CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-777

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-777
Drug Name:	AMRIX (cyclobenzaprine HCl modified release capsule) 15 and 30 mg
Indication(s):	Relief of muscle spasms
Applicant:	ECR Pharmaceuticals
Date(s):	Submitted: April 29, 2004 Received: April 30, 2004
Review Priority:	Standard review
Biometrics Division:	Division of Biometrics III (HFD-725)
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Keywords: missing data, chi-square test, Wilcoxon rank sum test

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Data from both Study 1105 and Study 1106 failed to show efficacy of cyclobenzaprine HCl modified release (CMR) in subjects with muscle spasm associated with acute painful musculoskeletal conditions. Neither Study 1105 nor Study 1106 showed statistically significant difference of subject's rating of medication helpfulness (SRMH) and physician's clinical global assessment (PCGA) as co-primary endpoints between CMR and placebo in the intent-to-treat (ITT) population.

The data from Study 1105 showed the statistical significance of CMR 30 mg compared to placebo with respect to SRMH only, but did not show the statistical significance of CMR compared to placebo with respect to PCGA.

The data from Study 1106 showed the statistical significance of CMR 15 mg compared to placebo with respect to SRMH only, but did not show the statistical significance of CMR compared to placebo with respect to PCGA.

1.2 Brief Overview of Clinical Study

The sponsor submitted the results of studies that document the efficacy and safety of cyclobenzaprine modified release capsule in patients with muscle spasms associated with acute painful musculoskeletal conditions. Study 1105 and Study 1106 of identical design were a **14-day**, double-blind, active-controlled, placebo-controlled, parallel 4-arm, multi-center study to investigate the safety and efficacy of **cyclobenzaprine HCl modified release capsule 15 mg and 30 mg once daily** in patients with muscle spasms.

In Study 1105, 254 patients were randomized to CMR 15 mg arm (n = 64), CMR 30 mg arm (n = 64), cyclobenzaprine 10 mg TID arm (n=62) and placebo arm (n = 64) in 1:1:1:1 ratio.
In Study 1106, 250 patients were randomized to CMR 15 mg arm (n = 63), CMR 30 mg arm (n = 62), cyclobenzaprine 10 mg TID arm (n=61) and placebo arm (n = 64) in 1:1:1:1 ratio.

The primary objective of the studies was to document an efficacy for therapy with cyclobenzaprine HCl modified release capsule 15 mg and 30 mg once daily on muscle spasm when compared to placebo.

The co-primary efficacy endpoints for the studies were the subject's rating of medication helpfulness and the physician's clinical global assessment on Day 4.

The SRMH and PCGA scores as ordered categorical data are described as follows:

SRMH		PCGA	
Score		Score	
0	poor	1	worse
1	fair	2	no change
2	good	3	slight improvement
3	very good	4	moderate improvement
4	excellent	5	marked improvement

Wilcoxon rank sum test was planned to use for comparison of the co-primary endpoints between treatment groups.

The secondary efficacy endpoints were subject-rated relief from local pain due to the muscle spasm, subject-rated clinical global impression of change, subject health status survey, restriction in activities of daily living, restriction of movement, daytime drowsiness, and quality of night-time sleep assessed on Days 4, 8, and 14. Wilcoxon rank sum test and ANCOVA were planned to use for comparison of the secondary endpoints between treatment groups.

1.3 Statistical Issues and Findings

For the primary efficacy analysis, the sponsor based its inferences on ITT data from Study 1105 and Study 1106 with last observation carried forward (LOCF) for missing SRMH and PCGA data and compared CMR 15 mg and CMR 30 mg with placebo in SRMH and PCGA on Day 4 for the statistical significance.

Bonferroni method was used to adjust for multiple comparisons in the primary efficacy analysis, CMR 15 mg versus placebo and CMR 30 mg versus placebo, with an alpha level for each comparison being adjusted to .025.

As a supportive analysis to the primary efficacy analysis, the sponsor proposed and conducted a responder analysis. A responder was defined as a subject who had both a rating of either "very good" or "excellent" for SRMH and a rating of either "moderate improvement" or "marked improvement" for PCGA on Day 4.

