA COMPARISON P-VALUE	
	PLA	50 MG	100 MG	200 MG	300 MG	200 MG	300 MG
HAM-D 17 Total							
Baseline	26.4	25.3	25.9	26.1	25.4	.62	.16
Week 6							
LOCF	-9.8	-12.0	-13.0	-13.3	-10.7	.04	.60
OC	-12.1	-15.2	-14.4	-16.4	-12.7	.02	.74
HAM-D Item #1							
Baseline	2.9	2.8	2.8	2.7	2.8	.31	.57
Week 6							
LOCF	-1.2	-1.5	-1.5	-1.5	-1.1	.31	.57
OC	-1.6	-1.9	-1.6	-1.8	-1.3	.54	.36
CGI Severity of Illness							
Baseline	4.6	4.6	4.6	4.5	4.6	.54	.90
Week 6							
LOCF	-1.3	-1.6	-1.7	-1.8	-1.6	.26	.32
OC	-1.8	-2.1	-1.9	-2.1	-1.9	.16	.37
CGI Global Improvement							
Week 6							
LOCF	2.7	2.4	2.4	2.4	2.4	.19	.44
OC	2.4	1.8	2.2	2.0	2.3	.18	.77

The HAM-D 17 Total results by week are depicted in Figure 1. The only statistically significant differences compared to placebo were: the 50 mg/day dose at Week 5 OC; the 100 mg/day dose at Weeks 4 LOCF, 5 LOCF + OC and 6 LOCF; and the 200 mg/day dose at Weeks 5 LOCF + OC and 6 LOCF + OC. The 300 mg/day group was not significantly different from placebo at any timepoint. The increase in HAM-D total seen at Week 5 was observed for about 25% of the patients in that group; the increase depicted in the graphs, then, was not due to outliers in the data.

Figure 1. Study 030A2 - 0007
HAM-D 17 Total by Week
Least Square Means



Reviewer's Comments on Fixed Dose Study 030A2-0007

The sponsor did not perform any dose response analyses (none were proposed in the protocol). Nevertheless the data in this trial does not suggest the presence of a strong dose-response relationship based on any of the 4 efficacy variables. In fact the treatment effects seen for the 200 mg/day dose are greater than the effects seen for the 300 mg/day. The latter result is inconsistent with the results observed in subsequent trials where minimal or no efficacy was noted for doses less than 300 mg/day.

Since patients in the 300 mg nefazodone group dropped sooner and at a higher rate than patients in the other groups, one might conjecture that the lack of efficacy was due to the dropouts. However, the observed cases data suggests otherwise; even the patients who remain on study do not show an improvement over placebo on the HAM-D 17 Total (treatment difference of 0.6, p=.74). See Figure 1.

The large number of patients dropping due to lack of efficacy (about 20% of the total sample) and the inability of the trial to demonstrate dose-response effects speaks to the inadequacy of the fixed dose trial design. Under these designs patients may not improve as well as in a titration study because dosing can not be adjusted according to the response of the patient.

This trial failed to show statistically that nefazodone is more effective than placebo for the treatment of depression.

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7.0 Efficacy Findings

7.1 Overview of Studies Pertinent to Efficacy

There were eleven controlled trials in the NDA including eight placebo-controlled trials and three two-arm, active-control trials conducted during Nefazodone's clinical development. These trials were primarily conducted in adult out-patients meeting RDC, DSM-III or DSM-IIIR criteria for major depressive episode. The eight double-blind, placebo-controlled trials were conducted in the United States and Canada.

Of the eight short-term, placebo-controlled studies, one was a fixed-dose design while the other seven were flexible-dose designs. These studies tested Nefazodone in doses from 50 mg up to 600 mg, although a number of studies did not reach the higher dose ranges.

These trials tend to look at the same group of efficacy variables; the HAM-D 17 total, the HAM-D depressed mood item, the clinical global impressions severity of illness score and the global improvement score.

For this group of studies the sponsor provided data from the intent-to-treat sample and results for both last observation carried forward and observed cases analyses were presented.

There is some consistency of demographic data throughout all of the studies. Two thirds of the patients enrolled in these trials were women. More than 80% of the patients were white and the average age was about 39 years.

Patients were required to have a score of at least 20 on the HAMD-17 to enter these trials.

There were 2 completed and 3 on-going active-controlled trials which do not show differences between treatment groups and do not contribute to the evaluation of efficacy.

7.2 Summaries of Placebo Controlled Studies Pertinent to Efficacy

7.2.1 Study CN104-005 (conducted 2/89 to 6/90)
A Double-Blind Trial of Nefazodone, Imipramine, and Placebo in the Treatment of Depressed Outpatients (Protocol CN104-005).

7.2.1.1 Investigators and Location

Two centers under the auspices of a single principal investigator, Karl Rickels, M.D., University Hospital, Philadelphia, Pennsylvania, U.S.A. Center 001 comprised six Psychiatric Practices located in Pennsylvania, Delaware, New Jersey, and West Virginia; Center 002 comprised seven Family Practices located in Pennsylvania, Delaware, and New Jersey.

7.2.1.2 Study Plan:

Objectives\Rational: To investigate the safety and efficacy of nefazodone, imipramine, and placebo in the treatment of patients with a non-psychotic Major Depressive Episode or Bipolar Disorder, Depressed, and

to provide data on the effective dose range.

Population to be Studied: Outpatients of either sex, 18 years of age or older, with a diagnosis of Major Depression (Single Episode or Recurrent) or Bipolar Disorder, Depressed (DSM-III-R).

Study Design: Multicenter, randomized, double-blind, parallel-group, 8-week comparison of the safety and efficacy of nefazodone, imipramine, and placebo. Rating scales included: 28-item Hamilton Rating Scale for Depression (HAM-D-28); Symptom Checklist-87 (SCL-87); Clinical Global Impression (CGI) Scale, Patient's Global Assessments (PGA) Scale, and the Hamilton Rating Scale for Anxiety (HAM-A). Two distinct practice settings, a Family Practice Group and a Psychiatric Practice Group, were established a priori to permit analyses of the relationship of response to treatment setting.

Analysis Plan: A two-way analysis of variance (ANOVA) model with study center (Family Practice or Psychiatric Practice), treatment, and study center by treatment interaction effects was used to test for baseline comparability as well as differences between treatments for the change from Baseline in HAM-D and CGI Severity scores. Categorical data such as CGI and PGA Improvement scores were analyzed within the framework of the generalized Cochran-Mantel-Haenszel (CMH) procedure. Both the two-way ANOVA and CMH models tested the differences between treatments averaged across the study centers. The planned sample size of 240 patients had a power of ≥ 80% to detect an average difference of 4 points in the HAM-D-17 Total Score between placebo and each of the other treatment groups (nefazodone, imipramine).

7.2.1.3 **Study Conduct/Outcome** (see appendix for related tables)

Patient Disposition: 283 patients at two study centers were randomized to three treatment groups. 260 patients were evaluable for efficacy.

Demographics: Of the 283 patients, 179 (63%) were women and 104 (37%) men. Patient age ranged from 19 to 81 years. 271 (96%) patients met DSM-III-R criteria for moderate to severe Major Depression (Single or Recurrent Episode) and 12 (4%) met the diagnostic criteria for Bipolar Disorder, Depressed; 159 (56%) patients experienced a previous depressive episode.

Dosing Information: Oral capsules administered QD or BID. Recommended dosage ranges: nefazodone (100-mg capsule) 100 to 600 mg/day; imipramine (50-mg capsule) 50 to 300 mg/day; placebo, one capsule/day to six capsules/day. The mean modal dose at Week 8 was 375.4 mg/day for the nefazodone group, 164.9 mg/day for the imipramine group, and 4.5 capsules/day for the placebo group.

Concomitant Medications: The protocol permitted the use of chloral hydrate for sleep and this was the most frequently used concomitant psychotropic medication. Seventeen patients took prohibited concomitant psychotropic medications (alprazolam, diazepam, lorazepam, amitriptyline, Librax, hydroxyzine HCl, fluoxetine HCl, caffeine, doxepin HCl, and prochlorperazine); however, these patients were not excluded from the analyses.

Efficacy Results: Patients were considered evaluable for efficacy (i.e., included in the Intent-to-Treat Sample) if they were randomized to

treatment, received a dose of study medication, and had an efficacy evaluation during treatment. Of the 260 patients evaluable for efficacy, 91 received placebo, 83 received imipramine, and 86 received nefazodone. Sixteen patients were lost to follow up.

There are no differences in the week 8 LOCF nefazodone and placebo results for center one. In Center 2 the nefazodone group was significantly different ($p<.001$) from placebo on the 4 efficacy measures. These differences are first apparent at week 3. The LOCF and OC results are also consistent.

Data is provided for the combined analysis in the appendix.

7.2.1.4 Conclusion: Center one, in this study, did not differentiate Nefazodone or Imipramine from placebo. Center two clearly does differentiate Nefazodone from placebo and the combined analysis isalso postive.

7.2.2 Study 03A0A-004B (8/87 to 5/89) A Double-Blind Trial of Two Daily Dose Ranges of Nefazodone and Placebo in the Treatment of Depressed Outpatients

7.2.2.1 Investigator/Locations: Joseph Mendels, M.D., Philadelphia Medical Institute, Philadelphia, PA (Study 2408); Frederick Reimherr, M.D., University of Utah, College of Medicine, Salt Lake City, UT (Study 2531).

03A0A-004B

7.2.2.2 Study Plan:

Objectives: To determine the safety and efficacy of nefazodone titrated in two dose ranges (recommended low-dose range 150-300 mg/day and recommended high-dose range 300-600 mg/day) as compared to placebo in the treatment of outpatients with moderate to severe depression.

Population to be Studied: Outpatients of either sex, 18 years of age or older, with a diagnosis of Major Depressive Episode or Bipolar Disorder, Depressed (DSM-III).

Study Design: Multicenter, randomized, double-blind, parallel group, 6-week comparison of the safety and efficacy of two dose ranges of nefazodone and placebo. Rating scales included: 17-Item Hamilton Rating Scale for Depression (HAM-D-17); Clinical Global Impressions (CGI) Scale; Inventory for Depressive Symptomatology - Clinician (IDS-C); and Inventory for Depressive Symptomatology -Self Report (IDS-SR). A narrative of the physician's overall assessment was collected on the End-of-Study Evaluation Form.

Plan for Analysis: A two-way analysis of variance (ANOVA) model with study center, treatment, and study center by treatment interaction effects was used to test for baseline comparability as well as differences between treatments for the change from Baseline in HAM-D and CGI Severity scores. Categorical data such as CGI Improvement scores were analyzed within the framework of the generalized Cochran-Mantel-Haenszel (CMH) procedure, using study center as the stratification variable. Both the two-way ANOVA and CMH models tested the differences between treatments averaged across the study centers. The planned sample size of 240 patients had a power of $\geq 80\%$ to detect an average difference of four points in the HAM-D-17 Total score between nefazodone and placebo.

7.2.2.3 Study Conduct/Outcome (see appendix for related tables)

Patient Disposition: 240 patients at two study centers were randomized to treatment. 231 patients were evaluable for efficacy.

Demographics: Of the 240 patients, 148 (62%) were women and 92 (38%) men. Patient age ranged from 18 to 79 years. 239 met the diagnostic criteria for Major Depression (DSM-III) and one met the criteria for Bipolar Disorder, Depressed; melancholia was diagnosed in 109 (45%) patients; 150 (62%) patients had recurrent episodes of depression; and 149 (62%) patients had their current episode of depression for at least 6 months.

Dosing Information: Oral capsules administered BID. Recommended dosage ranges: low-dose nefazodone, 150 to 300 mg/day (50-mg capsule), beginning at 100 mg/day; high-dose nefazodone, 300 to 600 mg/day (100-mg capsule), beginning at 200 mg/day; placebo 2-6 capsules per day. The mean modal dose at Week 6 was 246.6 mg/day for the low-dose nefazodone group, 396.8 mg/day for the high-dose nefazodone group, and 5.1 capsules/day for the placebo group.

Concomitant Medications: The protocol permitted the use of chloral hydrate for sleep and this was the most frequently used concomitant psychotropic medication. Fifteen patients took prohibited concomitant psychotropic medications (alprazolam, amitriptyline, caffeine, diazepam, fluoxetine HCl, imipramine, Librax, lorazepam, nortriptyline HCl, temazepam, chlormezanone, and unspecified sleeping pill); these patients were not excluded from the analyses.

Efficacy Results: Patients were considered evaluable for efficacy if they were randomized to treatment, received a dose of study medication, and had an efficacy evaluation during treatment. Of the 231 patients meeting these criteria, 75 received placebo, 78 received low-dose nefazodone; and 78 received high-dose nefazodone.

Low dose effects are not different from placebo. The high dose group was not significantly deferent from placebo on the HAM-D depressed mood item, but was on three other variables.

7.2.2.4 Conclusions:
Study 03A0A-004B does provide statistical evidence that the high doue of Nefazodone is effective compared to placebo for three of the four efficacy variables.

7.2.3 Study CN104-006 A Double-Blind Trial of Nefazodone, Imipramine, and Placebo in the Treatment of Depressed Outpatients (Protocol CN104-006).

7.2.3.1 Investigator\Locations: Louis Fabre, Jr., M.D., Ph.D, Research Testing Inc., Houston, Texas, and Dallas, Texas, USA; Cal K. Cohn, M.D., The Hauser Clinic and Associates, Houston, Texas, USA.

7.2.3.2 Study Plan:

Objectives: To determine the safety and efficacy of nefazodone, imipramine, and placebo in the treatment of moderately to severely

depressed outpatients meeting DSM-III-R criteria for Major Depression, Single Episode or Recurrent, or Bipolar Disorder, Depressed, and to provide data on the effective dose range.

Population to be Studied: Outpatients of either sex, 18 years of age or older, with a diagnosis of Major Depression (Single Episode or Recurrent) or Bipolar Disorder, Depressed (DSM-III-R).

Study Design: Multicenter, randomized, double-blind, parallel-group, eight-week comparison of the safety and efficacy of nefazodone, imipramine, and placebo. The trial was preceded by a one- to four-week baseline evaluation phase designed to ensure that all eligibility criteria were fulfilled and all relevant baseline data were recorded. Rating scales included: 28-Item Hamilton Rating Scale for Depression (HAM-D-28), Hamilton Rating Scale for Anxiety (HAM-A), Symptom Checklist-87 (SCL-87), Clinical Global Impressions (CGI) Scale, and Patient's Global Assessments (PGA) Scale.

Plan for Analysis: The statistical analyses included a two-way analysis of variance (ANOVA) model with study center, treatment, and study center by treatment interaction effects. This model was used to test for baseline comparability as well as differences between treatments for the change from Baseline in HAM-D and CGI Severity scores. Categorical data such as CGI and PGA Improvement scores were analyzed within the framework of the generalized Cochran-Mantel-Haenszel (CMH) procedure, using study center as the stratification variable. Both the two-way ANOVA and CMH models tested the differences between treatments averaged across the study centers. The planned sample size of 240 patients had a power of ≥ 80% to detect an average pairwise difference of four points in the HAM-D-17 Total Score between placebo and the other treatments (nefazodone, imipramine), within the range of variability projected for this study.

7.2.3.3 **Study Conduct/Outcome** (see related appendix tables)

Patient Disposition: 263 patients were randomized to three treatment groups. 237 patients were evaluable for efficacy.

Demographics: Of the 263 patients, 176 (67%) were women and 87 (33%) were men. Patient age ranged from 18 to 70 years. 259 (99%) patients met DSM-III-R criteria for moderate to severe Major Depression (Single or Recurrent Episode) and 3 (1%) met the diagnostic criteria for Bipolar Disorder, Depressed, and the diagnosis of one patient was unrecorded; 149 (58%) patients experienced a previous depressive episode.

Dosing Information: Oral capsules administered QD or BID. Recommended dosage ranges: nefazodone (100-mg capsule), recommended titration range 100 to 600 mg/day); imipramine (50-mg capsule), recommended titration range 50 to 300 mg/day; or placebo, recommended titration range one to six capsules/day. The mean modal dose at Week 8 was 363.6 mg/day for the nefazodone group and 160.5 mg/day for the imipramine group.

Concomitant Medications: The protocol permitted the use of chloral hydrate for sleep and this was the most frequently used concomitant psychotropic medication. Four patients took prohibited concomitant psychotropic medications (diazepam, fluoxetine HCl, Synalgos, and triazolam); however, these patients were not excluded from the analyses.

Efficacy Results: Patients were considered evaluable for efficacy (i.e., included in the Intent-to-Treat Sample) if they were randomized to treatment, received a dose of study medication, and had an efficacy

evaluation during treatment. Of 237 patients evaluable for efficacy, 78 received placebo, 79 received imipramine, and 80 received nefazodone.

The HAM-D results at week 8 for center 2 are borderline but the other 3 variables are strongly supportive with both LOCF and OC in agreement. For center one no efficacy variable is significantly different at any time.

Appendix results are presented for the combined analysis.

7.2.3.4 **Conclusions:**
This study shows that results from the two centers do not agree. Center one does not distinguish Nefazodone from placebo, however, Imipramine was not significantly different either. Center two is positive for both Nefazodone and Imipramine but the combined analysis for both centers is not positive.

7.2.4 **Study 03A0A-003 (conducted 11/86 to 6/90)**
A Multicenter, Double-Blind Comparison of Nefazodone, Imipramine, and Placebo in Patients with Moderate to Severe Depression (Protocol 03A0A-003).

7.2.4.1 **Investigators\Locations:** Neelakanta Nair, M.D., John Pecknold, M.D. and Syed Jamal Mirmiran, M.D., Verdun, Quebec and Pointe Claire, Quebec; Ronald A. Remick, M.D., Vancouver, British Columbia; Bishan Saxena, Ph.D. and Paul Grof, M.D., Hamilton, Ontario; Rejean Fontaine, M.D., Montreal, Quebec; Manuel Matas, M.D., Winnipeg, Manitoba.

7.2.4.2 **Study Plan:**

Objectives: To establish the safety and efficacy of nefazodone as compared to imipramine and placebo in the treatment of patients diagnosed with Major Depressive Disorder.

Population to be Studied: Outpatients of either sex, aged 18-65, with a diagnosis of Major Depressive Disorder (Research Diagnostic Criteria - that had been modified to require that dysphoric features be present for at least four weeks).

Study Design: Multicenter, randomized, double-blind, parallel group 6-week comparison of a high- and a low-dose of nefazodone, imipramine, and placebo. Ratings scales included: 25-Item Hamilton Rating Scale for Depression (HAM-D-25), Clinical Global Impressions (CGI) Scale, Patient's Global Assessments (PGA) Scale, Hamilton Rating Scale for Anxiety (HAM-A), and Symptom Checklist-90 (SCL-90).

Plan for Analysis: A two-way analysis of variance (ANOVA) model with study-center stratum, treatment, and study-center stratum by treatment interaction effects was used to test for Baseline comparability as well as differences between treatments for the change from Baseline in HAM-D and CGI Severity scores. Categorical data such as CGI and PGA Improvement Scores were analyzed within the framework of the generalized Cochran-Mantel-Haenszel (CMH) procedure, using study-center stratum as the stratification variable. Both the two-way ANOVA and CMH models were used to test the differences between treatments averaged across the study-center strata. The two-way ANOVA model also was used to test differences between treatments within each study-center stratum for the change from Baseline in HAM-D scores. A Fisher's Exact Permutation test was used to compare treatments within each study-center stratum for CGI and PGA. The

planned sample size of 240 patients had a power of ≥ 80% to detect an average difference of approximately 5 points in the HAM-D-17 Total Score between placebo and each of the other treatments (high- or low-dose nefazodone and imipramine), within the range of variability projected for this study.

7.2.4.3 Study Conduct/Outcome (see appendix for related tables)

Patient Disposition: 204 patients at five study centers received study medication. All 180 patients at Study Center 2191 were evaluable for efficacy and 23 of 24 patients were evaluable for efficacy at the four discontinued centers.

Demographics: Of the 180 patients Study Center 2191, 112 (62%) were women and 68 (38%) men. They ranged in age from 20 to 65 and 124 (69%) met DSM-III diagnostic criteria for Major Depression, Melancholic Subtype; of the patients whose status was known, 86 (54%) experienced a previous depressive episode.

Dosing Information: Oral capsules given BID or TID. Recommended dosage ranges: low-dose nefazodone, 50 to 250 mg/day; high-dose nefazodone, 100 to 500 mg/day; imipramine, 50 to 250 mg/day; placebo, two to 10 capsules/day. For patients at Center 2191 who had an efficacy evaluation at Week 6 the mean of the Modal Daily Dose at Week 6 was 245.6 mg/day for low-dose nefazodone, 462.1 mg/day for high-dose nefazodone, 215.7 mg/day for imipramine, and 9.9 capsules/day for placebo.

Concomitant Medications: The protocol permitted the use of chloral hydrate for sleep and this was the most frequently used concomitant psychotropic medication. Seventeen patients (14 in Center 2191) took prohibited concomitant psychotropic medications (diazepam, flurazepam, hydroxyzine, loctopam, lorazepam, maprotiline, oxazepam, thiopental, triazolam), but these patients were not excluded from the analysis.

Efficacy Results: Patients were considered evaluable for efficacy (i.e., included in the Intent-to-Treat Sample) if they were randomized to treatment, received a dose of study medication, and had an efficacy evaluation during treatment. One hundred eighty patients at Center 2191 were evaluable for efficacy; 44 received high-dose nefazodone, 46 received low-dose nefazodone, 45 received imipramine, and 45 received placebo.

There were no significant differences for the nefazodone low dose group at any time. The HAM-D 17 total LOCF was significant in the high nefazodone group at weeks 5 and 6. The OC effects were not significant for any variable.

Appendix data is provided only for center 2191.

7.2.4.4 **Conclusions:**

In this study, the low dose Nefazodone group was not effective. The high dose Nefazodone group beat placebo on all four efficacy variables when looking at the LOCF results. The OC results do not agree with the LOCF results. The combined analysis fails to distinguish nefazodone from placebo.

7.2.5 Study CN104-002 (conducted 7/88 to 11/90)
A Double-Blind Trial of Nefazodone, Imipramine, and Placebo in the Treatment of Depressed Outpatients (Protocol CN104-002).

7.2.5.1 Investigator\Location: John P. Feighner, M.D., Feighner Research Institute, Poway, California.

7.2.5.2 Study Plan:

Objectives: To determine the safety and efficacy of nefazodone, imipramine, and placebo in the treatment of moderately to severely depressed outpatients who met DSM-III-R criteria for Major Depression or Bipolar Disorder, Depressed.

Population to be Studied: Outpatients of either sex, aged 18 or older, with a DSM-III-R diagnosis of moderate or severe Major Depression, Single or Recurrent episode, or Bipolar Disorder, Depressed.

Study Design: Single-center, randomized, double-blind, parallel-group six-week comparison of the safety and efficacy of nefazodone, imipramine, and placebo. Ratings scales included: 28-Item Hamilton Rating Scale for Depression (HAM-D-28), Clinical Global Impressions (CGI) Scale, Patient's Global Assessments (PGA) Scale, Hamilton Rating Scale for Anxiety (HAM-A), and Symptom Checklist-87 (SCL-87).

Plan for Analysis: A one-way analysis of variance (ANOVA) model was used to test for baseline comparability as well as differences between treatments for the change from Baseline in HAM-D and CGI Severity scores. Categorical data such as CGI and PGA Improvement scores were analyzed using Fisher's Exact Permutation Test. The planned sample size of 180 patients had a power of ≥80% to detect an average difference of five points in the HAM-D-17 Total Score between placebo and each of the other treatment groups (nefazodone, imipramine).

7.2.5.3 Study Conduct/Outcome (see appendix for related tables)

Patient Disposition: 180 outpatients at one study center received study medication. 169 outpatients were evaluable for efficacy.

Demographics: Of the 180 outpatients, 107 (59%) were women and 73 (41%) men. They ranged in age from (99%) met DSM-III diagnostic criteria for Major Depression (Single or Recurrent) and two (1%) met DSM-III-R criteria for Bipolar Disorder, Depressed; in addition, 36 patients (20%) met DSM-III-R diagnostic criteria for Major Depression, Melancholic Subtype; and 85 (47%) experienced a previous depressive episode.

Dosing Information: One oral capsule given QD or two to six capsules equally divided BID. Recommended dosage ranges: nefazodone 50 to 300 mg/day; imipramine 50 to 300 mg/day; or placebo, two to six capsules/day. For outpatients who had an efficacy evaluation at Week 6, the mean of the Modal Daily Dose at Week 6 was 263.0 mg/day for nefazodone, 206.0 mg/day for imipramine, and 5.5 capsules/day for placebo.

Concomitant Medications: The protocol permitted the use of chloral hydrate for sleep and this was the most frequently used concomitant psychotropic medication. Three outpatients, two in the imipramine group and one in the placebo group, took prohibited concomitant psychotropic medication (diazepam, hydroxyzine HCL, and triazolam), but these outpatients were not excluded from the analyses.

Efficacy Results: Outpatients were considered evaluable for efficacy (i.e., included in the Intent-to-Treat Sample) if they were randomized to treatment, received a dose of study medication, and had an efficacy evaluation during treatment. One hundred sixty-nine outpatients were evaluable for efficacy; 57 received placebo, 55 received imipramine and 57 received nefazodone.

The Nefazodone response is not significant for the HAM-D 17 Total at week

6 LOCF while the imipramine response is. The LOCF results for the CGI and HAM-D depressed mood item suggest some improvement for Nefazodone.

7.2.5.4 Conclusions:
This study failed to show that Nefazodone is more effective than placebo for the treatment of depression. The imipramine response was significant for both LOCF and OC. The study had an absence of dropouts for adverse events and a large number of dropouts due to lack of efficacy suggesting that the dose in the study was too low.

CM104-002

7.2.6 Study 030A2-007 (conducted 12/85 to 4/89)
A Multicenter, Double-Blind Comparison of Four Fixed Doses of Nefazodone and Placebo in Patients with Moderate to Severe Depression (Protocol 030A2-0007).

7.2.6.1 Investigators\Locations: Jan Fawcett, M.D., Rush Presbyterian-St. Luke's Medical Center, Chicago, Illinois, USA; Yvon LaPierre, M.D., Royal Ottawa Hospital, Ottawa, Ontario, Canada; Sidney C. Lerfald, M.D., 5600 MacCorkle Ave. S.E., Charleston, West Virginia, USA; C. Leon McGahee, M.D. and Binni Bennett, M.S.W., Marshall University School of Medicine, Huntington, West Virginia, USA; John C. Pecknold, M.D. and Neelakanta P.V. Nair, M.D., St. Mary's Hospital, Montreal, Quebec, Canada, and Douglas Hospital Research Center, Verdun, Quebec, Canada; Gary Tollefson, M.D., Ph.D., St. Paul-Ramsey Medical Center, St. Paul, Minnesota, USA.

7.2.6.2 Study Plan:

Objectives: To determine the safety and efficacy of various doses of nefazodone as compared to placebo in the treatment of depressed patients.

Population to be Studied: Patients of either sex, aged 18-70 (18-65 at the two Canadian study centers), with a diagnosis of Major Depressive Disorder (Research Diagnostic Criteria - that had been modified to require that dysphoric features be present for at least four weeks).

Study Design: Multicenter, randomized, double-blind, parallel group 6-week comparison of four fixed doses of nefazodone and placebo. Ratings scales included: 25-Item Hamilton Rating Scale for Depression (HAM-D-25), Clinical Global Impressions (CGI) Scale, Patient's Global Assessments (PGA) Scale, Hamilton Rating Scale for Anxiety (HAM-A), and Symptom Checklist-90 (SCL-90).

Plan for Analysis: A two-way analysis of variance (ANOVA) model with study center, treatment, and study center by treatment interaction effects was used to test for baseline comparability as well as differences between treatments for the change from Baseline in HAM-D and CGI Severity scores. Categorical data such as CGI and PGA Improvement Scores were analyzed within the framework of the generalized Cochran-Mantel-Haenszel (CMH) procedure, using study-center as the stratification variable. Both the two-way ANOVA and CMH models were used to test the differences between treatments averaged across the study centers. The planned sample size of 250 patients had a power of ≥ 80% to detect an average difference of 4.9 points in the HAM-D-17 Total Score between a therapeutic dose level of nefazodone and placebo or a significant linear trend across placebo and the four nefazodone dose levels.

7.2.6.3 Study Conduct/Outcome (see appendix for related tables)

Patient Disposition: 234 patients at five study centers received study

medication. 223 patients were evaluable for efficacy.

Demographics: Of the 234 patients, 134 (57%) were women and 100 (43%) men. They ranged in age from 18 to 69 and 168 (72%) met DSM-III diagnostic criteria for Major Depression, Melancholic Subtype; 138 (59%) experienced a previous depressive episode.

Dosiug Information: 2 oral capsules given BID. Dosages: nefazodone 50 mg/day (one 25-mg capsule, one placebo capsule); nefazodone 100 mg/day, (two 25-mg capsules); nefazodone 200 mg/day, (two 50-mg capsules); nefazodone 300 mg/day, (one 100-mg capsule, one 50-mg capsule).

Concomitant Medications: The protocol permitted the use of chloral hydrate for sleep and this was the most frequently used concomitant psychotropic medication. Six patients, four on placebo and two on 50 mg/day nefazodone, took prohibited concomitant psychotropic medication (alprazolam, hydroxyzine, diazepam, and triazolam), but these patients were not excluded from the analyses.

Efficacy Results: (see appendix) Patients were considered evaluable for efficacy (i.e., included in the Intent-to-Treat Sample) if they were randomized to treatment, received a dose of study medication, and had an efficacy evaluation during treatment. Two hundred twenty-three patients were evaluable for efficacy; 47 received placebo, 43 received nefazodone 50 mg/day, 46 received nefazodone 100 mg/day, 46 received nefazodone 200 mg/day, 41 received nefazodone 300 mg/day, and 11 patients were lost to follow-up.

The week 6 results (LOCF and OC) for the CGI and the HAM-D Mood Item 1 were not significant at any dose level. In this study the treatment effects seen for the 200 mg/day dose are greater than the effects seen for the 300 mg/day.

03AP2-007

7.2.6.4 Conclusions: This trial failed to show statistically that Nefazodone is more effective than placebo for the treatment of depression.

7.2.7 03A0A-004A A Double-Blind Trial of Two Daily Dose Ranges of Nefazodone and Placebo in the Treatment of Depressed Outpatients

7.2.7.1 Investigator\Locations: James Claghorn, M.D., Clinical Research Associates, Houston, Texas, USA (Study 2407); A. John Rush, M.D., University of Texas, Health Science Center at Dallas, Dallas, Texas, USA (Study 2410).

7.2.7.2 Study Plan:

Objectives: To determine the safety and efficacy of nefazodone titrated in two dose ranges (recommended low-dose range 150-300 mg/day and recommended high-dose range 300-600 mg/day) as compared to placebo in the treatment of patients with moderate to severe depression.

Population to be Studied: Outpatients of either sex, 18 years of age or older, with a diagnosis of Major Depressive Episode or Bipolar Disorder, Depressed (DSM-III).

Study Design: Multicenter, randomized, double-blind, parallel-group, 6-week comparison of the safety and efficacy of two dose ranges of nefazodone and placebo. Rating scales included: 17-Item Hamilton Rating Scale for Depression (HAM-D-17); Clinical Global Impressions (CGI) Scale;

Inventory for Depressive Symptomatology - Clinician (IDS-C); and Inventory for Depressive Symptomatology -Self Report (IDS-SR). A narrative of the physician's overall assessment was collected on the End-of-Study Evaluation Form.

Plan for Analysis: A two-way analysis of variance (ANOVA) model with study center, treatment, and study center by treatment interaction effects was used to test for baseline comparability as well as differences between treatments for the change from Baseline in HAM-D and CGI Severity scores. Categorical data such as CGI Improvement scores were analyzed within the framework of the generalized Cochran-Mantel-Haenszel (CMH) procedure, using study center as the stratification variable. Both the two-way ANOVA and CMH models tested the differences between treatments averaged across the study centers. The planned sample size of 240 patients had a power of ≥ 80% to detect an average difference of four points in the HAM-D-17 Total score between nefazodone and placebo.

7.2.7.3 **Study Conduct/Outcome** (see related appendix table)

Patient Disposition: 240 patients at two study centers were randomized to treatment. 230 patients were evaluable for efficacy.

Demographics: Of the 240 patients, 144 (60%) were women and 96 (40%) men. Patient age ranged from years. 227 met the DSM-III criteria for Major Depression and 13 met the criteria for Bipolar Disorder, Depressed; melancholia was diagnosed in 26 (11%) patients; 158 (66%) patients had recurrent episodes of depression; and 151 (63%) patients had their current episode of depression for at least 6 months.

Dosing Information: Oral capsules administered BID. Recommended dosage ranges: low-dose nefazodone, 150 to 300 mg/day (50-mg capsule), beginning at 100 mg/day; high-dose nefazodone, 300 to 600 mg/day (100-mg capsule), beginning at 200 mg/day; placebo 2-6 capsules/day. The mean modal dose at Week 6 was 276.0 mg/day for the low-dose nefazodone group, 513.5 mg/day for the high-dose nefazodone group, and 5.5 capsules/day for the placebo group.

Concomitant Medications: The protocol permitted the use of chloral hydrate for sleep and this was the most frequently used concomitant psychotropic medication. Fifteen patients took prohibited concomitant psychotropic medications (alprazolam, amitriptyline, diazepam, hydroxyzine HCl, Librax, lorazepam, L-tryptophan, nortriptyline HCl, oxazepam, promethazine, Synalgos, and unspecified tranquilizer); these patients were not excluded from the analyses.

Efficacy Results: Patients were considered evaluable for efficacy if they were randomized to treatment, received a dose of study medication, and had an efficacy evaluation during treatment. Of the 230 patients meeting these criteria, 77 received placebo, 77 received low-dose nefazodone; and 76 received high-dose nefazodone.
In 004A the low dose and high dose effects are not different from placebo effects.

7.2.7.4 **Conclusions:** In 04A, neither the low or high dose group is superior to placebo in any efficacy variable. The lack of a active control group make interpretation difficult and OC results favor placebo.

7.2.8 **030A2-004/005** Multi-Center, Double-Blind Comparison of Nefazodone, Imipramine, and Placebo in Patients with Moderate to Severe Depression (Protocols 030A2-0004 and 030A2-0005)

7.2.8.1 **Investigator, Locations:** Jambur Ananth, M.D., Harbor U.C.L.A. Medical Center, Torrance, California; John P. Feighner, M.D., Feighner Research Institute, Encinitas, California; David L. Dunner, M.D., University of Washington, Harborview Medical Center, Seattle, Washington; Joseph Mendels, M.D., Philadelphia Medical Institute, Philadelphia, Pennsylvania; Robert A. Riesenberg, M.D., Biobehavioral Associates, Decatur, Georgia; Carl Wellish, M.D., Arizona Psychiatric Associates, Ltd., Phoenix, Arizona.

7.2.8.2 **Study Plan:**

Objectives: To determine the safety and efficacy of nefazodone as compared to imipramine and placebo in the treatment of depressed patients, and to provide further data on the effective dose range of nefazodone.

Population to be Studied: Patients of either sex, 18 to 70 years of age, with a diagnosis of Major Depressive Episode with Melancholia (DSM-III) and Endogenous Major Depressive Disorder (RDC); dysphoric features must have been present for at least four weeks.

Study Design: Multicenter, randomized, double-blind, parallel-group, 6-week comparison of the safety and efficacy of nefazodone, imipramine, and placebo. Rating scales included: 25-Item Hamilton Rating Scale for Depression (HAM-D-25), Clinical Global Impressions (CGI) Scale, Patient's Global Assessments (PGA) Scale, Hamilton Rating Scale for Anxiety (HAM-A), and Symptom Checklist-90 (SCL-90).

Plan for Analysis: Sample means for Baseline values and weekly changes from Baseline for the HAM-D-17 Total score, the HAM-D Depressed Mood Item (Item 1) and the CGI: Doctor's Opinion of Severity. A responder/non-responder categorization was used to summarize data for the CGI: Doctor's Opinion of Improvement and the PGA: Patient's Opinion of Improvement.

7.2.8.3 **Study Conduct/Outcome** (see related appendix tables)

Patient Disposition: 226 patients at six study centers were randomized to treatment. 219 patients were evaluable for efficacy.

Demographics: Of the 240 patients, 109 (48%) were women and 117 (52%) men. Patient age ranged from years. All 226 patients met the DSM-III criteria for Major Depressive Episode with Melancholia Depressed and the RDC criteria for Endogenous Major Depressive Disorder. 122 (55%) patients had recurrent episodes of depression; and 103 (46%) patients had their current episode of depression for at least 12 months.

Dosing Information: Oral capsules administered BID or TID. Recommended dosage ranges: nefazodone, 50 to 250 mg/day (25-mg capsule); imipramine, 50 to 250 mg/day (25-mg capsule); placebo 2-10 capsules/day. The mean modal dose at Week 6 was 175.0 mg/day for the nefazodone group, 155.8 mg/day for the imipramine group, and 6.7 capsules/day for the placebo group.

Concomitant Medications: The protocol permitted the use of chloral hydrate for sleep and this was the most frequently used concomitant psychotropic medication. Four patients took prohibited concomitant

psychotropic medications (diazepam, lorazepam, and promethazine); these patients were not excluded from the analyses.

Efficacy Results: Patients were considered evaluable for efficacy if they were randomized to treatment, received a dose of study medication, and had an efficacy evaluation during treatment. Of the 219 patients meeting these criteria, 70 received placebo, 75 received imipramine; and 74 received nefazodone.

7.2.8.4 Conclusions
This was the first study and did not show significant results. The low nefazodone dose probably contributes to this finding.

7.3 Active Control Trials

Three studies that compared the activity of nefazodone to tricyclic antidepressants were conducted in Europe. Study 03A0A-006 in France, compared the activity of nefazodone to clomipramine in a sample of hospitalized, depressed patients. Study CN104-003, conducted in Belgium, compared the activity of nefazodone to that of imipramine in a sample of depressed outpatients. Study CN104-016, also conducted in Belgium, compared the activity of nefazodone to that of amitriptyline in a sample of depressed hospitalized patients.

All three studies employed a flexible dose-titration strategy whereby nefazodone was given in divided doses ranging from 100 to 400 mg/day in Studies CN104-003 and CN104-016, and from 100 to 600 mg/day in Study 03A0A-006. Study CN104-016 differed from CN104-003 and 03A0A-006 in that a much slower dose progression and suboptimal nefazodone dose was specified by protocol. This resulted in a markedly lower nefazodone dose (mean 243.5 mg/day) in CN104-016 compared to the other studies. The DSM-III or DSM-III-R diagnostic criteria were used for patient inclusion.