Sponsor's ITT population was defined as all subjects who received at least 1 dose of study medication.

Based on our review of the data up to 14 days, we conclude the following.

Study 1105

The statistically significant difference in SRMH as a co-primary endpoint was shown when comparing CMR 30 mg with placebo in ITT LOCF analysis (p=.007).
But the statistically significant difference in PCGA as a co-primary endpoint was not shown when comparing CMR with placebo in ITT LOCF analysis (p-values > .025).
The responder analysis did not show a statistically significant difference in the responder rate between CMR and placebo (p-values > .05).

Study 1106

The statistically significant difference in SRMH as a co-primary endpoint was shown when comparing CMR 15 mg with placebo in ITT LOCF analysis (p=.018).
But the statistically significant difference in PCGA as a co-primary endpoint was not shown when comparing CMR with placebo in ITT LOCF analysis (p-values > .025).
The responder analysis did not show a statistically significant difference in the responder rate between CMR and placebo (p-values > .05).

2. INTRODUCTION

2.1 Overview

2.1.1 Drug class and regulatory history

Cyclobenzaprine hyprochloride (HCl) is a centrally acting skeletal muscle relaxant. It is related to the tricyclic antidepressants and acts mainly at the brain stem to decrease tonic somatic motor activity. Both alpha and gamma motor systems are influenced by cyclobenzaprine HCl. Additional activity at spinal cord sites may be involved. The effects of cyclobenzaprine HCl begin with one hour following oral administration; and the effects of a single dose have been reported to last as long as 12 to 24 hours. Cyclobenzaprine HCl is used as an adjunct in the symptomatic treatment of the painful muscle spasm associated with musculoskeletal conditions.

A modified release (MR) formulation of cyclobenzaprine HCl has been developed by ECR Pharmaceuticals to provide patients with an improved form of treatment.

The key agreements from the sponsor and the FDA interactions regarding statistical significance of drug efficacy were as follows:

1. January 30, 2003:
   efficacy will be concluded if both the subject's rating of medication helpfulness and the physician's global assessment are statistically significant
2. April 29, 2003:
   proposed method of adjustment for multiple testing is acceptable to the agency; both co-primary efficacy endpoints must show statistical significance for the same dose level.

2.1.2 Proposed Indication for AMRIX (cyclobenzaprine HCl modified release capsule)

AMRIX is indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions.

2.2 Data Sources

The original submission on April 30, 2004 can be found on paper submission with CDER electronic document room (EDR) data.

Final Report:
Paper Submissions
Document Room
9201 CORP

Data set:
\\Cdsesub1\n21777\N_000\2004-04-29

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Study 1105 and Study 1106 of identical design were a 14-day, multi-center, double-blind study of the safety and efficacy of cyclobenzaprine HCl modified release 15 mg and 30 mg once a day in patients with muscle spasms. Patients were randomized to CMR 15 mg or CMR 30 mg or cyclobenzaprine 10 mg TID or placebo in 1:1:1:1 ratio.

Figure 1 in Appendix shows schematic of study design for Study 1105 and Study 1106, respectively.

Thirty one investigators enrolled subjects from US sites and participated in the clinical trial Study 1105.

Thirty five investigators enrolled subjects from US sites and participated in the clinical trial Study 1106.

As the co-primary efficacy endpoints, the subject's rating of medication helpfulness and the physician's clinical global assessment on Day 4 were evaluated.

The co-primary endpoints were compared between treatment groups using Wilcoxon rank sum test.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

As shown in Table 1 in Appendix, during the treatment period of 14 days, about 39% and 30% (at the Day 4 visit, about 18% and 13%) of the patients discontinued from Study 1105 and Study 1106, respectively.

For the missing data due to discontinuation, LOCF was used in the efficacy analysis on ITT data from two studies.

Table 2 in Appendix shows patient demographics and baseline characteristics by treatment groups for Study 1105 and Study 1106, respectively. There were no statistically significant imbalances among treatment groups with respect to demographic and baseline characteristic variables in both Study 1105 and Study 1106.