There are no between group differences which would be supportive of efficacy. The active-control trials do not offer any help with the question of efficacy over and above what can be learned from the results of the placebo-controlled trials.

7.4 Summary of Data Pertinent to Important Clinical Issues

7.4.1 Clinical Predictors of Response

The sponsor has examined pretreatment (Baseline) characteristics that might predict response to nefazodone therapy. Since no single study is large enough to permit an assessment of outcome in subgroups of patients, meta-analyses of the efficacy data for all patients enrolled in the eight placebo-controlled studies were performed. Four stratification criteria were used to establish different patient subgroups relating to severity of illness: 1) patients with severe depressive symptoms (Baseline Clinical Global Impressions (CGI) Severity of Psychopathology score of at least 5 (markedly ill); 2) Baseline 17-item Hamilton Depression (HAM-D-17) score ≥ 27); 3) patients meeting DSM-III or DSM-III-R criteria for Major Depression, Melancholic Subtype; and 4) patients with Recurrent Major Depression. An additional meta-analysis of patients stratified by pretreatment level of anxiety was done that included those placebo-controlled trials where HAM-A in addition to HAM-D ratings were carried out. Efficacy analyses utilized the Last Observation Carried Forward (LOCF) data set and were based on the Intent-to-Treat patient sample. The

Table 5.1.1.3

Enumeration of Patients Exposed to Study Medications, by Data Set

Long-Term Safety of Nefazodone

Data Set	Number of Trials	Number of Patients				
		Placebo	SSRI[a]	Tricyclic	Nefazodone	Totals
Placebo Controlled	8	197	37	127	327	688
Active-Controlled	3	0	0	31	55	86
Open Trials	3	0	0	0	418	418
Total	14	197	37	158	800	1192

Selective serotonin re-uptake inhibitors

5.1.2 DEMOGRAPHICS

Demographic profiles are provided separately for Phase 1 studies and for Phase II-III studies in the following tables. The vast majority of these phase I patients are white males under the age of 35. There is little difference among the treatment groups.

TABLE 5.1.2.1
Demographic Profile for Phase I Studies[a]

	Nefazodone n=424	Placebo n=98	Active-Control	
			SSRI n=0	Tricyclic n=24
AGE				
Mean (yrs)	37	35		55
Range (yrs)				
Groups (%)				
<35 yrs	267 (63)	67 (68)		3 (13)
35-64 yrs	95 (22)	18 (18)		8 (33)
≥65 yrs	62 (15)	13 (13)		13 (54)
SEX (%)				
Female	71 (17)	9 (9)		9 (38)
Male	353 (83)	89 (91)		15 (63)
RACE (%)				
White	366 (86)	85 (87)		22 (92)
Non-White	56 (13)	11 (11)		2 (8)
Race unknown	2 (<1)	2 (2)		0
MEAN WEIGHT (lb)	163	161		153

a Subjects in some studies received other drugs in addition to nefazodone or tricyclics.

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1: Psychopharmacol Bull. 1989;25(2):219-21.

Link

A comparison of nefazodone, imipramine, and placebo in patients with moderate to severe depression.

Feighner JP, Pambakian R, Fowler RC, Boyer WF, D'Amico ME.

In this sample of moderately to severely depressed outpatients, nefazodone therapy proved superior to placebo. Nefazodone therapy was also associated with fewer dropouts from adverse effects than was imipramine. In view of these efficacy findings as well as the promising side effect and safety profile of nefazodone, further research is warranted to evaluate its therapeutic potential in the treatment of depressive illness.

PMID: 2690165 [PubMed - indexed for MEDLINE]

Related Links

A double-blind comparison of nefazodone, imipramine, and place [J Clin Psychiatry. 1994]

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1: J Clin Psychiatry. 1996;57 Suppl 2:15-8.

Responders to antidepressant drug treatment: a study comparing nefazodone, imipramine, and placebo in patients with major depression.

Cohn CK, Robinson DS, Roberts DL, Schwiderski UE, O'Brien K, Ieni JR.

Cohn Center, Houston, Tex, USA.

BACKGROUND: Nefazodone hydrochloride, an antidepressant that acts as a 5-HT2 antagonist and serotonin (5-HT) and norepinephrine uptake inhibitor, was evaluated in a double-blind, imipramine- and placebo-controlled study involving 128 patients with major depression. METHOD: Eligible patients were randomly assigned to receive placebo (2 to 6 capsules/day), imipramine (100 to 300 mg/day), or nefazodone (200 to 600 mg/day) for 8 weeks. The principal efficacy outcome measure assessed was the number of patients who experienced an adequate response during treatment. RESULTS: Based on global improvement (Clinical Global Impressions-Improvement), 67% of nefazodone-treated patients (p < or = .01) and 63% of imipramine-treated patients (p < or = .05) responded during 8 weeks of treatment, compared with 36% of placebo controls. Sixty-two percent of nefazodone-treated, 53% of imipramine-treated, and 26% of placebo-treated patients had 17-item Hamilton Rating Scale for Depression (HAM-D-17) scores < or = 10 on completion of acute treatment. Nefazodone-treated patients had a lower incidence of premature treatment discontinuation and fewer dropouts for adverse events than the imipramine group. CONCLUSION: In a three arm comparison with imipramine and placebo, nefazodone had the greatest number of patients with major depression who responded to therapy. Nefazodone, a new antidepressant with novel pharmacology, is a well-tolerated, efficacious antidepressant.

PMID: 8626358 [PubMed - indexed for MEDLINE]

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Results Available: **5**
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Result 1.

Accession Number CN-00064536

Author Feighner JP, Pambakian R, Fowler RC, Boyer WF, D'Amico MF

Title A comparison of nefazodone, imipramine, and placebo in patients with moderate to severe depression.

Source Psychopharmacology bulletin. 25(2):219-21, 1989.

Abstract In this sample of moderately to severely depressed outpatients, nefazodone therapy proved superior to placebo. Nefazodone therapy was also associated with fewer dropouts from adverse effects than was imipramine. In view of these efficacy findings as well as the promising side effect and safety profile of nefazodone, further research is warranted to evaluate its therapeutic potential in the treatment of depressive illness.

Result 2.

Accession Number CN-00106126

Author Rickels K, Schweizer E, Clary C, Fox I, Weise C

Institution Department of Psychiatry, University of Pennsylvania, Philadelphia.

Title Nefazodone and imipramine in major depression: a placebo-controlled trial.

Source The British journal of psychiatry : the journal of mental science. 164(6):802-5, 1994 Jun.

Abstract Nefazodone is a phenylpiperazine antidepressant with 5-HT2 antagonism and 5-HT reuptake inhibition. Two hundred and eighty-three out-patients with a diagnosis of DSM-III-R major depression of at least one-month duration (65% ill for over 6 months), and a mean score of 24 on the 17-item Hamilton Rating Scale for Depression (HRSD), were randomised to treatment with nefazodone, imipramine, or placebo. The double-blind treatment period was 8 weeks in duration. Nefazodone's antidepressant efficacy was comparable with imipramine's, with both drug treatments significantly better than placebo in a variety of outcome measures. For example, after 8 weeks of therapy, 78% of nefazodone and 83% of imipramine but only 55% of placebo patients ($P < 0.01$) were globally much or very much improved. Nefazodone was better tolerated than imipramine, with fewer drop-outs and a lower incidence of side-effects during treatment.

Result 3.

Accession Number	CN-00103953
Author	Fontaine R, Ontiveros A, Elie R, Kensler TT, Roberts DL, Kaplita S, Ecker JA, Faludi G
Institution	Louis-H. Lafontaine Hospital, Research Centre, Montreal, Quebec, Canada.
Title	A double-blind comparison of nefazodone, imipramine, and placebo in major depression.
Source	The Journal of clinical psychiatry. 55(6):234-41, 1994 Jun.
Abstract	**BACKGROUND:** Nefazodone is a 5-HT2-receptor antagonist and serotonin (5-HT) selective reuptake inhibitor. This study evaluates the safety and efficacy of nefazodone in patients with major depressive disorder (MDD) in comparison to imipramine and placebo treatments. It also compares two dose ranges of nefazodone to investigate its optimal dose range. **METHOD:** Nefazodone was evaluated in a 6-week, double-blind trial of novel design involving 180 patients meeting Research Diagnostic Criteria for major depressive disorder and having a minimum pretreatment score of 22 on the first 17 items of the Hamilton Rating Scale for Depression (HAM-D). Patients were randomly assigned to placebo (2-10 capsules/day), imipramine (50-250 mg/day), or nefazodone in two dose ranges (50-250 mg/day or 100-500 mg/day). **RESULTS:** Improvement on depression measures with nefazodone in the 100-500-mg/day dose range (endpoint mean = 460 mg/day) and imipramine (endpoint mean = 214 mg/day) exceeded that with placebo. Some benefit was also observed in the nefazodone 50-250-mg/day treatment group (endpoint mean = 242 mg/day), but it was suboptimal. Evidence of nefazodone's efficacy as an antidepressant was consistently observed on physician- (HAM-D, Clinical Global Impressions [CGI]) and patient-rated (CGI-patient rated) scales. By patient self-report, improvement of anxiety symptoms associated with depression was evident with nefazodone as early as the first week of treatment, and benefit was seen with both nefazodone dosage groups. Analyses of the physician's global assessments of therapeutic effect and side effects at end of treatment showed therapeutic benefit for both nefazodone and imipramine treatments; however, patients in the nefazodone treatment groups were significantly less troubled by adverse experiences than were imipramine-treated patients, resulting in a lower dropout rate for adverse experience. **CONCLUSION:** Nefazodone is a well-tolerated and effective antidepressant for the treatment of major depressive disorder.

Result 4.

Accession Number	CN-00092545
Author	Frewer LJ, Lader M
Institution	Department of Psychiatry, Institute of Psychiatry, Denmark Hill, London, UK.
Title	The effects of nefazodone, imipramine and placebo, alone and combined with alcohol, in normal subjects.
Source	International clinical psychopharmacology. 8(1):13-20, 1993.
Abstract	Nefazodone (200 mg, 400 mg/day) imipramine (150 mg/day) and placebo were administered to 12 normal, healthy volunteer subjects for a period of 8 days each. A measured dose of alcohol was consumed with the drug on day 8. A battery of physiological, psychomotor, cognitive and subjective tests was carried out before drug administration and 2 h after drug administration on days 1, 7, and 8. Nefazodone had little effect on heart rate and blood pressure whereas imipramine increased both heart rate and diastolic blood pressure. Nefazodone 400 mg impaired the critical flicker fusion threshold. Dose-dependent improvements in psychomotor

performance (Gibson Spiral Maze) and complex memory performance (learning, pursuit rotor, and visual working memory) were produced by nefazodone while imipramine administration impaired performance on these tasks. Subjective changes in alertness and bodily symptoms were produced by all active compounds. While nefazodone failed to potentiate the sedative-hypnotic (depressant) effects of alcohol, imipramine tended to enhance them for psychomotor performance, memory assessments, and some subjective ratings. Thus, nefazodone, particularly at lower dose levels, causes less disruption of human performance than imipramine. This effect probably reflects the lack of anticholinergic activity of nefazodone. Also, nefazodone failed to potentiate the depressant effects of alcohol, perhaps because of its minimal alpha-blockade.

Result 5.

Accession Number	CN-00124712
Author	Cohn CK, Robinson DS, Roberts DL, Schwiderski UE, O'Brien K, Ieni JR
Institution	Cohn Center, Houston, Tex, USA.
Title	Responders to antidepressant drug treatment: a study comparing nefazodone, imipramine, and placebo in patients with major depression.
Source	The Journal of clinical psychiatry. Vol.57 Suppl 2, pp.15-8, 1996.
Abstract	**BACKGROUND:** Nefazodone hydrochloride, an antidepressant that acts as a 5-HT2 antagonist and serotonin (5-HT) and norepinephrine uptake inhibitor, was evaluated in a double-blind, imipramine- and placebo-controlled study involving 128 patients with major depression. **METHOD:** Eligible patients were randomly assigned to receive placebo (2 to 6 capsules/day), imipramine (100 to 300 mg/day), or nefazodone (200 to 600 mg/day) for 8 weeks. The principal efficacy outcome measure assessed was the number of patients who experienced an adequate response during treatment. **RESULTS:** Based on global improvement (Clinical Global Impressions-Improvement), 67% of nefazodone-treated patients ($p < or = .01$) and 63% of imipramine-treated patients ($p < or = .05$) responded during 8 weeks of treatment, compared with 36% of placebo controls. Sixty-two percent of nefazodone-treated, 53% of imipramine-treated, and 26% of placebo-treated patients had 17-item Hamilton Rating Scale for Depression (HAM-D-17) scores < or = 10 on completion of acute treatment. Nefazodone-treated patients had a lower incidence of premature treatment discontinuation and fewer dropouts for adverse events than the imipramine group. **CONCLUSION:** In a three arm comparison with imipramine and placebo, nefazodone had the greatest number of patients with major depression who responded to therapy. Nefazodone, a new antidepressant with novel pharmacology, is a well-tolerated, efficacious antidepressant.

Statistical Review and Evaluation

NDA #: 20-152/ Class 1-S

NOV 19 1993

Applicant: Bristol-Myers Squibb Pharmaceutical Research Institute

Name of Drug: SERZONE (nefazodone hydrochloride)

Indication: Treatment of depression

Documents Reviewed: Volumes 1.1, 1.94 to 1.183, 1.186

Medical Input: Dr. Earl Hears: (HFD-120) has been consulted during the process of this review.

Introduction

This review focuses primarily on the results of 8 placebo-controlled, randomized, double-blind studies designed to show the safety and efficacy of nefazodone for the treatment of depression. In addition, the results of 2 inpatient studies and the sponsor's meta-analysis of the long-term data are summarized in this review. Characteristics of the 8 efficacy studies are summarized in the table below. The studies are presented in the table and in this review in chronological order.

STUDY	DATE INITIATED	TREATMENT ARM AND PEAK DOSE ALLOWED (MG/DAY)	# OF PATIENTS EVALUATED	DURATION OF TREATMENT
030A2-0004/0005 Dose Titration	6/85	Nefazodone 250 Imipramine 250 Placebo	74 75 70	6 weeks
030A2-0007 Fixed Dose	12/85	Nefazodone 50 Nefazodone 100 Nefazodone 200 Nefazodone 300 Placebo	43 46 46 41 47	6 weeks
03A0A-003 Dose Titration	11/86	Nefazodone 250 Nefazodone 500 Imipramine 250 Placebo	51 50 50 52	6 weeks
03A0A-004A Dose Titration	4/87	Nefazodone 300 Nefazodone 600 Placebo	77 76 77	6 weeks
03A0A-004B Dose Titration	8/87	Nefazodone 300 Nefazodone 600 Placebo	78 78 75	6 weeks
CN104-002 Dose Titration	7/88	Nefazodone 300 Imipramine 300 Placebo	57 55 57	6 weeks
CN104-006 Dose Titration	1/89	Nefazodone 600 Imipramine 300 Placebo	80 79 78	8 weeks
CN104-005 Dose Titration	2/89	Nefazodone 600 Imipramine 300 Placebo	86 83 91	8 weeks

MEMORA ·I

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

Date: NOV 20 1991

From: Mathematical Statistician (HFD-713)

Subject: Problems with Nefazodone analyses (NDA 20-152)

To: File (NDA 20-152, Nefazodone)

There are three main problems within the analyses the sponsor presents in the original Nefazodone NDA submission. The sponsor should reanalyze the data to address these issues. The following information should be conveyed to the sponsor.

The first issue involves the transformation of two secondary efficacy variables. In all of the trials, the 7 point scores for CGI Doctor's Opinion of Improvement and Patient's Global Assessment were collapsed into dichotomous variables whose categories were responder/non-responder. The criterion for determining whether subjects were classified as "responders" or "non-responders" is not provided. All trials using the dichotomized version of these scores should be reanalyzed using the original 7 point scores.

The second issue concerns the designation of centers within individual trials. While there are no exact definitions of what constitutes a center, trial CN 104-005 presents an example of what should not be considered a center.

The sponsor states that trial CN 104-005 contains two centers. An examination of the list of investigators and their addresses reveals that each center contains numerous subcenters, and several investigators are associated with each subcenter. Appendix C-1 lists 6 subcenters within Center 001:

1) Philadelphia, PA; Drs. Berwish, Chung, Csanalosi, Schweizer, Mandos and Weiss; 30 patients
2) Philadelphia, PA; Drs. Amsterdam, Berwish and James; 36 patients
3) Wilmington, DE; Drs. Clary, Swenson and Gross; 18 patients
4) Willingboro, NJ; Drs. Fox and Francesco; 24 patients
5) Charleston, WV; Dr. Puzzouli; 13 patients
6) Charleston, WV; Drs. Cavender, Cavender, Harshbarger and Weise; 24 patients.

A similar list shows Center 002 contains 7 subcenters.

It is important to note that the subcenters in Center 001 cover 4 states and 3 metropolitan areas (Philadelphia, Wilmington, Charleston); based on geography alone, the claim that they constitute a single center is dubious. If all the investigators involved in this center received the same training in the administration of the instruments used to collect information and the patients were appropriately randomized, then perhaps Center 001 can be treated as a single center. Center 001 could be broken into 3 centers reflecting the 3 metropolitan areas and analyzed accordingly. The sponsor must either regroup the investigators into reasonable centers and reanalyze the data accordingly or provide an adequate explanation of why the above subcenters constitute a single center. The same attention must be paid to Center 002.

Further complications are evident in trial CN 104-005. Dr. Rickels is listed as the principal investigator for the trial and for Center 001 but did not examine any patients. Dr. Schweizer, however, examined patients as an investigator at subcenter 1 in Center 001 but examined no patients in Center 002 where he was a co-principal investigator with Dr. Rickels.

Other multicenter trials which potentially contain subcenters within individual centers are: 03AOA-003, 030A2-0007, CN 104-002 (Feighner), CN 104-006 (Fabre/-Cohn), and 03AOA-004A (Claghorn/Rush). Trial 03AOA-003 contains one large center and four very small centers. The sponsor chose the largest center for analysis and dropped the other four. An analysis that somehow accounts for the four small centers (e.g. grouping them into one center and performing a two center analysis) should be provided.

The sponsor should provide analyses of these studies adjusting for subcenters along with the rationale for defining subcenters.

The third problem involves trial 030A2-0004/030A2-0005. As the trial number suggests, two protocols have been combined to create one trial. Each protocol called for a multicenter trial with three centers; the two protocols together create one multicenter trial with six centers. The sponsor must explain why these protocols were combined and whether they were combined before or after subject recruitment began. This trial will require further attention if data were combined after subject recruitment began, especially if two randomization schemes were employed.

Kenneth R. Petronis, M.S., M.P.H.
Mathematical Statistician

concur: Dr. Nevius 11-20-91

cc:
Orig. NDA 20-152
HFD-120
HFD-120/PLeber
HFD-120/EHearst
HFD-120/PDavid
HFD-713/SDubey [File: DRU 1.3.2]
HFD-713/ENevius
HFD-713/KPetronis
Chron.
KRPetronis/x4710/SERB:krp:11/19/91

This memorandum contains 3 pages.

PHASE II/III STUDIES

PLACEBO-CONTROLLED TRIALS

CN104-045 USA	Multicenter, double-blind, randomized, placebo-controlled, parallel-group; depressed outpatients (N=220), ≥ 18 years of age, 81 men and 139 women; Nefazodone 100-400 mg/day. QD or BID; 6 weeks.
CN104-054 USA	Multicenter, double-blind, randomized, placebo-controlled, parallel-group; depressed outpatients (N=191), ≥ 18 years of age, 62 men and 129 women; Nefazodone 100-600 mg/day, divided doses, BID; fluoxetine 20 mg/day, QD; 8 weeks.
CN104-056 USA (ongoing)	Multicenter, double-blind, randomized, placebo-controlled, parallel-group; depressed outpatients (N=80), ≥ 65 years of age, 28 men and 42 women; Nefazodone 100-400 mg/day, divided doses, BID; fluoxetine 20 mg/day, QD; 8 weeks.
CN104-058 USA (ongoing)	Multicenter, double-blind, randomized, placebo-controlled, parallel-group; depressed outpatients (N=57), ≥ 65 years of age, 24 men and 33 women; Nefazodone 100-600 mg/day, divided doses, BID; 6 weeks.
CN104-076 USA (ongoing)	Multicenter, double-blind, randomized, placebo-controlled, parallel-group; depressed inpatients (7 days during baseline and 7 days on double-blind medication) (N=28), ≥ 18 years of age; Nefazodone 100-600 mg/day, divided doses, BID; 6 weeks.

ACTIVE-CONTROLLED TRIALS

CN104-027 Germany (ongoing)	Multicenter, double-blind, randomized, parallel-group; elderly depressed inpatients (N=44), ≥ 60 years of age, 40 men and 4 women; Nefazodone 50-150 mg/day, divided dose, BID; maprotiline 25-75 mg/day, divided doses, BID; 6 weeks.
CN104-031 UK, Holland (ongoing)	Multicenter, double-blind, randomized, parallel-group; outpatients with mood disorders (N=39), ≥ 18 years of age, 15 men and 24 women; Nefazodone 100-200 mg BID, 500 mg QD; Fluoxetine 20-40 mg QD; 6 weeks.

CN104-052 Italy (ongoing)	Multicenter, double-blind, randomized, parallel-group; outpatients with mood disorders, (N=97), ≥ 18 years of age, 28 men and 69 women; Nefazodone 200-600 mg/day, divided doses, BID, fluoxetine 20-40 mg/day, QD; 8 weeks.
CN104-055 France (ongoing)	Multicenter, double-blind, randomized, parallel-group; patients with mood disorders (N=45), ≥ 18 years of age, 18 men and 27 women; Nefazodone 200-600 mg/day, divided doses, BID; fluoxetine 20 mg/day QD; 8 weeks.

UNCONTROLLED TRIALS

CN104-007 USA	Multicenter, open; outpatients with Obsessive Compulsive Disorder (N=20), ≥ 18 years of age, 10 men and 10 women; Nefazodone 100-600 mg/day, divided doses, QD or BID; 8 weeks.
CN104-051 Italy (ongoing)	Multicenter, open; outpatients with mood disorders (N=68), ≥ 18 years of age, 25 men and 43 women; Nefazodone 200-400 mg/day, divided doses, BID; 8 weeks.
CN104-080 USA (ongoing)	Multicenter, open; patients with mood disorders (N=85), ≥ 18 years of age, 34 men and 50 women; Nefazodone 100-600 mg/day, divided doses, BID; 8 weeks.
CN104-903 USA (ongoing)	Multicenter, open, compassionate use study; depressed patients (N=12), ≥ 18 years of age; Nefazodone 100-600 mg/day, divided doses, BID, up to 12 months.

a One patient received only placebo (during the baseline phase) and was inadvertently included in the nefazodone database.

S.D. = single dose; M.D. = multiple dose; QOD = every other day; QD = daily; sol. = solution; i.v. = intravenous; p.o. = orally; A.M. = morning; P.M. = evening; BID = twice a day; TID = three times a day.

findings of these analyses are summarized in the sections that follow.

7.4.1.1 Severity of Depressive Symptoms

The objective of this meta-analysis was to determine if the severity of depression at baseline affected response to nefazodone. Two criteria were used to stratify the sample of patients: a Baseline CGI Severity of Psychopathology score of at least 5 (markedly ill); or a Baseline HAM-D-17 score of at least 27. The HAM-D stratification results were consistent with the CGI stratification analysis, hence only the latter are presented here.

For more severely ill patients (CGI Severity Score ≥ 5), both nefazodone and imipramine produced significantly greater improvement than placebo treatment in HAM-D-17 (change from Baseline) and in responder rates (based on the CGI Doctor's Opinion of Improvement). The degree of improvement was similar with both nefazodone and imipramine treatments.

For those patients categorized as being moderately ill (CGI Severity Score ≤ 4) both active agents were superior to placebo as well. Both nefazodone and imipramine produced significantly greater improvement than placebo treatment (HAM-D assessment and CGI Global responder rates), and the extent of improvement was similar for the two treatments.

7.4.1.2 Melancholia

A meta-analysis stratifying for patients who met DSM-III or DSM-III-R criteria for Major Depression, Melancholic Subtype, was done to evaluate nefazodone's efficacy as a function of diagnostic subtype. Approximately half of the patients from the adequate and well-controlled studies met criteria for Melancholic Subtype.

In the subgroup of patients with Melancholic Subtype, both nefazodone and imipramine treatments were significantly superior to placebo. Both active treatments produced comparable levels of improvement based on change from baseline in HAM-D-17 and HAM-D Retardation Factor scores. Both treatments resulted in approximately 60% of patients being rated as treatment responders (CGI Improvement Scale: rating of "much improved" or "very much improved").

Patients treated with nefazodone with non-melancholic Major Depression (47% of the sample) also improved significantly in HAM-D-17 (change score) and CGI Improvement Scale compared to placebo. In the moderately ill depressed patient group, imipramine treatment also had a higher CGI Global response rate than placebo, but mean improvement in HAM-D-17 (change score) with imipramine treatment compared to placebo treatment showed only a trend favoring active drug.

7.4.1.3 Recurrence

The objective of this meta-analysis was to determine nefazodone's efficacy in patients with a history of depressive episode before the index episode of depression (recurrent episode) as compared to the therapeutic response of patients during their first depressive episode (single episode). Among patients with recurrent episodes of depression, those treated with nefazodone or imipramine improved more than patients receiving placebo treatment, based on significant differences in HAM-D-17 Total, Retardation Factor, and CGI Improvement ratings at end of treatment.

Results were similar for those patients with single episode depression. Nefazodone and imipramine treatments produced significantly greater

improvement than did placebo on che three principal efficacy outcome measures.

In summary, nefazodone and imipramine were as effective in treating patients with recurrent depressive episodes as those with a first depressive episode. The extent of improvement was similar for the two active drug treatments in these groups.

7.4.1.4 Anxiety

A meta-analysis of 6 placebo-controlled trials where Hamilton Anxiety (HAM-A) ratings were available examined the association of severity of anxiety symptoms and response to treatment. Baseline Hamilton Anxiety (HAM-A) Total scores were used to stratify patients into highly anxious (HAM-A $\geq$ 19) or less anxious (HAM-A < 19) patient groups. Compared to the treatment response of the placebo group there was significantly greater improvement of the nefazodone and imipramine groups in CGI: Doctor's Opinion of Improvement, and HAM-D-17 scores (mean). This is true for both the highly anxious and less anxious patients with Major Depression. Nefazodone's effects sre equal in patients with Major Depression, irrespective of baseline level of anxiety.

7.4.2 DOSING STRATEGY

Three study designs employing differing nefazodone dosing strategies were conducted during nefazodone's clinical development in order to obtain complementary information about therapeutic dose: fixed drug doses vs. placebo; titration of drug dose within two dose ranges vs. placebo; and dose-titration vs. placebo where nefazodone could be administered within the lower-dose range or across the full therapeutic dose range. It was recommended in most protocols that nefazodone be administered b.i.d. Target dose ranges were generally from 100-300 mg/day (lower dose range) or 100-600 mg/day (higher dose range).

Meta-analyses of the results of placebo-controlled, flexible-dose titration trials (nefazodone n=696) were conducted to assess dose-response relationships. These analyses corroborated the findings of individual studies, yielding a quadratic dose-response curve showing best response rates for patients receiving endpoint doses of 300-500 mg/day.

The overall results of these analyses provide information to guide the clinician in dosing nefazodone appropriately. Nefazodone therapy should usually be initiated at 200 mg/day (100 mg b.i.d.) with dose increases for most patients, after assessing response to drug, to 300 or 400 mg/day within the first two weeks of treatment. For some patients a subsequent increase to 500 mg/day may be needed to maximize response. At the highest dose (600 mg/day) nefazodone was found to be safe although associated with lower response rates than at lower doses, suggesting that the maximum dose should not exceed 600 mg/day. Separate studies of patients $\geq$ 65 years of age indicate that the therapeutic dose is lower for the elderly (100-400 mg/day).

7.4.3 MAGNITUDE OF DRUG EFFECT

In three of the studies (03A0A-004B, 03A0A-003-2191, and CN104-005) nefazodone given in therapeutic doses is the treatment regimen consistently associated with favorable response. The magnitude of treatment effect observed in these studies is both statistically and clinically significant, with response rates ranging from 58% to 66%, compared to responder rates of placebo control groups that are at least 19% lower than the comparative nefazodone group. The mean difference in HAM-D improvement scores between the nefazodone and placebo treatment

groups varied from 3.2 to 4.2 change units in favor of nefazodone; improvement with imipramine treatment was generally similar.

Findings of a fourth dose-titration study (CN104-002) in which the nefazodone dose was limited to a maximum of 300 mg/day (dose range 50-300 mg/day) show that this lower dose range study also detected therapeutic benefit of nefazodone treatment. The treatment effect was less compared to the imipramine treatment effect, presumably due to the lower dose range for nefazodone in relation to the imipramine dose. The magnitude of the change from Baseline in the HAM-D-17 Total score compared to placebo in this study was intermediate between that of treatment groups where nefazodone has been administered in its therapeutic dose range or a lower range in other studies.

7.4.4 MAINTENANCE OF EFFECT - LONG TERM EFFICACY

An approach undertaken by Bristol-Myers Squibb is to evaluate long-term efficacy utilizing the double-blind continuation treatment experience of patients who successfully completed short-term treatment in a double-blind, placebo-controlled efficacy study[1]. The decision to continue double-blind therapy was made by the treating physician based on initial clinical response of the patient. This double-blind extension phase was incorporated in all controlled nefazodone efficacy trials conducted by Bristol-Myers Squibb (where permitted by health authorities).

A survival meta-analysis of long term data derived from the double-blind extension phase of 6- and 8-week controlled trials of nefazodone, where drug treatment effect was detected, was performed Patients who had responded to treatment with nefazodone, imipramine, or placebo during the initial phase could remain on double-blind treatment for 6 months if continuation therapy was judged to be clinically indicated by the treating physician. During the long-term extension phase discontinuation for lack of efficacy was used as an indicator of relapse. Discontinuation for treatment failure (i.e. toxicity or lack of efficacy) during the entire course of the study (acute phase and long-term extension phase) was used as an indicator of the net benefit of continuing drug treatment.

Survival analysis was performed using the Kaplan-Meier method to estimate survival curves for time to discontinuation. Log rank tests stratified by study were used to assess pairwise differences in time to treatment discontinuation for nefazodone (n=163) versus placebo (n=94) and imipramine (n=84) versus placebo. During the long-term extension phase both drugs were effective in preventing relapse, $p = 0.04$ for nefazodone and $p = 0.03$ for imipramine.

The net benefit of drug treatment was evaluated in a similar survival analysis, in which time to treatment failure was assessed from start of treatment. Nefazodone (n = 356) demonstrated superiority (p vs placebo = 0.03) over placebo (n = 278), but imipramine (n = 194) did not (p vs placebo = 0.31).

[1]Greenhouse, Joel B., Stangl, Dalene, Kupfer, David J. Prien, Robert F. "Methodologic Issues in Maintenance Therapy Clinical Trials" Archives of General Psychiatry 48: 313-318, 1991.

7.5 Efficacy Summary

Study 03A0A-004B is positive with positive results on three efficacy variables but not on the HAMD depressed mood item. Study CN104-006, center two, is positive with a HAMD total results borderline significant but the other three variables positive. Study CN104-005, center two, is positive with very positive results from both LOCF and OC data sets. Overall Nefazodone demonstrates efficacy for the higher dose ranges in these double blind, controlled trials.

8.0 Safety Findings:

8.1 Methods:

My approach to evaluating the safety of nefazodone included the following: (1) an assessment of the routinely collected and reported safety data in order to describe the common adverse event profile for the drug, (2) a review of all patient narratives for discontinuations for adverse experiences, serious adverse experiences, and deaths, (3) statistical comparisons using the Fisher's Exact Test for a pool of double-blind controlled trials providing comparisons of laboratory findings, vital signs, ECG findings and adverse events, (4) a search of the medical literature for safety reports, (5) and a review of all information available in the data base related to drug demographic interaction, drug disease interaction, drug/drug interactions, withdrawal phenomenon/abuse potential, and human reproductive data.

The following findings are based on the safety update data base except as otherwise noted. The cut-off dates are listed in 5.1.1.

8.2 Deaths:

Three nefazodone-treated patients and one imipramine-treated patient died during treatment in an open or double-blind short-phase study. None of the deaths were attributable to the use of study medication. Table 8.2.1 gives information regarding the nefazodone- and active control-treated patients who died in a short-term trial.

Table 8.2.1
Deaths in Nefazodone- and Active Control-Treated Patients
Short-Term Safety of Nefazodone

Protocol Number	Study Center-Patient Number	Maximum Dose (mg/day)	Study Day	Cause of Death
Nefazodone				
CN104-003	001	300	14	Suicide by hanging
CN104-016	001	300	24	Suicide by drowning
CN104-029	001	200	33	Suicide by hanging
Imipramine				
CN104-005	002	100	15	Homicide-fatal gunshot wound

Stat

The first trial listed in the table above (Study 030A2-0004/0005) will not be reviewed in detail but will be included in summary tables in the appendix. The nefazodone dose (175 mg/day) used in this trial was less than half the dose generally shown to be required to demonstrate efficacy for nefazodone over placebo; therefore it is not surprising that this study failed to differentiate nefazodone from placebo.

For the other 7 trials, the focus of this review will be the results of four efficacy variables; HAM-D 17 Total, HAM-D depressed mood item, Clinical Global Impression Severity of Illness score and Global Improvement score. For a description of other efficacy variables measured in these trials, see Dr. Hearst's medical review.

Nefazodone dosing is discussed on pages 44 to 48 of this review. Summary Tables II. and III. on pages 55 and 56 summarize the dosing in each trial.

Basically the same statistical analyses were performed by the sponsor for all the studies. Only data from the intent-to-treat (ITT) sample was analyzed and results for both last-observation-carried-forward (LOCF) and observed cases (OC) analyses were presented. All four efficacy variables were analyzed using an analysis of variance model including terms for treatment, treatment by center and center. Effects were assessed using Type III/IV sum of squares. Where baseline differences occurred, an analysis of covariance model was used with baseline as the covariate. (The assumption of equal slopes for this model was tested by the sponsor and results were presented in an appendix to the study report.) In addition, the CGI scores and the HAM-D Depressed Mood Item were analyzed categorically using the Cochran-Mantel-Haenszel procedure.

For each study, tables showing the number of patients on study and the reasons for dropouts are provided. These tables were created using the sponsor's data in Appendix E, Table 5.2 and Table 5.4 of each study report. The number of patients on study are the number of patients who completed the study week and entered the next week.

The demographics across all the studies were generally consistent. All the patients were all treated as out-patients. Approximately two-thirds of the patients enrolled in these 8 placebo-controlled trials were women. More than 85% of the patients were white and the average age of the patients was about 39 years (range of 18 to 81 years).

To enter these trials patients were required to have a score of at least 20 on the HAM-D 17 Total. To establish eligibility, a baseline washout period varying from 4 days to 4 weeks preceded the treatment period.

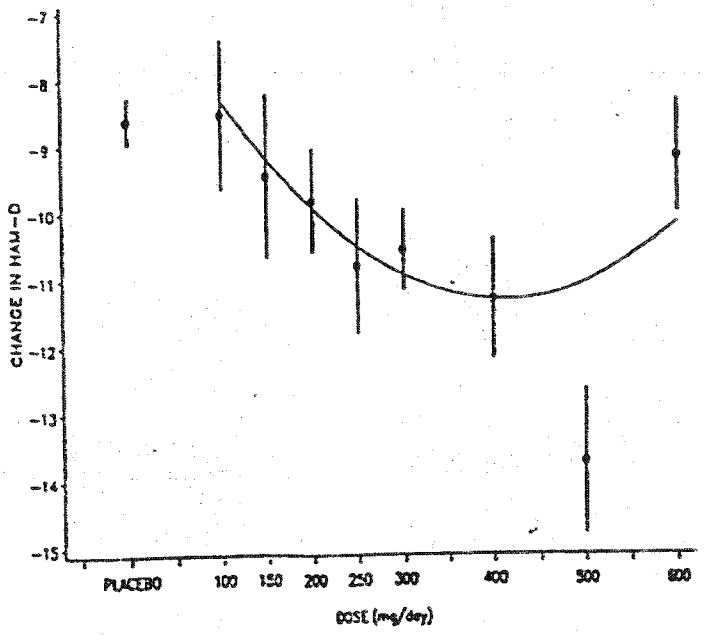
Dosing

The dosing data in all trials was presented as modal dose. The mean modal dose refers to the mean of the patients' weekly modal doses.

High dose in this section refers to titration of the dose to peaks of 500 or 600 mg/day while low dose refers to doses under 300 mg/day.

The sponsor examined the dosing effects of nefazodone by pooling the nefazodone data from the 7 titration studies (excluding the fixed dose study). An ANCOVA with baseline HAM-D and study as covariates revealed a U-shaped relationship between dose and HAM-D change from baseline. The sponsor concluded that "most patients experience optimal improvement when receiving doses between 400 and 500 mg/day". It is clear from the graph below that the curve from about 350 to 600 mg/day is not well-defined and that it is difficult to verify the sponsor's conclusion.

HAM-D-17 Total Score:
Mean Change from Baseline *vs.* Endpoint Modal Dose
Placebo-Controlled, Dose-Titration Studies
Nefazodone Overview of Clinical Findings



Reviewer's Comments on Dosing

This reviewer was concerned that the modal dose may overestimate the dose given since missed doses would not be considered. From data provided by the sponsor, this reviewer found that the mean modal dose was about 5 to 15 mg/day higher than the mean dose, in general. Compliance then appears to have been high so the use of modal doses does not appreciably overestimate the dose used. (It should be noted here that the sponsor presented compliance data by patient but no summary data was presented in the submission.)

Low Dose Nefazodone Versus High Dose Nefazodone

The sponsor has conducted 4 placebo-controlled trials which utilized multiple doses of nefazodone. One fixed dose study (Study 030A2-0007) was conducted and has been already discussed in this review. This study failed to show a relationship between dose and efficacy (see Figure 1 on page 5), probably due to poor trial design or insufficient dose range.