3.1.3 Statistical Methodologies

In the primary efficacy analysis of Study 1105 and Study 1106, the sponsor employed the Wilcoxon rank sum test to compare SRMH and PCGA between treatment groups based on ITT population with LOCF method for missing data.

In the supportive responder analysis, the sponsor employed continuity-adjusted chi-square test for responder rate comparison between treatment groups.

In the secondary efficacy analysis, the sponsor employed Wilcoxon rank sum test for ordinal categorical variables and ANCOVA for continuous variables.

3.1.4 Results and Conclusions

Tables 3.1 – 4.3 in Appendix present the statistical analyses done by sponsor and reviewer. Following are review results of the analyses.

Study 1105

The statistically significant difference in SRMH as a co-primary endpoint was shown when comparing CMR 30 mg with placebo in ITT LOCF analysis (p=.007). (See Table 3.1 in Appendix.)
But the statistically significant difference in PCGA as a co-primary endpoint was not shown when comparing CMR with placebo in ITT LOCF analysis (p-values > .025). (See Table 3.2 in Appendix.)
The responder analysis did not show a statistically significant difference in the responder rate between CMR and placebo (p-values > .05). (See Table 3.3 in Appendix.)

Study 1106

The statistically significant difference in SRMH as a co-primary endpoint was shown when comparing CMR 15 mg with placebo in ITT LOCF analysis (p=.018). (See Table 4.1 in Appendix.)
But the statistically significant difference in PCGA as a co-primary endpoint was not shown when comparing CMR with placebo in ITT LOCF analysis (p-values > .025). (See Table 4.2 in Appendix.)
The responder analysis did not show a statistically significant difference in the responder rate between CMR and placebo (p-values > .05). (See Table 4.3 in Appendix.)

3.2 Evaluation of Safety

Safety analyses were done by Clinical reviewer, Christina Fang, M.D.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

No examination of subgroups was performed by the sponsor or reviewer.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

5.1.1 Statistical Issues

For the primary efficacy analysis, the sponsor based its inferences on ITT data from Study 1105 and Study 1106 with last observation carried forward (LOCF) for missing SRMH and PCGA data and compared CMR 15 mg and CMR 30 mg with placebo in SRMH and PCGA on Day 4 for the statistical significance.

Bonferroni method was used to adjust for multiple comparisons in the primary efficacy analysis, CMR 15 mg versus placebo and CMR 30 mg versus placebo, with an alpha level for each comparison being adjusted to .025.

As a supportive analysis to the primary efficacy analysis, the sponsor proposed and conducted a responder analysis. A responder was defined as a subject who had both a rating of either "very good" or "excellent" for SRMH and a rating of either "moderate improvement" or "marked improvement" for PCGA on Day 4.

Sponsor's ITT population was defined as all subjects who received at least 1 dose of study medication.

5.1.2 Collective Evidence

Based on our review of the data up to 14 days we conclude the following.

Study 1105

The statistically significant difference in SRMH as a co-primary endpoint was shown when comparing CMR 30 mg with placebo in ITT LOCF analysis (p=.007).
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But the statistically significant difference in PCGA as a co-primary endpoint was not shown when comparing CMR with placebo in ITT LOCF analysis (p-values > .025).
The responder analysis did not show a statistically significant difference in the responder rate between CMR and placebo (p-values > .05).

5.2 Conclusions and Recommendations

Data from both Study 1105 and Study 1106 failed to show efficacy of cyclobenzaprine HCl modified release (CMR) in subjects with muscle spasm associated with acute painful musculoskeletal conditions. Neither Study 1105 nor Study 1106 showed statistically significant difference of subject's rating of medication helpfulness (SRMH) and physician's clinical global assessment (PCGA) as co-primary endpoints between CMR and placebo in the intent-to-treat (ITT) population.