The other 3 placebo-controlled trials were dose-titration trials of 2 dose levels of nefazodone. The HAM-D Total data by treatment group for these trials is depicted in Figures 3 (page 13), 4 (page 18) and 5 (page 21). From these figures it is clear that the low dose of nefazodone is not more effective than placebo. (Also see Summary Table III on page 52.) In general, pairwise comparisons performed by the sponsor showed that the high dose was significantly different from both placebo and low dose and that the low dose was not different from placebo. This reviewer does not think that a trend analysis would provide additional information on the relationship between the 2 doses since the trend would most likely be positive primarily due to the difference between the high dose and placebo.

High Dose Nefazodone

Five studies had a high dose nefazodone treatment arm; Studies 03A0A-003, 03A0A-004A + B, CN104-006 and CN104-005. Only Study 03A0A-004A is not looked at by center because the results for the 2 centers were very similar.

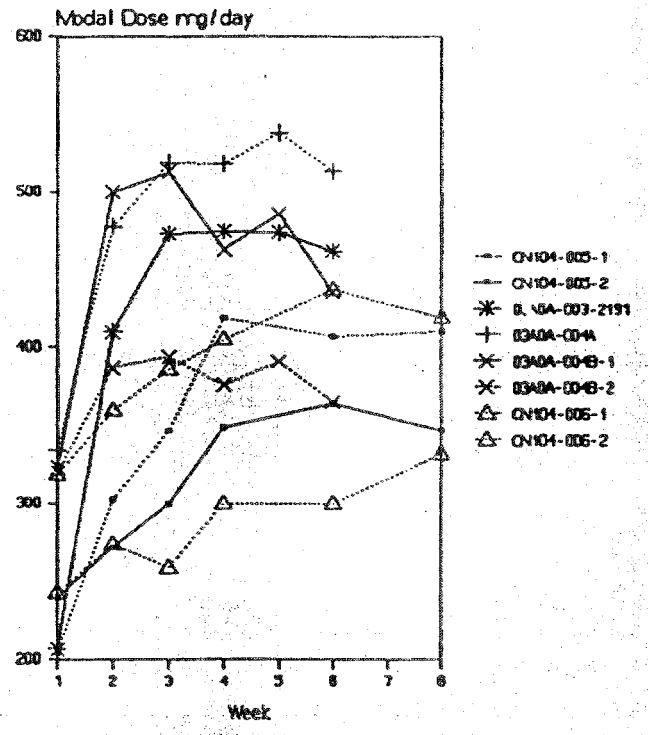
This reviewer looked at the effects of high dose nefazodone in two ways; 1) plotted the mean modal doses over time for the 5 studies that used high dose nefazodone (Figure 11) and 2) graphed the HAM-D effects by dose for the completers in each of the 5 studies (Figure 12). The objective of the first graph is to see if there is a relationship between the escalation of the dose and the presence of a positive outcome; note on this graph that solid lines denote centers that showed positive effects. The objective of Figure 12 is to see if the final dose level was related to the final response for completers.

From Figure 11[1] it can be seen that dosing was increased during the first 3 to 4 weeks of the studies and then maintained for the remaining weeks as dictated by the protocols. There appears to be no clear-cut relationship between the escalation of dosing and trial outcome. The only similarities are between Center 2191 of Study 03A0A-003 and Center 1 (Mendels) of Study 03A0A-004B; both show peak doses at Week 3 above 450 mg/day. (This seems to support the sponsor's recommendation of doses of 400 to 500 mg/day.) The other positive center was Center 2 of Study 104-005; the doses here are considerably lower, peaking at about 350 mg/day (it should be recalled that the placebo response was unusually low in this center which may suggest that the center is atypical in other ways.) The center showing the lowest doses (Center 2 of Study CN104-006; lowest dotted line with triangular symbols) produced borderline significant results for the HAM-D 17 total (see Table 24 on page 32).

Figure 11, when presented at the Psychopharmacologic Drugs Advisory Committee on July 19, 1993, stimulated a discussion of nefazodone dosing and response. Subsequently, this reviewer requested additional dosing data from the sponsor to examine dosing in each study. That data is summarized in the table on the following page. All patients treated with nefazodone in these studies are included in this table. Remember in the 03A0A studies, patients were titrated to a low or a high dose of nefazdone while in the CN104-005 and 006 studies all patients could be titrated to a high dose of 600 mg/day.

This reviewer performed regression analyses for each study to examine the relationship between the mean overall modal dose (the mean of the weekly modal doses) or the modal dose at the last week treated (LOCF dose) and the HAM-D 17 Total change from baseline (LOCF). The results were the same for both the overall and last dose.

Figure 11. Dosing by Study and Center
High Dose Nefazodone



[1] Solid lines represent centers that showed statistically significant treatment effects on the HAM-D 17 Total.

As might be expected, only the results from the low/high dose studies (the 03A0A studies) showed a statistically significant relationship between dose and HAM-D 17 total change from baseline. It is most interesting to note that a significant dose relationship was observed in Study 03A0A-004A (the only negative placebo-controlled study).

Dosing and Response Summary Data

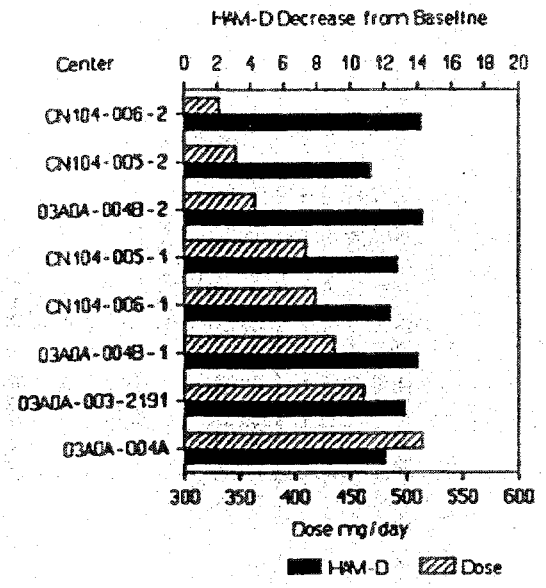
	Mean Overall Modal Dose				
STUDY LOCF Mean Results	≤200 Mean (SD)	≤300 Mean (SD)	≤400 Mean (SD)	≤500 Mean (SD)	>500 Mean (SD)
03A0A-003-1					
N	57	37	15	28	NA
Modal Dose mg/day	46 (94)	259 (35)	410 (93)	500 (0)	
HAM-D 17 Change	-6.1 (8.6)	-9.6 (7.5)	-8.1 (7.1)	-13.2 (8.2)	
03A0A-004A					
N	27	62	13	12	39
Modal Dose	172 (76)	289 (46)	369 (75)	475 (122)	590 (38)
HAM-D 17 Change	-5.2 (5.5)	-9.1 (7.1)	-11.5 (6.8)	-8.3 (9.8)	-10.4 (7.4)
03A0A-004B					
N	28	67	18	28	15
Modal Dose	139 (63)	266 (70)	333 (141)	453 (123)	587 (35)
HAM-D 17 Change	-10.7 (8.9)	-10.4 (8.6)	-14.6 (6.5)	-11.6 (8.0)	-13.2 (6.6)
CN104-002					
N	15	42	NA	NA	NA
Modal Dose	193 (42)	284 (32)			
HAM-D 17 Change	-9.4 (7.9)	-11.3 (7.1)			
CN104-005-1					
N	8	5	17	10	1
Modal Dose	175 (71)	280 (45)	418 (101)	530 (95)	600
HAM-D 17 Change	-10.1 (10.2)	-14.6 (5.8)	-14.3 (6.4)	-11.3 (6.8)	-15.0
CN104-005-2					
N	12	11	15	2	5
Modal Dose	158 (67)	273 (79)	393 (59)	550 (71)	520 (178)
HAM-D 17 Change	-9.9 (7.4)	-11.8 (6.5)	-12.1 (7.6)	-10.5 (7.8)	-10.6 (6.2)
CN104-006-1					
N	6	12	12	5	6
Modal Dose	167 (52)	292 (79)	433 (65)	540 (134)	600 (0)
HAM-D Change	-8.5 (4.6)	-9.5 (7.4)	-8.8 (8.0)	-0.6 (7.1)[1]	-8.8 (8.1)
CN104-006-2					
N	11	15	9	3	1
Modal Dose	173 (47)	287 (74)	433 (122)	600 (0)	600
HAM-D 17 Change	-12.1 (9.3)	-12.7 (7.4)	-12.1 (5.9)	-10.0 (10.6)	-10.0

no pbo large fish BL

[1] Two of the 5 patients showed increases in HAM-D 17 total (+7 and +5). Only 1 of the 5 patients completed the study (change = -11.0).

In Figure 12, the results are ordered by increasing final dose. There is clearly no relationship between the final dose used and the HAM-D change from baseline for the completers looking across the studies. This is a rather simplistic approach to the dose-effect relationship for the studies combined, however since the studies had different designs and were not designed to study this relationship, a more complex approach is not warranted.

Figure 12. Dose and HAM-D For Last Week Completers Only



Efficacy results from the 8 placebo-controlled studies suggest that doses below 300 mg/day are not effective. The optimum range of dosing is not clear since a range of doses above 300 mg/day was not adequately studied (see the table on the previous page).

Summary

The results for the 8 placebo-controlled studies are summarized in Summary Tables I, II and III on pages 54 to 56. Summary Tables I and II present details about the 5 studies that had a high dose nefazodone treatment arm while Summary Table III presents the results for the low dose nefazodone groups by study. This reviewer separated the results for the two arms because the results for low dose nefazodone were consistently not different from placebo; for some centers the placebo change from baseline was larger than the change observed for the low dose group. Also, in studies with more than one dose of nefazodone, no dose-response relationship was noted. To compare the low and high dose nefazodone arms within a trial, the reader should refer to the figures provided in the text of this review.

Summary Table II presents the HAM-D 17 Total results by study for high dose nefazodone, placebo and imipramine. The HAM-D 17 Total change from baseline means (LOCF) for the studies which provide statistical evidence of efficacy for high dose nefazodone over placebo are bolded and shaded in the table. Note that the magnitude of the nefazodone response is highly consistent across the studies whereas the placebo response is not.

The table below summarizes this reviewer's interpretation of the results by study; for more details see the referenced pages.

Study	Reviewer's Comments	Statistical Evidence[1]	Reference Pages
030A2-0004/0005	First study; dose too low.	Failed	Not reviewed
030A2-0007	Inadequate fixed-dose design; low dose range.	Failed	3-6
03A0A-003	3 centers discontinued enrollment.		7-10
Center 2191	Longitudinal data analyses yielded positive results similar to the LOCF results.	Positive	11-14
03A0A-004A	Lack of active control group makes interpretation difficult. OC results favor placebo.	Negative	15-18
03A0A-004B	Positive results on 3 efficacy variables; not on HAM-D Depressed Mood item.	Positive	19-22
CN104-002	Dose too low; LOCF and OC results do not agree. Imipramine results were very positive.	Failed	23-26
CN104-006			
Center 1 (Febre)	Very large dropout rate; imipramine failed.	Failed	28-30
Center 2 (Cohn)	HAM-D Total results borderline significant; other 3 variables positive.	Positive	31-34
CN104-005			
Center 1 (Psych.)	Large placebo response; imipramine failed.	Failed	36-38 39-43
Center 2 (Fam. Prac.)	Unusually small placebo response; very positive results for both LOCF and OC datasets.	Positive	

[1] One study which did not show a difference between placebo and nefazodone is considered a negative study due to the lack of an active control group from which to assess the validity of the test situation. Studies which did not show a difference between placebo and nefazodone and also did not distinguish imipramine from placebo are considered failed studies. These studies exhibit the lack of sensitivity of the test situation, therefore the evidence against nefazodone cannot be considered negative. Studies using only a low dose of nefazodone are considered failed studies due to inadequate dosing.

Joy D. Mele, M.S.
Mathematical Statistician

Concur: Dr. Nevius 11-16-93

Dr. Dubey

cc:
Orig. NDA 20-152
HFD-120
HFD-120/Drs. Leber, Laughren and Hearst
HFD-120/Mr. David
HFD-713/Dr. Dubey [File: DRU 1.3.2]
HFD-713/Group 2 File
HFD-713/Ms. Mele
HFD-344/Dr. Lisook
Chron.

Mele/x1780/SERB/WordPerfect-nef.rev/June 30, 1993
This review consists of 56 pages.

SUMMARY TABLE I
TRIALS WITH HIGH DOSE NEFAZODONE ARM

STUDY	ENROLLMENT DATES	INVESTIGATORS	DESIGN	NEFAZODONE N (%)[1]	PLACEBO N (%)	IMIPRAMINE N (%)
03A0A-003		Canadian	High/Low Dose Titration 6 Weeks			
2191	11/86-6/90	Fontaine	4 arms	44 (75%)	45 (53%)	45 (58%)
OTHERS	5/87-4/88	5 centers	2 nef/pla/imp	6 (67%)	7 (71%)	6 (67%)
03A0A-004A			High/Low Dose Titration 6 Weeks			NA
CENTER 1	4/87-2/90	Claghorn	3 arms	40 (58%)	40 (58%)	
CENTER 2	4/87-5/90	Rush	2 nef/pla	40 (70%)	40 (63%)	
03A0A-004B			High/Low Dose Titration 6 Weeks			NA
CENTER 1	8/87-4/89	Mendels	3 arms	40 (73%)	40 (60%)	
CENTER 2	10/87-5/89	Reimherr	2 nef/pla	40 (85%)	40 (85%)	
CN104-006			Dose Titration 8 Weeks			
CENTER 1	1/89-6/90	Fabre	3 arms	45 (33%)	44 (41%)	46 (41%)
CENTER 2	5/89-4/90	Cohn	nef/pla/imp	43 (65%)	43 (72%)	42 (57%)
CN104-005		Rickels	Dose Titration 8 Weeks			
CENTER 1	2/89-2/90	Psychiatric	3 arms	48 (58%)	48 (69%)	49 (55%)
CENTER 2	6/89-4/90	Family Practices	nef/pla/imp	48 (71%)	47 (55%)	43 (49%)

[1] N is the number of patients randomized and % is the percentage of patients completing the study.

SUMMARY TABLE II
HIGH DOSE NEFAZODONE
HAM-D 17 TOTAL RESULTS

STUDY	NEF MODAL DOSE Mean	NEF HIGH LOCF Mean	PLA LOCF Mean	NEF VS PLA[1] p-value	IMP MODAL DOSE Mean	IMP LOCF Mean	IMP VS PLA p-value
03A0A-003 COMBINED				.90 int. .22			
2191	462 mg	-11.0	-6.8	.03 (.50)	216 mg	-10.8	.04 (.07)
OTHERS	350 mg	-12.2	-15.7	.47 (.41)	194 mg	-11.4	.41 (.32)
03A0A-004A					na	na	na
CENTER 1	518 mg	-10.2	-9.4	.7			
CENTER 2	508 mg	-8.8	-8.4	.9			
03A0A-004B COMBINED		-12.7	-9.5	.02 (.08) int. .70	na	na	na
CENTER 1	436 mg	-11.8	-7.6	.03 (.20)			
CENTER 2	365 mg	-13.6	-11.4	.24 (.24)			
CN104-006 COMBINED				.35 int. .27			
CENTER 1	419 mg	-8.0	-8.6	.72 (.53)	176 mg	-8.9	.85 (.85)
CENTER 2	332 mg	-12.1	-9.2	.09 (.07)	148 mg	-13.0	.03 (.01)
CN104-005 COMBINED				<.001 int. <.02			
CENTER 1	410 mg	-12.8	-11.6	.65 (.15)	189 mg	-10.9	.48 (.12)
CENTER 2	347 mg	-11.2	-4.3	<.001	136 mg	-9.6	<.001

[1] P-values for combined effects and center by treatment effects using LOCF data are listed first followed by p-values for each center. P-values in parentheses are for the OC results.

SUMMARY TABLE III.
LOW DOSE NEFAZODONE
HAM-D 17 TOTAL RESULTS

STUDY	NEF MODAL DOSE - Mean	NEF LOW LOCF Mean	PLA LOCF Mean	NEF VS PLA p-value[1]	IMP MODAL DOSE Mean	IMP LOCF Mean	IMP VS PLA p-value
030A2-0004-5	175 mg	-10.0	-9.8	not done	156 mg	-10.9	not done
030A2-0007 FIXED DOSE	300 mg 200 mg	-10.7 -13.3	-9.8	.60 (.74) .04 (.02)	na	na	na
03A0A-003 2191 OTHERS	 246 mg 217 mg	 -8.2 -6.6	 -6.8 -15.7	 .45 (.55) .08 (.13)p	 216 mg 194 mg	 -10.8 -11.4	 .04 (.07) .41 (.32)
03A0A-004A CENTER 1 CENTER 2	 288 mg 258 mg	 -9.5 -7.2	 -9.4 -8.4	 .97 .50p	 na	 na	 na
03A0A-004B CENTER 1 CENTER 2	 275 mg 224 mg	 -8.6 -11.1	 -7.2 -11.4	 .43 (.75) .84 (.68)p	 na	 na	 na
CN104-002	263 mg	-10.8	-8.2	.08 (.72)	206 mg	-13.8	<.001 (all vars)

[1] P-values are LOCF results followed by OC results in parentheses. A "p" indicates that the results favor placebo over low dose nefazodone.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-152

JAN - 7 1992

Bristol-Myers Squibb Company
Pharmaceutical Research Institute
Attention: Jay K. Gunther, Ph.D.
5 Research Parkway
P.O. Box 5100
Wallingford, Connecticut 06492-7660

Dear Dr. Gunther:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nefazadone Hydrochloride tablets dated and received September 6, 1991.

Reference is also made to a telephone conversation on October 23, 1991, between yourself and Mr. Paul David of this Agency, informing you that a detailed letter requesting reanalysis of certain studies submitted to the original NDA would be forthcoming.

Our Division of Biometrics has completed a preliminary review of the application, and has identified the following three major problems within the study analysis:

1. The first issue involves the transformation of two secondary efficacy variables. In all of the trials, the 7 point scores for CGI Doctor's Opinion of Improvement and Patient's Global Assessment were collapsed into dichotomous variables whose categories were responder/nonresponder. The criterion for determining whether subjects were classified as "responders" or "non-responders" is not provided. All trials using the dichotomized version of these scores should be reanalyzed using the original 7 point scores.

2. The second issue concerns the designation of centers within individual trials. While there are no exact definitions of what constitutes a center, trial CN 104-005 presents an example of what should not be considered a center.

   We note that your application states that trial CN 104-005 contains two centers. An examination of the list of investigators and their addresses reveals that each center contains numerous subcenters, and several investigators are associated with each subcenter. Appendix C-1 lists 6 subcenters within Center 001:

1) Philadelphia, PA; Drs. Berwish, Chung, Csanalosi, Schweizer, Mandos and Weiss; 30 patients
2) Philadelphia, PA; Drs. Amsterdam, Berwish and James; 36 patients
3) Wilmington, DE; Drs. Clary, Swenson and Gross; 18 patients
4) Willingboro, NJ; Drs. Fox and Francesco; 24 patients
5) Charleston, WV; Dr. Puzzouli; 13 patients
6) Charleston, WV; Drs. Cavender, Cavender, Harshbarger and Weise; 24 patients.

A similar list shows Center 002 contains 7 subcenters.

It is important to note that the subcenters in Center 001 cover 4 states and 3 metropolitan areas (Philadelphia, Wilmington, Charleston); based on geography alone, the claim that they constitute a single center is dubious. If all the investigators involved in this center received the same training in the administration of the instruments used to collect information and the patients were appropriately randomized, then perhaps Center 001 can be treated as a single center. Center 001 could be broken into 3 centers reflecting the 3 metropolitan areas and analyzed accordingly. We request that you either regroup the investigators into reasonable centers and reanalyze the data accordingly or provide an adequate explanation of why the above subcenters constitute a single center. The same attention must be paid to Center 002.

Further complications are evident in trial CN 104-005. Dr. Rickels is listed as the principal investigator for the trial and for Center 001 but did not examine any patients. Dr. Schweizer, however, examined patients as an investigator at subcenter 1 in Center 001 but examined no patients in Center 002 where he was a co-principal investigator with Dr. Rickels.

Other multicenter trials which potentially contain subcenters within individual centers are: 03AOA-003, 030A2-0007, CN 104-002 (Feighner), CN 104-006 (Fabre/Cohn), and 03AOA-004A (Claghorn/Rush). Trial 03AOA-003 contains one large center and four very small centers. One approach for this study would be to analyze the large center alone in addition to performing a two-center analysis with the four small centers combined as one center.

Additionally, please provide analyses of these studies adjusting for subcenters along with the rationale for defining subcenters.

The enzyme systems metabolizing nefazodone and its intermediary metabolites have not been identified; CYP450 IID6 does not appear to be involved, but nefazodone might be a substrate for CYP450 IIIA4. The latter conjecture derives from the observations that 1) the clearances of both triazolam and alprazolam are significantly reduced in patients treated with nefazodone and 2) that CYP450 IIIA4 is believed to be involved in the catabolism of these 2 triazolo-benzodiazepines. (If so, this holds important implications for the concomitant use of not only nefazodone and the triazolobenzodiazepines but drugs like astemizole and terfenidine; See comments in safety section).

Effectiveness for Use:

Evidence of effectiveness in acute depression

The Division's review team has concluded that the reports submitted to the file of the Serzone NDA provide 'substantial' evidence of nefazodone's efficacy as an antidepressant drug product. Although the PDAC AC [July 19, 1993] unanimously endorsed this conclusion, the basis for it requires careful explication. Indeed, had it not been for the extremely painstaking and scholarly review by Dr. Joy Mele[1] of the 8 nominally adequate and well controlled clinical trials[2] that the sponsor submitted to the NDA, a negative view of the evidence supporting the effectiveness of nefazodone might well have emerged. The reason is that the Serzone NDA presents a showcase of virtually every knotty and vexing problem that confront those who conduct and analyze clinical investigations intended to assess the effectiveness of antidepressant drug products.

Among the clinical studies reported to the NDA as nominally adequate and well controlled are those that evaluated subtherapeutic doses of nefazodone (i.e., **030A2-0004/0005**), those that produced inconsistent

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[1] The agency's biostatistician who performed the primary review of the application

[2] controls employed were either placebo alone or both imipramine and placebo

results (i.e., **030A2-0007**: a fixed dose study in which the 200 mg/day placebo difference attains statistical significance but the 300 mg/day placebo difference does not even come close), those that lacked assay sensitivity (i.e., **03AOA-004A, CN104-006-site 1** and **CN104-005-site 1** all were unable to discriminate imipramine, an antidepressant of known effectiveness, from placebo). Treatment by investigator (i.e., clinic or site) interactions confounded the analysis of 3 of three important multiclinic studies (i.e., **03AOA-003, CN104-006** and **CN104-005**)[3]. Most studies, including those that were eventually deemed to provide support for nefazodone's effectiveness (**CN104-005-site 2** is the best example), were marred by high premature discontinuation rates.

In several studies, analyses based on the last available assessment (i.e., last observation carried forward [**LOCF**]) for all[4] patients randomized disagreed with those based on the subset of patients actually evaluated at the study's protocol specified last visit (i.e., Observed Cases [**OC**]). **Study 03AOA-003/Center 2191** is a good example; the LOCF for the Hamilton Depression Scale total score contrast between 500 mg/d of nefazodone and placebo attains statistical significance ($p = 0.03$), but the OC data set analysis does not ($p = 0.5$)[5].

Because the interpretation of discordant LOCF and OC analyses plays an important role in the review team's analysis of the NDA, a brief digression about the generic aspects of the issue seems worthwhile.

To begin, discrepancies between LOCF and OC analyses of the sort

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[3] It deserves note that single clinics from each of these 3 multiclinic investigations serve as independent sources that contribute to the substantial evidence supporting the effectiveness of nefazodone.

[4] Actually, the LOCF sample is not strictly composed of all patients randomized. Typically, at least as used by DNDP, it consists of all randomized who received at least one dose of the assigned treatment and had at least one on treatment assessment.

[5] Further compounding the interpretation of this particular study is the fact that the imipramine placebo contrast on the same outcome measure nearly achieves significance ($p = 0.07$) in the OC data set based analysis.

described are not uncommon in antidepressant clinical trials. They presumably occur because censoring patterns differ between treatments. To illustrate, depressed patients of the sort typically entered in clinical trials generally improve with the passage of time regardless of treatment assignment. Importantly, the magnitude of the mean within subject improvement is typically larger (e.g., 10 units or so on the Hamilton Depression Scale Total Score over a period of 6 weeks) than the between treatment difference (e.g., 3 to 4 units) upon which the estimate of the experimental drug's treatment effect is derived in either an LOCF or OC analysis. As a consequence, an LOCF analysis, which carries forward scores of patients who discontinue prematurely, tends differentially to penalize treatment groups that have high rates of discontinuations early in the course of a study. Thus, if there are more early discontinuations among placebo than drug assigned patients, (historically, the more typical case), the LOCF analysis tends to provide a larger estimate of a drug's treatment effect than the OC analysis. This is not always the case, however. In particular, when the common untoward side effects of an active treatment are very unpleasant, patients assigned to high doses of the active treatment may withdraw more often early in the study than do subjects assigned to other treatments and, as a consequence, the LOCF analysis can provide a smaller estimate of the drug's effect than the OC analysis. This scenario has been offered as an explanation for the relatively poor track record of clinical trials employing a fixed graded dose parallel design.

Unfortunately, the logic of the explanations offered notwithstanding, it is all too often impossible to determine with certainty what accounts for a discrepancy between the LOCF and OC results in any particular study. As a consequence, the interpretation of the evidence from such controlled clinical studies remains as much a matter of informed judgment as it is a one of objective data analysis[6].

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[6] It deserves note that Masa Takeuchi, Sc.D. employed a generalized estimating equation approach (his review of July 2, 1993) to study 03AOA-003 in an attempt to determine which of its discordant results (OC vs LOCF) provided the more reliable basis for inference about the effect of nefazodone. His analysis suggests that the individuals censored under different treatments were not behaving similarly. Placebo patients who discontinued early were getting worse and those who discontinued on nefazodone or imipramine were getting better. If Dr.

Sources of substantial evidence:

Based upon a review of the reports and analyses submitted to the Serzone™ NDA, the Division's review team, with the endorsement of the PDAC AC, has concluded that there is 'substantial evidence' of nefazodone's efficacy as an antidepressant when it is administered at daily doses in the range of 300 mg to 600 mg. This statement is not intended to imply that every individual involved in the analysis of the data has given the same weight to the findings of each of the controlled clinical trials. To the contrary, it is to be expected that individual analysts will differ about the relative importance and weight they assign to particular pieces of evidence. Nevertheless, these differences acknowledged, all analysts on the agency's review team agree that the same four independent sources of clinical evidence contribute to the finding of substantial evidence.

Among the sources of evidence, **Study 03AOA-004B** is the easiest to evaluate. In this two level titration design, acutely depressed patients assigned to a maximum daily dose of **600 mg** of nefazodone enjoyed an unequivocally better response than those assigned to placebo.

The interpretation of the remaining sources of evidence, **Studies 03AOA-003, CN104-006** and **CN104-005**, is less straightforward, however.

Study **03AOA-003** is a multiclinic trial, and when analyzed as such, provides no support for the effectiveness of nefazodone. Most of the data, however, were obtained at **Center 2191**. Dr. Mele argues persuasively that it is inappropriate, therefore, to apply the usual ANOVA type III SS model to the analysis of the study because, in arriving at its estimate of the effect of treatment, this model gives Center 2191 and centers with only a handful of subjects equal weight (a result of the way least square means are estimated by Type III Sums of Squares). Accordingly, Dr. Mele evaluated Center 2191 as an independent study. Although the OC analysis of Center 2191 is not significant, the LOCF analysis provides support for

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Takeuchi's model is correct, the LOCF analysis result is to be preferred over the OC analysis.

the effectiveness of nefazodone when administered to depressed patients at doses as high as 500 mg/day. Which analysis best reflects the true performance of nefazodone? After reviewing Dr. Takeuchi's analysis of the time trends among scores of the discontinued patients, I am persuaded that the **LOCF** provides a more reliable estimate of nefazodone's treatment effect than the **OC** analysis. Accordingly, I find **Study 03AOA-003/Center 2191** to be an independent source of clinical data that contributes to the overall finding of substantial evidence of the effectiveness of nefazodone when administered at maximum daily doses of 500 mg..

Study **CN104-006** was planned as a two clinic study. Analyzed as a single trial it does not provide support for the efficacy of nefazodone. However, a closer examination of its components suggests a reasonable case can be made for evaluating them separately as independent studies. **CN104-006-site 1, considered on its own, is a 'failed' study**; that is, it lacks the capacity to discriminate imipramine, a standard control of proven effectiveness, from placebo. In contrast, **CN104-006-site 2, has 'assay sensitivity.'** Accordingly, Dr. Mele argues it is not logical to base an estimate of nefazodone's effect on the combined results from two such discrepant centers. While the nefazodone (600 mg/day) placebo contrast at site 2 does not quite achieve nominal significance on the Hamilton Depression Total Score, statistically significant drug placebo differences are found for the 3 other ~~primary outcome measures~~ not primary — really pending over-inclusive (Ham D depression item, Clinical Global Severity and Clinical Global Improvement). Thus, **CN104-006-site 2** provides **evidence** that nefazodone, at doses to a maximum of **600 mg/day**, exerts an antidepressant effect.

Study **CN104-005**, like Study CN104-006, has two centers that provide highly discordant results. The two situations are not precisely parallel, however, because an analysis of the combined LOCF data set from CN104-005's two sites does attain nominal statistical significance for the nefazodone placebo contrast on the Hamilton Depression Scale Total score. However, I believe this is largely a technical distinction. A closer examination of the evidence reveals, as in the case of CN104-006, that the evidence supporting the effectiveness of nefazodone comes predominantly from one of the two centers.

Evaluated as an independent study, **CN104-005- Site 1**, provides no support for the efficacy of nefazodone or, critically, imipramine. Thus, site one is a 'failed' experiment. **CN104-005- Site 2**, in contrast, detected an extremely large difference favorable to both nefazodone (maximum of **600 mg/day**) and imipramine. The difference between the two sites is readily attributable to a difference in placebo response. At site 1, (a psychiatric clinic), all subjects improved regardless of treatment assignment. At site 2 (a general practice environment), there was virtually no placebo response ('p' value <0.001 for the 600 mg/d versus placebo contrast on the LOCF data set). It seems likely that effect estimated from the LOCF analysis of site 2 results is inflated somewhat by the high drop out rate among placebo assigned patients (45%).

Before leaving the issue of nefazodone's effectiveness, it is important to emphasize that there is a critical difference between clinical trials that fail to provide support for a drug's effectiveness and those that fail to provide interpretable evidence. To begin, from an epistemological perspective, it is impossible to prove that a drug does not work. A trial that fails to find a difference between a drug and placebo no more proves the drug is ineffective that a failure to discriminate a standard active control from an investigational drug proves the latter is effective. In short, only differences can be interpreted unambiguously. Based on this reasoning, I regularly distinguish between 'failed' trials and 'negative' ones. In my usage, a failed trial is one in which a standard treatment control cannot be discriminated from placebo; a negative trial is one in which the standard drug can, but the experimental drug cannot. (My definition set differs from Dr. Mele's in that I would not consider a trial without a standard as negative or failed, only uninterpretable).

These points deserve emphasis because a number of studies the sponsor conducted failed to detect differences between nefazodone and placebo. I am not surprised. Several, as Dr. Mele notes, were conducted at inadequate doses. I acknowledge that 03A0A-004A favored placebo over both doses of nefazodone, but, antidepressant studies, our experience long documents, frequently fail even when seemingly adequate doses of drug are administered.

Lack of evidence to support the effectiveness of nefazodone in extended use.

Changing views about the spectrum of activities a drug must possess to be declared an antidepressant.

For a period of close to 30 years it has been customary for experts to accept parallel, blinded, randomized controlled clinical investigations of several weeks (4-6) duration as an adequate test of the efficacy of an antidepressant drug product. Substantial evidence of efficacy, accordingly, has come to be identified with the finding in more than one clinical investigation of such design of statistically significant drug placebo differences on appropriate measures of the depressive syndrome symptomatology (e.g., HAM-D, CGI).

In recent years, there has been growing dissatisfaction with this de facto regulatory requirement, however.

Evidence of effectiveness in sustained use and evidence of a capacity to reduce the risk of recurrent depression is as important as evidence of effectiveness in acute use

Let us consider the reasons why experts in the field currently believe that more than a showing of efficacy in acute use is required to document the clinical utility of an antidepressant.

Current theory holds that an index depressive episode lasts, despite phenomenologic remission induced by pharmacological treatment, anywhere from several months to more than a year. Accordingly, evidence that a drug can cause symptomatic remission at point several weeks after the initiation of treatment cannot possibly speak to its effectiveness in the continued treatment of an index episode (i.e., the drug's capacity to prevent relapse over the duration of the episode). To be fair, it is generally assumed that a drug which suppresses the acute signs and symptoms of depression ought to continue to work, certainly this appears to hold with already marketed drugs. However, what if a new drug did not exhibit sustained effectiveness? Obviously, the marketing of such a product would pose a risk, one that could be avoided if premarket

continuation in gen'l section

[10] Beginning of Discussion: "The most important finding reported here is the dose-response relationship with citalopram. . . best response seen on the 40-mg dose of citalopram and poorest response on placebo, with the 20-mg dose lying in between." According to the primary analysis, neither dose group separated from placebo, though 40 mg was less nonsignificant than 20 mg.

[11] See Appendix. Separate studies, 3 significant and 1 NS, combined post-hoc into one larger (and therefore more highly powered) "study", reported as p≤.05.

[12] See Appendix. Similar to above—4 significant and 2 NS studies combined post-hoc into single very large (N=469) "study", reported as p≤.05.

[13] Two-sample Wilcoxon rank sum test

[14] p<.10 one-tailed (equivalent to two-tailed p<.20) "should be interpreted in the light of the small sample size available." Usual criterion is two-tailed p<.05 (equivalent to one-tailed p<.025).

[15] Lilly asked the FDA to let mixed model repeated measures (MMRM) serve as primary method. FDA did not agree. Review makes clear that LOCF was primary, MMRM secondary, and mentions a memo it sent to Lilly in this regard.

[16] Article states, "Evaluable patients were classified as those who took study medication on or after the 11th day of the double-blind phase, who had efficacy assessments on or after study day 11, and who were not major protocol violators." Analyses based on "evaluable patients" shown in Figure 1 and Table 1, while those based on ITT patients appear pages later in Table 5.

[17] Significant findings mentioned first in abstract relate to those shown in Figure 1 and use observed cases (ie. completers only). Regarding LOCF, mean scores by group mentioned without results from ANCOVA promised in methods section. However, LOCF scores were used in later "trend analysis".

[18] Positive dose-response trend highlighted in abstract and the subject of Table 2. However, finding of trend (with LOCF approach) contradicted by relative performance of doses shown (with observed cases approach) in Figure 1, where 50-75mg dose was outperformed by 25-mg groups on both HAMD and MADRS.

MEMORANDUM

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

DATE: NOV 22 1993

FROM. Group 2 Leader, Statistical Evaluation & Research Branch (HFD-713)

THRU: Satya D. Dubey, Ph.D. SDD
Chief, Statistical Evaluation & Research Branch (HFD-713)

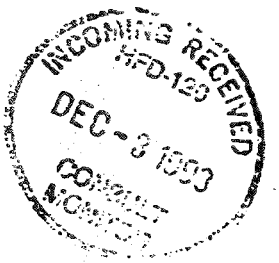
SUBJECT: Serzone (nefazodone) analyses

TO: File (NDA 20-152)

The attached memorandum gives details of longitudinal data analyses performed by Masa Takeuchi, Sc.D., to assist Joy Mele in the review of NDA 20-152. Ms. Mele has utilized these analyses as well as others done by herself and the sponsor in her comprehensive review of this application.

S Edward Nevius
S. Edward Nevius, Ph.D.

cc:
Orig. NDA 20-152
HFD-120 ✓
HFD-120/Drs. Hearst, Laughren, Leber
HFD-120/Mr. David
HFD-713/Group 2 File
HFD-713/Dr. Takeuchi
HFD-713/Ms. Mele
HFD-713/Dr. Dubey [File: DRU 1.3.2]
Chron



The attached memorandum contains 8 pages of text followed by 7 pages of graphs.

APPENDIX 2.0
Table of All New Studies

Protocol	Study Information
PHASE I STUDIES	
SAFETY/TOLERABILITY STUDIES	
CN104-023 USA	Double-blind, randomized, placebo-controlled, single-dose, crossover with 7-day washout between treatments; healthy volunteers (N=33), ≥ 18 years of age; Nefazodone 100 mg or 300 mg QD, diazepam 20 mg QD, and dextroamphetamine 30 mg QD.
PHARMACODYNAMICS STUDIES	
CN104-020 UK	Double-blind, randomized, placebo-controlled, crossover with 14-day washout between 8-day treatment sessions; healthy volunteers (N=15), 18-41 years of age; Nefazodone 100 or 200 mg BID, imipramine 150 mg QD.
CN104-028 UK	Single-blind, parallel-group; healthy male volunteers (N=34), ≥ 18 years of age; (1) Nefazodone 50, 100, or 200 mg BID, placebo S.D. with 5-14 day washout between treatments; (2) Nefazodone 100 mg BID M.D., gepirone challenge prior to and after 7 days treatment; (3) Lithium 800 mg QD M.D., gepirone challenge prior to and after 7 days treatment; (4) Nefazodone 100 mg BID M.D., lithium 800 mg QD M.D., gepirone challenge prior to and after 7 days treatment.
CN104-035	Netherlands Double-blind, randomized, placebo-controlled, multiple-dose, crossover with 7-day washout between 7-day treatment sessions; normal healthy adult and elderly volunteers (N=26); Nefazodone 100 or 200 mg BID, imipramine 50 mg BID.
CN104-063 USA	Double-blind, parallel-group, placebo-controlled, randomized; healthy male volunteers (N=27), 18-40 years of age; Single-blind placebo run-in, nefazodone 50 or 200 mg BID, fluoxetine 20 mg QD; 23 days.

CN104-075 USA	Double-blind, randomized, placebo-controlled, parallel-group; healthy volunteers (N=23), 18-35 years of age; Nefazodone 100-200 mg BID; 19 days.

ABSORPTION, METABOLISM, AND EXCRETION STUDIES

CN104-074 USA	Open, 3-way crossover with 7-day washout between 4.5-5 hour treatment sessions; healthy male volunteers (N=11), 18-40 years of age; Period I: Nefazodone 400 mg solution infused to the distal small intestine, Period II: Nefazodone 400 mg solution infused to the proximal small intestine, Period III: Nefazodone 400 mg solution p.o.