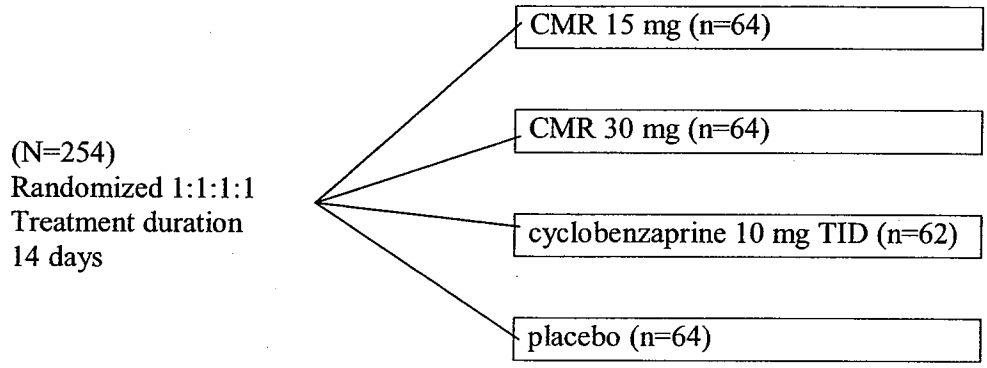
The data from Study 1105 showed the statistical significance of CMR 30 mg compared to placebo with respect to SRMH only, but did not show the statistical significance of CMR compared to placebo with respect to PCGA.

The data from Study 1106 showed the statistical significance of CMR 15 mg compared to placebo with respect to SRMH only, but did not show the statistical significance of CMR compared to placebo with respect to PCGA.

6. APPENDIX

Figure 1. Schematic of Study Design

Study 1105:



Study 1106:

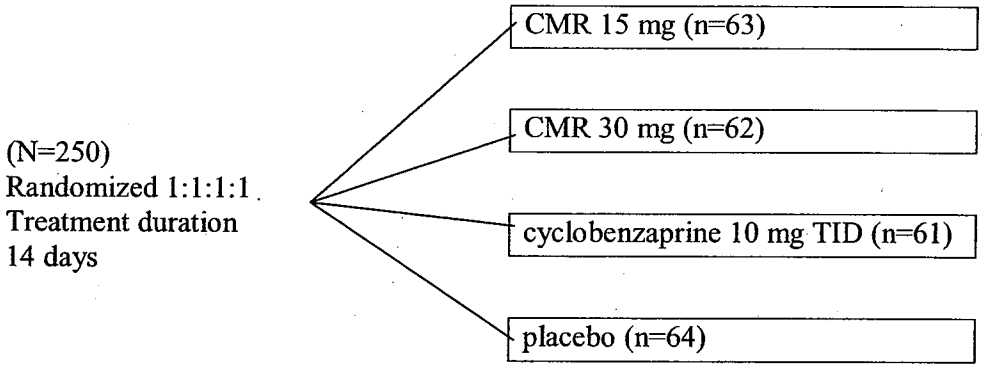


Table 1. Patient Disposition

Study 1105:

	placebo	CMR 15 mg	CMR 30 mg	cyclobenzaprine 10 mg TID
RANDOMIZED:	64	64	64	62
COMPLETED:	38 (59.4%)	45 (70.3%)	42 (65.6%)	31 (50.0%)
DISCONTINUED:	26 (40.6%)	19 (29.7%)	22 (34.4%)	31 (50.0%)
Adverse Event	2	1	3	9
Insufficient Response	2	1	2	4
Sufficient Response	6	2	3	3
Lost to Follow-up	5	3	2	3
Protocol Violation	7	6	9	4
Other	4	6	3	7

Study 1106:

	placebo	CMR 15 mg	CMR 30 mg	cyclobenzaprine 10 mg TID
RANDOMIZED:	64	63	62	61
COMPLETED:	45 (70.3%)	44 (69.8%)	41 (66.1%)	44 (72.1%)
DISCONTINUED:	19 (29.7%)	19 (30.2%)	21 (33.9%)	17 (27.9%)
Adverse Event	1	1	3	5
Insufficient Response	2	1	0	3
Sufficient Response	1	1	1	0
Lost to Follow-up	3	3	2	0
Protocol Violation	5	4	8	3
Other	7	9	7	6