PHARMACOKINETICS STUDIES

CN104-018 France	Open, parallel-group, single- and multiple-dose; normal and hepatically impaired volunteers (N=34), 18-65 years of age; Nefazodone 50, 100, 200 mg BID; 19 days.
CN104-038 USA	Open, 3 sessions; healthy male volunteers (N=13), 18-40 years of age; Session 1: 0.5 mg/kg Indocyanine Green, 10 mg/kg antipyrine 60 minutes later, Session 2: Nefazodone 200 mg BID for 8 days, 200 mg on day 9, 0.5 mg/kg Indocyanine Green 60 minutes later, 10 mg/kg antipyrine 60 minutes later, Session 3: 0.5 mg/kg Indocyanine Green, 10 mg/kg antipyrine 60 minutes later on day 15 (five days after last dose of nefazodone).
CN104-053 USA	Open, dose escalation/de-escalation, multiple dose; healthy male volunteers (N=25), 18-40 years of age; Nefazodone 100 mg BID, 7 days; Nefazodone 200 mg BID, 7 days, nefazodone 100 mg BID, 7 days.
CN104-068 USA	Open, parallel-group, matched-pair, single- and multiple-dose; patients with hepatic cirrhosis and healthy controls (N=24), 18-65 years of age; Nefazodone 100 mg BID, 10 days.
N104-082 USA	Open, randomized, multiple-dose, 3-way crossover with 7-day washout between 7-day sessions; healthy male volunteers (N=25), 18-40 years of age; Nefazodone 200 mg QD for 2 days and 400 mg QD A.M. for 5 days, nefazodone 200 mg QD for 2 days and 400 mg QD P.M. for 5 days, nefazodone 200 mg BID for 7 days.

INTERACTION STUDIES

CN104-021 USA	3x3 Latin square; healthy male volunteers (N=28), 19-40 years of age; Nefazodone: (1) Single dose segment: 200 mg (2x100 mg capsules) or solution; (2) Multiple dose segment: 200 mg (2x100 mg capsules) BID; 4 weeks.
CN104-040 USA	Double-blind, randomized, placebo-controlled, crossover with 7-10 day washout between 7-day treatment sessions; volunteer patients with Chronic Obstructive Pulmonary Disease on a stable dose of theophylline (N=15), ≥ 40 years of age; Nefazodone 200 mg BID.
CN104-057 USA	Open, randomized, 3x3 Latin square design, crossover with 10-day washout between 9-day treatment sessions; healthy male volunteers (N=18), 18-40 years of age; Nefazodone 200 mg BID, digoxin 0.2 mg QD, or both.
CN104-066 USA	Open baseline, double-blind treatment, randomized, parallel-group; healthy volunteers (N=19), 18-40 years of age; Warfarin ≥ 10 mg/day, 12-14 days during baseline; Nefazodone 400 mg/day and warfarin, placebo and warfarin; ≥ 21 days.
CN104-069 USA	Double-blind, randomized, placebo-controlled, parallel-group; healthy male volunteers (N=50), 18-40 years of age, extensive dextromethorphan metabolizers; Nefazodone 100 mg BID, alprazolam 0.5 mg BID or both; 10 days.
CN104-078 USA	Open, randomized, multiple-dose, 3-way crossover with 14-day washout between 7-day treatment sessions; healthy male volunteers (N=21), 18-40 years of age; Nefazodone 200 mg BID, propranolol 40 mg BID, or both.
CN104-081 USA	Double-blind, randomized, placebo-controlled, parallel-group; healthy male volunteers (N=49), 18-40 years of age; Nefazodone 100 mg BID, lorazepam 1.0 mg BID or both; 10 days.

Inpatient Studies

The sponsor presented the results of two inpatient studies which are summarized briefly below. For both studies, no placebo group was utilized. Therefore it is difficult to assess the effectiveness of nefazodone since one does not know what contribution hospitalization alone makes to the improvement of the patient.

Study 030A2-0002 (Conducted 10/84 to 11/85)

Study 030A2-0002 is a double-blind multicenter clinical trial designed to compare 3 doses (75, 150 and 300 mg/day) of nefazodone in hospitalized patients for a duration of 4 weeks. The objective of this study was to gain dosing information to be used in future placebo-controlled trials.

Patients were hospitalized during the 7-day placebo phase-in period and for a minimum of 7 additional days. After a minimum of 14 days in the hospital, the patient could continue in the study as an outpatient. The HAM-D 21, MADRS, CGI, Raskin-Covi, and SCL-56 were measured at baseline and on Days 4, 7, 14, 21 and 28.

A total of 53 patients were enrolled at 6 centers (17 in the 75 mg/day group, 18 in the 150 mg/day group and 18 in the 300 mg/day group). A total of 17 patients discontinued treatment due to the reasons shown in the table below. Due to the small ~~sample size the sponsor did not perform the~~ statistical analyses proposed in the protocol.

	NEFAZODONE		
REASON FOR DROPOUT	75 mg/day	150 mg/day	300 mg/day
Lack of Efficacy	4 (24%)	5 (58%)	2 (11%)
Adverse Experience	0 (0%)	1 (6%)	0 (0%)
Other	1 (6%)	2 (12%)	2 (12%)

The HAM-D 17 Total LOCF results are summarized in the table. The least squares means are the group change from baseline means adjusted for baseline. An ANCOVA performed by this reviewer showed no differences among the 3 doses. In light of the results from subsequent trials, it is clear that the doses used in this trial were suboptimal, particularly for inpatients.

	HAM-D 17 TOTAL RESULTS		
Dose	75 mg/day	150 mg/day	300 mg/day
Baseline	32.8	28.7	26.7
LS Means	-10.3	-11.0	-9.7

Study 03A0A-006 (Conducted 10/87 to 1/90)

Study 03A0A-006 is a multicenter, randomized, double-blind, active-controlled trial that was conducted at 16 centers in France. Inpatients (hospitalized for a minimum of 2 weeks of this 8-week trial), with a minimum score of 27 on the Montgomery-Asberg Depression Rating Scale (MADRS) at the end of the 4-7 day placebo-washout period, were randomized to either nefazodone (titration range 200 to 600 mg/day) or clomipramine (titration range 50 to 150 mg/day).

The rating scales employed in this study were the MADRS, Hamilton Rating Scale for

Depression (HAM-D 21 and HAM-D 17), the Clinical Global Impression Scale (CGI), Patient's Global Assessment Scale (PGA) and Symptom Checklist-90-R.

No analyses were performed by the sponsor even though analysis of variance methods were proposed in the protocol.

A total of 163 patients (80 nefazodone and 83 clomipramine) were enrolled in this study. About 2/3's of the patients were female and 98% were white. The average age was about 46 years with ages ranging from 18 to 69 years.

The weekly mean modal doses of nefazodone used in this study are summarized in the table below. (The mean modal doses for Clomipramine ranged from 106 to 121 mg/day.) The doses for nefazodone are notably higher during the early weeks than the doses used in the placebo-controlled trials (see Figure 11, page 46 of this review).

Mean Modal Dose of Nefazodone (mg/day)

WEEK	1	2	3	4	6	8
N	80	77	74	66	54	47
MEAN	441	504	523	506	500	479

Forty-five percent of the patients dropped out during this study (47.5% of the nefazodone patients and 43.4% of the clomipramine patients) for the reasons listed below. A higher percentage of nefazodone patients than clomipramine patients dropped due to lack of efficacy while more clomipramine patients experienced adverse side effects than nefazodone patients.

Patient Disposition

	NEFAZODONE	CLOMIPRAMINE
Randomized	80	83
Reason for Dropout		
Lack of Efficacy	24 (30%)	14 (17%)
Adverse Experience	6 (8%)	13 (16%)
Improvement	3 (4%)	2 (2%)
Other	5 (6%)	7 (8%)

The efficacy results for the 2 groups did not differ significantly, however a larger change from baseline was seen for the clomipramine group.

HAM-D 17 Total Results

	NEFAZODONE	CLOMIPRAMINE
Baseline	27.3	27.5
Week 8		
LOCF	-12.4	-15.0
OC	-17.3	-20.1

Long Term Extension

The sponsor analyzed long term data for patients in Studies 03A0A-004B, CN104-002, CN104-005 and CN104-006. Approximately 40% of the completers in those studies were eligible to continue on treatment for an extended period of time (up to 46 weeks).

This reviewer does not believe that the long-term extension data analysis offers useful information regarding the long-term efficacy of nefazodone for the following reasons.

1. The primary comparison criterion was dropout due to lack of efficacy; however, the definition of "lack of efficacy" was not specified in the protocol.

2. The long-term dosing regimen varied among the studies.

3. The duration of follow-up varied among the patients appreciably.

4. The inclusion criteria for the long-term extension phase varied among the studies.

5. The patients entering the long-term extension phase are probably not be representative of the original randomized groups.

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: April 13, 1994

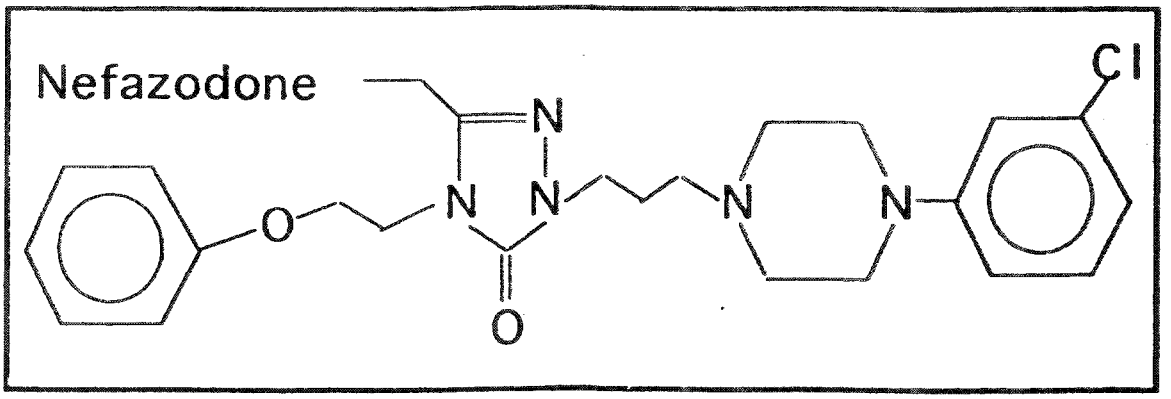
FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: NDA 20-152, Division Director's Approvable Action Memorandum

TO: File NDA 20-152, Serzone (nefazodone)
&
Robert Temple, M. D.
Director,
Office of Drug Evaluation I
HFD-100

This memorandum conveys my formal recommendation that Bristol-Myers Squibb Company's NDA 20-152 for Serzone (nefazodone) be declared approvable.

Nefazodone: the drug and its metabolites:

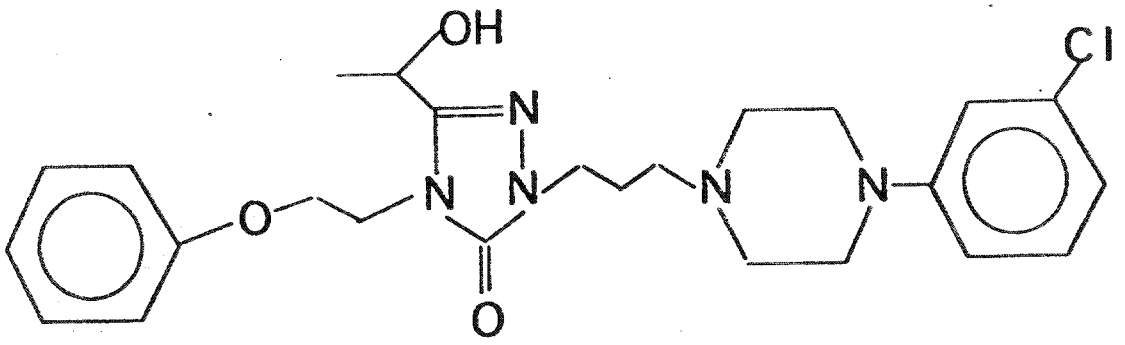


Nefazodone, a phenylpiperazine, (pictured above), has been shown to interact with neuronal receptors and uptake sites that exhibit high affinity for a number of different endogenous neurotransmitter substances. Which, if any, of these demonstrated pharmacologic

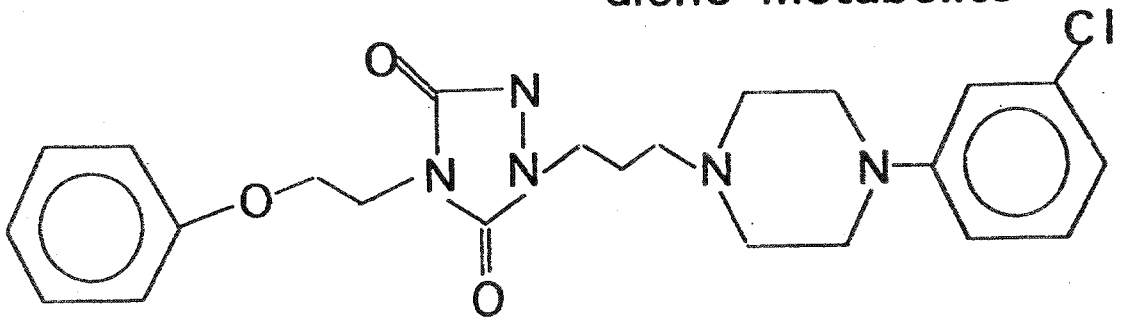
activities of nefazodone (e.g. serotonin {5-HT} and Norepinephrine {NE} uptake site inhibition, $5HT_2$ blockade, etc.) is linked to its clinical antidepressant action is unknown, however.

Nefazodone is metabolized to a number of different metabolites, at least 3 of which (hydroxy-nefazodone, triazolodione and mCPP) have been shown to retain one or more of its pharmacological activities.

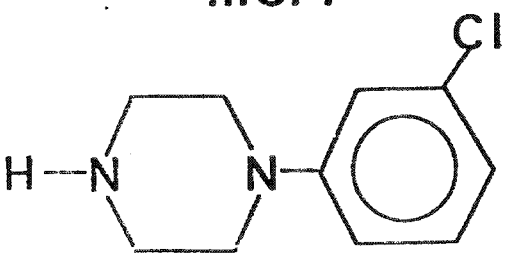
Hydroxy-nefazodone



dione metabolite



mCPP



documentation of the capacity to maintain remissions were required.

Furthermore, it is now generally agreed that a substantive proportion of depressed patients suffer repeated episodes of depression over their lifetimes. Because there is evidence indicating that long term antidepressant treatment during periods of euthymia will reduce the risk for such recurrences, marketed antidepressant drugs are regularly given to euthymic individuals who have 'recovered' from a prior depressive episode. The capacity of a drug to prevent recurrence, obviously, cannot be evaluated in short term studies. Again, therefore, there is interest in making sponsor's evaluate a new product's capacity to prevent recurrence prior to marketing.

Interim policy on long term efficacy applied to nefazodone

Given the importance of these current uses/goals of antidepressant treatment and evolving sentiment among experts, we have contemplated, most recently in the course of our deliberations involving Effexor (venlafaxine), making formal clinical investigations of the two long term treatment objectives just described a formal premarketing requirement for all new antidepressants.

Not unexpectedly, a number of practical factors make it difficult to revise our existing regulatory standards, despite their de facto origins. Accordingly, until we are able to promulgate revised standards, we have adopted an interim policy of seeking 'voluntary' commitments from sponsors to conduct such studies; we do so again in the approvable action letter to Bristol-Myers Squibb.

Safety in Use:

The review team has concluded that nefazodone, if marketed under the labeling developed by the Division, will be "safe for use." This conclusion must be accompanied by a generic caveat.

Generic Caveat:

"Safe for use" is a regulatory term of art; no drug is risk free. The conclusion, therefore, that nefazodone is 'safe for use' reflects a judgment that the evidence contained in reports submitted to the Serzone™ NDA, taken in concert with other relevant information (literature, reports from foreign regulatory agencies, etc.), supports a conclusion that the benefits associated with the use of nefazodone are sufficient to outweigh the harm likely to be associated with that use. It is virtually certain, however, that nefazodone, once marketed, will be reported to be the cause of injuries not observed, reported, or attributed to it during the course of its premarketing evaluation. This prediction, admittedly generic, is offered because 1) the conditions of premarket drug evaluation [patient characteristics, disease type/severity, duration of use, doses in use] are not reliably representative of the actual conditions under which a drug product is used once marketed, and 2) the limited size of drug development cohorts gives them very low power to detect risks that occur at low rates in the general population or at high rates in subgroups of the general population not adequately represented in a drug development cohort.

Absence of identified serious unique risks

As to the evidence of risks specifically associated with nefazodone, nothing of major import has been identified in our review of clinical reports obtained from the more than 2700 subjects and patients (more than 400 in Phase 1 and more than 2200 in phases 2 and 3) exposed to it during its development. There are, not surprisingly, a number of events, some with potentially serious consequences (e.g., orthostatic hypotension) that appear to occur at higher frequency among nefazodone than placebo treated patients.

Potential for metabolic interactions with terfenidine and astemizole

One potential risk that may exist requires emphasis, however. As noted earlier, nefazodone has the capacity to interfere with the clearance of triazolam and alprazolam, a finding that suggests it interferes with their

metabolism, possibly by inhibiting CYP450 IIIA4. If this is the mechanism involved, the concomitant use of nefazodone with drugs like astemizole and terfenidine poses a potentially serious risk. Unfortunately, the firm did not do a comprehensive evaluation of the metabolic pathways involved in the catabolism of nefazodone and its metabolites, nor an evaluation of these species on the clearance of other drug product. In the absence of the information necessary to resolve this question, I believe we have no choice but to label Serzone™ as if it were a potent inhibitor of CYP450 IIIA4.

Recommendation:

Issue the approvable action letter.

Paul Leber, MD
4/13/94

doc Serzone™ [4/13/94] approvable
NDA 20-152
HFD-100 Temple
HFD-120
    Katz
    Laughren
    Fitzgerald
    Blum
    David
HFD-710
    Nevius
    Mele

David

M E M O R A N D U M

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

DATE: February 8, 1994

FROM: Thomas P. Laughren, M.D. TPL
Group Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for Serzone (nefazodone)

TO: File NDA 20-152
[**Note:** This overview should be filed with the 6-6-91 original submission.]

1.0 BACKGROUND

Nefazodone is a phenylpiperazine that is being proposed for use in the treatment of depression. Its pharmacological actions can be characterized predominantly as $5HT_2$ antagonism and 5HT reuptake inhibition. However, it also has the following actions: weak $alpha_1$ adrenergic blocking activity and weak norepinephrine reuptake inhibition. The sponsor argues that nefazodone may have the following advantages compared to some other drugs available for the treatment of depression: less anticholinergic, sedative, and cardiovascular adverse effects.

IND for nefazodone was originally submitted 10-18-83. Several critical meetings were held during the development of nefazodone:

March 13, 1990: This was technically an end-of-phase 2 meeting, however, given that all of the critical studies were underway at this point, it was more accurately an early pre-NDA meeting. Various chemistry, biopharmaceutical, and clinical issues were discussed.

February 11, 1991: This was the more typical pre-NDA meeting, with a primary focus on clinical issues. We discussed in some detail our preferred approach to the analysis of efficacy data and the formatting of the Integrated Safety Summary.

The original NDA 20-152 for nefazodone was submitted 6-6-91. A major safety update was submitted 1-17-92. The final safety update was submitted 10-28-93.

Nefazodone was the subject of a 7-19-93 meeting of the PDAC, and the Committee voted unanimously in favor of both its efficacy and safety.

2.0 CHEMISTRY

Methods validation has not been completed at this time, however, this is not needed for an approvable action. It is my understanding that all but one of the manufacturing sites have passed inspection, and the final inspection is underway. Finally, our review of the environmental assessment has not been completed as of the date of this memo. Otherwise, there are no remaining chemistry issues that need resolution.

3.0 PHARMACOLOGY

Preclinical studies have shown that nefazodone inhibits neuronal uptake of serotonin and norepinephrine and, in addition, it antagonizes $5HT_2$ serotonergic receptors. Nefazodone also has some $alpha_1$ adrenergic receptor blocking properties, and this may be the basis for the orthostatic effects seen with this drug. Nefazodone has little affinity for $alpha_2$ and beta adrenergic, $5HT_{1A}$, muscarinic, dopaminergic, or benzodiazepine receptors.

The pharmacology group has recommended substantial changes to the Pharmacodynamics subsection of Clinical Pharmacology because of our quite different interpretation of preclinical studies than the sponsor. This may be a controversial point, and I have explained our modifications to this subsection in detail in a bracketed comment for that section. The pharmacology group has also recommended changes for Carcinogenesis, etc. and for the Pregnancy section, i.e., Category C rather than Category B. We have explained the basis for this change both in bracketed comments and in the approvable letter. We have suggested in the letter a cross-fostering study to help determine the role of pre- vs post-natal drug exposure in producing the observed effects. Finally, we have asked for additional studies to explore teratogenicity in the rabbit, given the failure to demonstrate that an adequate high dose level was used in the Segment II rabbit study.

Nefazodone has been to the CAC (1-25-94), and they concluded that there were no findings that would raise any concerns about a potential for human carcinogenesis.

4.0 BIOPHARMACEUTICS

Nefazodone has extensive presystemic metabolism, with an absolute bioavailability estimated to be 15-23%. The three known active metabolites, with AUC ratio (metabolite to parent) in parenthesis,

clear relationship emerged. She concluded that nefazodone doses below 300 mg/day are not likely to be effective, but that doses above 300 mg/day were not sufficiently well studied to draw any conclusions about the optimum dose in the 300-600 mg/day range.

The sponsor looked at a pool of data from the 7 titration studies to explore for dose/response, and they fitted a U-shaped dose/response curve suggesting that doses of 350-450 mg/day may be optimal. The problem, of course, in titration designs is that the highest dose patients may not be doing as well because they are non-responsers rather than the existence of an actual U-shaped curve. In the proposed labeling, the sponsor suggests a target dose range of 300 to 500 mg/day. As a slight alternative to this suggestion, I recommend a target range of 300 to 600 mg/day for adults (since this was the effective dose range utilized in the positive studies). Although there was no definitive data source from which to select a target dose range for the elderly, debilitated, and hepatically impaired, it would not be unreasonable to extrapolate from the adult range to arrive at a slightly lower range of 200 to 400 for this group (as suggested by the sponsor).

Analysis of Plasma Level/Response Data

Plasma samples were obtained during week 6 in several of the efficacy trials, and nefazodone concentration was measured by HPLC. Time of sampling relative to dosing was recorded, and a plot of hours since dosing vs nefazodone concentration, categorized by endpoint modal dose, suggested that samples drawn 8-12 hours post dosing approximated Cmin values. Plasma nefazodone concentrations for 97 patients whose samples were drawn in the 8-12 hour post-dosing time window were plotted against HAMD total change scores (BL to 6 weeks). The best fit regression line was curvilinear, tending to support the sponsor's suggestion that optimal response occurs in a dose window. The problem of course with this kind of analysis is that it is based on data from titration studies in which patients with both higher doses and higher plasma nefazodone concentrations may be non-responders. Consequently, nothing can be concluded from this analysis.

Clinical Predictors of Response

The sponsor did a number of exploratory meta-analyses for the pool of 8 placebo controlled efficacy studies to search for predictors of response. (1) Severity of illness (based on baseline CGI severity score, where $\geq$ 5 = markedly ill, and $\leq$ 4 = moderately ill): Nefazodone was superior to placebo in both subgroups. (2) Depression with prominent anxiety (based on baseline HAM-A total score, where $\geq$ 19 = 'high anxiety,' and < 19 = 'lower anxiety'): Nefazodone was superior to placebo in both subgroups (This analysis was based on the pool of 6 placebo controlled studies that included HAM-A assessments.). (3) Sex: Nefazodone was superior to placebo in both male and female subgroups. (4) There were too few patients

in the elderly and non-Caucasian categories to justify exploratory analyses for these subgroups. (5) Melancholic subtype of major depression: As noted earlier, none of the placebo controlled studies (except for 0004/0005, which was a failed study) specifically recruited patients with melancholia, although some of these patients were included in all of these studies (approximately 50% of the total sample). Nefazodone was superior to placebo in both melancholic and non-melancholic subtypes. (6) Depressed inpatients: Neither of the two inpatient depression studies, both of which were active controlled, succeeded in discriminating between treatment groups. (7) History of recurrent depression (based on division of patients at baseline into those with their first depressive epidose and those with a history of at least one prior depressive episode before the index episode): Nefazodone was superior to placebo in both subgroups.

While these exploratory analyses are suggestive of the general usefulness of nefazodone across a spectrum of depressed patients, they can only suggest hypotheses about the effectiveness of nefazodone in the various subgroups examined, and are not tests of those hypotheses.

Size of Treatment Effect

While it is difficult to characterize treatment effect size for antidepressant therapy, the data from the positive studies/centers among the 8 placebo controlled short-term studies perhaps provide some insight into what can be expected from nefazodone. The differences between nefazodone (high dose arm) and placebo in the mean changes from baseline for the three key efficacy variables were as follows:

Size of Treatment Effect in Positive Nefazodone Studies (Difference Between Nefazodone and Placebo in Mean Change from Baseline on 3 Key Efficacy Variables--LOCF)

Study/Center	HAMD Total	HAMD (Item 1)	CGI Severity
003 (Ctr 2191)	-4.2	-0.5	-0.8
004B	-3.2	-0.2	-0.5
006 (Ctr 2)	-2.9	-0.5	-0.5
005 (Ctr 2)	-6.9	-0.9	-0.9
Mean Effect	-4.3	-0.5	-0.7

These differences are comparable to the differences seen with other antidepressants that have been approved recently in the US. While any definitive statement about comparable efficacy would need to be based on actual between drug comparisons, these findings

suggest that nefazodone might be characterized as comparable in efficacy to other drugs in this class. It might, in addition, be pointed out that, given a mean baseline HAMD Total score (17-item) of roughly 25 for these 4 studies/centers, a mean decrease of roughly 12 HAMD units in the nefazodone group would still leave a number of patients in a non-euthymic state. Nevertheless, the effect can be characterized as clinically meaningful.

Duration of Treatment

One of the failings of this program is the absence of adequate relapse prevention data. Recent examples set by other antidepressant NDAs have led us to expect some data from specific relapse prevention trials (i.e., Zoloft and Paxil), and the PDAC has also been increasingly focused on this issue. Several of the short-term placebo controlled trials did provide for placebo controlled, double-blind, long-term (up to 1 year) extensions of responders, and these data were pooled for a meta-analysis. Discontinuation for lack of efficacy was used as an indicator of relapse during the extension phase. While the cumulative probability of relapse was significantly lower for nefazodone compared to placebo, this analysis was not based on the originally randomized sample, and there were other problems as well. Consequently, I don't think this analysis can be considered as an adequate substitute for a well designed relapse prevention trial.

5.2 Safety Data

5.2.1 Original Submission and First Safety Update

The safety data for nefazodone, including the original submission, the 1-17-92 safety update, and the numerous amendments in response to our requests for additional information, were reviewed by Dr. Earl Hearst (review dated 11-23-93). This original review was based an integrated database (with a cutoff date of 6-1-91 for North American trials, 9-15-91 for European trials, and 6-15-91 for clinical pharmacology trials) and on serious event reporting with a cutoff date of 4-15-93.

2737 human subjects were exposed to nefazodone in the sponsor's development program (in the integrated database available with the first safety update), including 424 in phase 1 studies and 2313 in phase 2-3 studies (the figure 2256 is used throughout the review for phase 2-3 studies, due to an inadvertant exclusion of 57 patients who had been switched to nefazodone for long-term extensions after failing on the originally assigned short-term treatment; although adverse events for these patients were not included in most of the pooled analyses, they were considered in the overall safety assessment for nefazodone). Serious events were provided for additional patients not yet included in the integrated database. Patients in phase 2-3 studies were roughly two-thirds female, predominantly white, and predominantly middle-aged. There

were 127 patients over age 65. Approximately 81% of nefazodone-treated patients in these phase 2-3 studies received mean nefazodone doses in a range of 200 to 600 mg/day, and approximately 86% of exposures were for 6 months or less. Nevertheless, there were approximately 308 patients who received nefazodone for 6 months or more.

The common and drug-related adverse event profile for nefazodone included the following: dry mouth, nausea, somnolence, dizziness, constipation, asthenia, lightheadedness, and blurred vision.

A careful look at all the other routinely collected safety variables, including serum chemistry, hematology, urinalysis, vital signs, and ECGs revealed only three findings suggestive of potentially clinically important nefazodone-related changes:

(1) Hypotension

In the vital signs data, 5% of nefazodone patients met our criteria for a potentially important drop in systolic blood pressure ($\leq$ 90 mmHg and a change of $\geq$ 20 mmHg) compared to 3% of placebo patients ($p<0.05$) [Note: This finding was supported by other data suggestive of orthostatic hypotension in association with nefazodone use--see later].

(2) Decreased Hematocrit

In the hematology data, 3% of nefazodone patients met our criteria for a potentially important decrease in hematocrit ($\leq$ 37% male or $\leq$ 32% female) compared to 1% of placebo patients ($p<0.01$). An evaluation of individual cases did not suggest that these represented important and drug-related changes.

(3) Sinus Bradycardia

In the ECG data, 0.98% of nefazodone patients met the sponsor's criteria for sinus bradycardia ($\leq$ 50 bpm and a decrease of $\geq$ 15 bpm) compared to 0.14% of placebo patients ($p<0.05$). An evaluation of individual cases did not suggest that these represented important and drug-related changes.

There were 9 deaths among nefazodone-treated patients overall, including 5 in the integrated database for which the denominator and full exposure data were available. When adjusted for duration of exposure, the mortality rates were comparable for nefazodone and active control. However, the numbers of events overall were too small to evaluate [5 deaths for nefazodone (all suicides), 1 for active control (homicide), and none for placebo]. All 9 of the nefazodone deaths were due to suicide, not an unusual or unexpected finding for this population (more about this later).

An examination of adverse dropouts revealed a profile of common events causing dropout for nefazodone that closely mimicked the common event profile for nefazodone overall. There were no serious adverse events associated with nefazodone dropout at unexpected or disproportionate rates.

Two special searches were conducted for nefazodone, including: suicidality and serious events (using FDA's definition). While all of the suicides occurred among nefazodone patients, this was not surprising given the much greater cumulative exposure for nefazodone compared to active control and placebo. Nefazodone had no greater risk of suicide attempts than the active control or placebo groups. While other serious events were also reported among nefazodone patients in this large population, neither the types of events nor their numbers were unexpected for the population.

A sleep lab study was done to compare nefazodone, trazodone, buspirone, and placebo with regard to effects on sleep architecture and penile tumescence, primarily out of concern for the finding of priapism with trazodone, a drug that is structurally related to nefazodone. While both buspirone and trazodone were associated with a decrease in REM sleep, nefazodone was associated with an increase in REM sleep, compared to placebo. Both trazodone and nefazodone were associated with an increase in total tumescence time (TTT), however, the ratio of TTT to total REM time was unchanged, relative to placebo, for nefazodone, but dramatically increased for trazodone. The sponsor explained this on the basis of the dramatically increased time for detumescence with trazodone, and based on this finding, added a reassuring statement in labeling in regard to penile tumescence. It is not clear to me how easily one can extrapolate from this finding to predictions about priapism, consequently, I am not inclined to think this finding even merits a mention in labeling. Whether or not nefazodone will be associated with priapism remains to be seen.

Except for pk studies in subjects with renal or hepatic impairment, there were no systematic attempts to explore for drug/disease interactions. A decreased clearance of nefazodone was found for hepatically impaired but not renally impaired patients.

Interaction studies of nefazodone with triazolam, alprazolam, and haloperidol revealed a significantly decreased clearance of triazolam and alprazolam, and a modestly decreased clearance of haloperidol, when administered with nefazodone. None of these three drugs had an effect on nefazodone pharmacokinetics. An interaction study of nefazodone with cimetidine revealed no pharmacokinetic interaction. While the effect of $P_{450}IID_6$ status has not been formally studied with nefazodone, informal observations suggest that metabolizer status for this enzyme is not a factor in nefazodone pharmacokinetics. (see Biopharm section).

Our attempt to explore for drug-demographic interactions was limited to age and sex, and these analyses did not reveal any important differences. However, there was limited power to detect any but very substantial differences.

Since the sponsor did not collect any adverse event data following withdrawal of nefazodone, there was no opportunity to look for withdrawal phenomena/abuse potential.

There were 4 pregnant women exposed to nefazodone during the development program. The outcomes of these pregnancies were not suggestive of any particular teratogenic risk associated with nefazodone, but obviously, this experience is too limited to be a basis for any definitive statement.

The overdose experience with nefazodone consisted of 2 patients, one of whom ingested 3400 mg and the other, 3600 mg, of nefazodone. Both patients recovered fully.

The following were the adverse events associated with nefazodone use that we felt deserved some special mention in labeling:

Activation of Mania/Hypomania: For unipolar patients, activation of mania/hypomania occurred in approximately 0.4% of nefazodone-treated patients, compared to 0.3% for tricyclics and 0% for placebo. For bipolar patients, activation of mania/hypomania occurred in approximately 3.2% of nefazodone-treated patients, compared to 10% for tricyclics and 0% for placebo.

Seizures: There was only 1 seizure reported among the more than 2700 patients exposed to nefazodone, and that seizure occurred in a patient with a known history of petit mal epilepsy. There were no seizures among active control or placebo patients.

Postural Hypotension/Syncope: As noted earlier, nefazodone was associated with a significantly greater incidence of patients meeting criteria for a potentially important drop in systolic blood pressure on treatment than the placebo group. Another approach to this question was to look at reports of events occurring during clinical trials and coded under COSTART as either 'syncope' or 'postural hypotension.' For syncope, there was no difference between nefazodone (0.49%) and placebo (0.45%). For postural hypotension, the rates were as follows: nefazodone (3.5%), tricyclic (10.3%), SSRI (1.0%), and placebo (0.9%). Thus, it appears that nefazodone is associated with some risk of orthostatic hypotension, perhaps somewhat less than that seen with TCAs, but sufficient to merit, in my view, a Precautions statement.

Triazolobenzodiazepine Interactions: The prominent interactions between nefazodone and both triazolam and alprazolam merit a prominent Warning statement about this potential problem.

5.2.1 Final Safety Update

The final safety update (10-28-93) included safety data (for the integrated database) for an additional 1240 patients in phase 2-3 studies (yielding a phase 2-3 total of 3496) and an additional 365 subjects in phase 1 studies (yielding a phase 1 total of 788). The new cutoff date for the integrated safety database was 4-15-93, and the new cutoff date for serious event reporting was 7-31-93.

There were no deaths previously unknown to us. Dr. Hearst reviewed the listings of new adverse dropouts and serious events, and he discovered no new important events that he judged could be reasonably attributed to nefazodone use. The profiles for common adverse events, laboratory, ECG, and vital signs data all were quite comparable to the data in the original database. There were 3 additional cases of overdose that permitted us to update this section of labeling. Overall, the safety update did not reveal any new important adverse events that could be reasonably attributed to nefazodone use or any important change in the common events profile for nefazodone. However, it was necessary to make some slight modifications in labeling on the basis of the safety update.

5.3.3 Conclusions Regarding Safety Data for Nefazodone

In conclusion, the safety experience for almost 4400 patients/subjects exposed to nefazodone in the premarketing program revealed no adverse findings that would preclude its use as an antidepressant.

5.3 Clinical Sections of Labeling

I have substantially rewritten the clinical sections of the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

6.0 WORLD LITERATURE

Dr. Hearst reviewed the published literature for nefazodone included in the original NDA and did not discover any previously unrecognized important safety concerns for this drug.

In a 10-26-93 amendment (087), the sponsor provided a literature update. They identified 65 additional papers regarding nefazodone in the published literature not referenced in the original NDA, including 48 clinical papers and 17 nonclinical. The sponsor has

warranted that (1) any safety data contained in the 48 clinical papers are already included in the 10-28-93 safety update, and (2) there are no new findings pertinent to the safety of nefazodone in the nonclinical papers.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, nefazodone is approved in only 1 country, i.e., the UK, but not actually marketed there as yet. Registration applications have been filed in 17 other countries (besides the US), and these applications are under active review in 8 of these countries. Only 2 countries have raised issues of concern: (1) a concern about inconsistent or insufficient efficacy data (Netherlands, Sweden), (2) a question about possible negative effects of nefazodone's metabolites on efficacy results and a possible contribution to adverse events (Sweden), and (3) a concern about the safety margin of the highest recommended dose, based on preclinical toxicology data (Netherlands). I don't view any of these as concerns that would preclude our proceeding with an approvable action for this product.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

A meeting of the PDAC was held on 7-19-93 to discuss the safety and efficacy of nefazodone for the treatment of depression. As noted above, the Committee voted unanimously in favor of both its efficacy and safety.

9.0 DSI INSPECTIONS

Only one of the two studies considered definitely positive has been inspected thus far, i.e., 004B. Both centers from that study, i.e., Mendels and Reimherr, were inspected, and both received VAI-2 ratings. These ratings were based on fairly minor protocol violations, so this study can be considered to have passed inspection. The other study considered to be definitely positive, i.e., 005 (Rickels), is in the process of being inspected. Inspections have not been conducted for the two studies considered supportive, i.e., 003 (a Canadian study) and 006. However, Dr. Cohn, the principal investigator at the positive center in 006 is well known to us and has passed inspection in the recent past for other NDAs.

10.0 LABELING, SBA, AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, I have made substantial changes to the sponsor's draft dated 11-17-93. Other sections have also been substantially modified.

10.2 Foreign Labeling

I reviewed the approved labeling from the UK in preparation for modifying the clinical sections of labeling.

10.3 Draft SBA

We have not drafted an SBA for nefazodone. In my view, the primary reviews are sufficient to serve as an alternative to an SBA.

10.4 Approvable Letter

The approvable letter letter includes (1) draft labeling, (2) a suggestion to do depression studies in children and adolescents, (3) a suggestion to do relapse prevention studies, (4) a suggestion to do a cross-fostering study to clarify the basis for decreased pup weights and survival in the Segment III rat study, (5) a suggestion for further rabbit studies given the failure to use an adequate high dose in the Segment II rabbit study, (6) a suggestion to do additional studies to clarify the important isozymes in the metabolism of nefazodone, and (7) dissolution specifications.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that the sponsor has submitted sufficient data to support the conclusion that nefazodone is effective and acceptably safe in the treatment of depression. I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests, in anticipation of final approval.

cc:
Orig NDA
HFD-120
HFD-120/TLaughren/PLeber/EHearst/PDavid
HFD-100/RTemple

DOC: MEMNEFAZ.AE1