Table 2. Demographic and Baseline Characteristics by Treatment Group: ITT

Study 1105:

	placebo		CMR 15 mg		CMR 30 mg		cyclobenzaprine 10 mg TID		p-value
	N	%	N	%	N	%	N	%	
Total	**64**	**25.2**	**64**	**25.2**	**64**	**25.2**	**62**	**24.4**	
Age (years)									
Mean (SD)	42.7 (13.58)		39.6 (13.76)		42.3 (13.13)		40.3 (12.19)		.455
Gender									
Male	29	45.3	25	39.1	37	57.8	28	45.2	.189
Female	35	54.7	39	60.9	27	42.2	34	54.8	
Race									
Caucasian	56	87.5	53	82.8	55	85.9	53	85.5	.597
Black	3	4.7	5	7.8	6	9.4	5	8.1	
Hispanic	4	6.3	4	6.3	3	4.7	4	6.5	
Asian	0	0.0	2	3.1	0	0.0	0	0.0	
Other	1	1.6	0	0.0	0	0.0	0	0.0	
Weight (kg)									
Mean (SD)	88.1 (25.68)		82.8 (21.39)		85.9 (22.99)		84.6 (22.01)		.624
Location of Muscle Spasms									
Lower Back	44	68.8	45	70.3	43	67.2	40	64.5	.913
Neck	20	31.3	19	29.7	21	32.8	22	35.5	
Intensity of Muscle Spasms									
None	0	0.0	0	0.0	0	0.0	0	0.0	.763
Mild	0	0.0	0	0.0	0	0.0	0	0.0	
Moderate	31	48.4	29	45.3	23	35.9	27	43.5	
Moderately Severe	28	43.8	28	43.8	33	51.6	26	41.9	
Severe	5	7.8	7	10.9	8	12.5	9	14.5	

Study 1106:

	placebo		CMR 15 mg		CMR 30 mg		cyclobenzaprine 10 mg TID		p-value
	N	%	N	%	N	%	N	%	
Total	**64**	**25.2**	**63**	**25.2**	**62**	**25.2**	**61**	**24.4**	
Age (years)									
Mean (SD)	40.6 (12.32)		37.6 (11.72)		37.5 (13.19)		41.0 (13.27)		.241
Gender									
Male	30	46.9	27	42.9	29	46.8	26	42.6	.936
Female	34	53.1	36	57.1	33	53.2	35	57.4	
Race									
Caucasian	48	75.0	45	71.4	46	74.2	46	75.4	.221
Black	7	10.9	8	12.7	10	16.1	11	18.0	
Hispanic	9	14.1	8	12.7	3	4.8	1	1.6	
Asian	0	0.0	2	3.2	2	3.2	3	4.9	
Other	0	0.0	0	0.0	1	1.6	0	0.0	
Weight (kg)									
Mean (SD)	86.0 (23.53)		85.4 (23.25)		85.9 (22.05)		78.6 (17.44)		.168
Location of Muscle Spasms									
Lower Back	41	64.1	47	74.6	40	64.5	35	57.4	.246
Neck	23	35.9	16	25.4	22	35.5	26	42.6	
Intensity of Muscle Spasms									
None	0	0.0	0	0.0	0	0.0	0	0.0	.470
Mild	0	0.0	2	3.2	0	0.0	0	0.0	
Moderate	30	46.9	28	44.4	29	46.8	33	54.1	
Moderately Severe	32	50.0	28	44.4	29	46.8	25	41.0	
Severe	2	3.1	5	7.9	4	6.5	3	4.9	

Table 3.1 Study 1105 Analysis of SRMH at Day 4: ITT with LOCF

	Placebo (N=64)	CMR 15 mg (N=64)	CMR 30 mg (N=64)	cyclobenzaprine 10 mg TID (N=62)
Excellent	1 (1.6%)	0 (0.0%)	3 (4.7%)	2 (3.2%)
Very Good	5 (7.8%)	8 (12.5%)	13 (20.3%)	11 (17.7%)
Good	15 (23.4%)	22 (34.4%)	22 (34.4%)	18 (29.0%)
Fair	24 (37.5%)	18 (28.1%)	20 (31.3%)	19 (30.6%)
Poor	10 (15.6%)	10 (15.6%)	5 (7.8%)	7 (11.3%)
Missing	9 (14.1%)	6 (9.4%)	1 (1.6%)	5 (8.1%)
P-value		.290	**.007**	.061

P-values vs. placebo calculated from the two sample Wilcoxon rank sum test.

Table 3.2 Study 1105 Analysis of PCGA at Day 4: ITT with LOCF

	Placebo (N=64)	CMR 15 mg (N=64)	CMR 30 mg (N=64)	cyclobenzaprine 10 mg TID (N=62)
Marked Improvement	8 (12.5%)	5 (7.8%)	8 (12.5%)	9 (14.5%)
Moderate Improvement	14 (21.9%)	17 (26.6%)	19 (29.7%)	19 (30.6%)
Slight Improvement	20 (31.3%)	27 (42.2%)	24 (37.5%)	19 (30.6%)
No Change	11 (17.2%)	12 (18.8%)	7 (10.9%)	10 (16.1%)
Worse	1 (1.6%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Missing	10 (15.6%)	2 (3.1%)	6 (9.4%)	5 (8.1%)
P-value		.609	.365	.408

P-values vs. placebo calculated from the two sample Wilcoxon rank sum test.

Table 3.3 Study 1105 Responder Analysis at Day 4: ITT with LOCF

	Placebo (N=64)	CMR 15 mg (N=64)	CMR 30 mg (N=64)	cyclobenzaprine 10 mg TID (N=62)
Responder	6 (9.4%)	5 (7.8%)	10 (15.6%)	10 (16.1%)
Non-responder	58 (90.6%)	59 (92.2%)	54 (84.4%)	52 (83.9%)
P-value		1.000	.423	.384

P-values vs. placebo calculated from the continuity-adjusted chi-square test.

Table 4.1 Study 1106 Analysis of SRMH at Day 4: ITT with LOCF

	Placebo (N=64)	CMR 15 mg (N=63)	CMR 30 mg (N=62)	cyclobenzaprine 10 mg TID (N=61)
Excellent	1 (1.6%)	2 (3.2%)	3 (4.8%)	1 (1.6%)
Very Good	10 (15.6%)	12 (19.0%)	9 (14.5%)	10 (16.4%)
Good	14 (21.9%)	21 (33.3%)	18 (29.0%)	29 (47.5%)
Fair	16 (25.0%)	17 (27.0%)	19 (30.6%)	18 (29.5%)
Poor	19 (29.7%)	6 (9.5%)	8 (12.9%)	3 (4.9%)
Missing	4 (6.3%)	5 (7.9%)	5 (8.1%)	0 (0.0%)
P-value		**.018**	.092	**.007**

P-values vs. placebo calculated from the two sample Wilcoxon rank sum test.

Table 4.2 Study 1106 Analysis of PCGA at Day 4: ITT with LOCF

	Placebo (N=64)	CMR 15 mg (N=63)	CMR 30 mg (N=62)	cyclobenzaprine 10 mg TID (N=61)
Marked Improvement	10 (15.6%)	10 (15.9%)	8 (12.9%)	12 (19.7%)
Moderate Improvement	14 (21.9%)	18 (28.6%)	21 (33.9%)	21 (34.4%)
Slight Improvement	23 (35.9%)	23 (36.5%)	20 (32.3%)	20 (32.8%)
No Change	11 (17.2%)	3 (4.8%)	6 (9.7%)	4 (6.6%)
Worse	1 (1.6%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Missing	5 (7.8%)	8 (12.7%)	7 (11.3%)	4 (6.6%)
P-value		.164	.235	.047

P-values vs. placebo calculated from the two sample Wilcoxon rank sum test.

Table 4.3 Study 1106 Responder Analysis at Day 4: ITT with LOCF

	Placebo (N=64)	CMR 15 mg (N=63)	CMR 30 mg (N=62)	cyclobenzaprine 10 mg TID (N=61)
Responder	9 (14.1%)	13 (20.6%)	10 (16.1%)	10 (16.4%)
Non-responder	55 (85.9%)	50 (79.4%)	52 (83.9%)	51 (83.6%)
P-value		.457	.940	.910

P-values vs. placebo calculated from the continuity-adjusted chi-square test.

SIGNATURES/DISTRIBUTION LIST

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Date: February 7, 2005

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