CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-411

<u>STATISTICAL REVIEW(S)</u>

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 22-411

Drug Name: Trazodone

Indication(s):   Unipolar Major Depressive Disorder

Applicant: Labopharm

Date(s):   Initial submission date: September 18, 2008

Review Priority: Standard

Biometrics Division: Division of Biometrics I

Statistical Reviewer: George Kordzakhia, Ph.D.

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Key Words   ANCOVA

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1.1 CONCLUSIONS AND RECOMMENDATIONS

The sponsor submitted results of one pivotal phase III study (04ACL3-001) in support of efficacy of once daily Trazodone Contramid OAD (flexible dose design with titration to one of the following dosages: 150mg, 225mg, 300mg, or 375mg) versus Placebo for the treatment of Unipolar Major Depressive Disorder.

In the primary analysis of HAMD-17 Total score, adult patients (18 to 80 years of age) with Unipolar Major Depressive Disorder on Trazodone Contramid OAD (flexible dose titrated up to one of the 4 dosages: 150mg, 225mg, 300mg, or 375mg) were observed to show statistically significant improvement over patients in the placebo treatment group.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

This is an original New Drug Application for Trazodone Contramid OAD, Extended Release, submitted under section 505(b)(2) for the treatment of Major Depressive Disorder in adults. Reference is made to the Pre-NDA meeting held on February 28, 2008. At this meeting it was agreed that this original New Drug Application 22411 for Trazodone Contramid OAD, Extended Release can be filed under section 505(b)(2) for the treatment of Major Depressive Disorder in adults, and the NDA would include 3 PK studies and 1 short-term clinical efficacy and safety study.

The sponsor submitted results of one pivotal phase III study (04ACL3-001) in support of efficacy of once daily Trazodone Contramid OAD (flexible dose design with titration to one of the following dosages: 150mg, 225mg, 300mg, or 375mg) versus Placebo for the treatment of Unipolar Major Depressive Disorder.

This was an 8-week multicenter, double-blind, randomized, parallel-group, placebo controlled, Phase III study of the efficacy and safety of Trazodone Contramid OAD at a flexible dose (titrated up to one of the 4 dosages:150mg, 225mg, 300mg, 375mg) given once daily as monotherapy in the treatment of patients with unipolar major depressive disorder. Study 04ACL3-001 was conducted at 38 active centers in the United States and Canada. There were 412 patients randomized to either Trazodone Contramid® OAD or Placebo (206 to each arm); a total of 406 patients received at least one dose of study drug and completed at least one post-baseline HAMD-17 assessment (FA population); a total of 307 (74.5%) patients completed the study.

1.3 STATISTICAL ISSUES AND FINDINGS

Trazodone Contramid OAD treatment group (flexible dose titrated up to one of the 4 dosages: 150mg, 225mg, 300mg, or 375mg) was statistically significantly superior to placebo in mean change from baseline to Week 8 in HAMD-17 total score. The p-value of comparison with placebo obtained from LOCF ANCOVA model with treatment group and pooled study site as factors, and the baseline HAMD-17 total score as a covariate was 0.0119. Several secondary endpoints were analyzed, but none was pre-specified as a key secondary endpoint and no multiple testing procedure was applied to control the overall studywise Type I error rate.

2 INTRODUCTION

2.1 OVERVIEW

This is an original New Drug Application for Trazodone Contramid OAD, Extended Release, submitted under section 505(b)(2) for the treatment of Major Depressive Disorder in adults. Reference is made to the Pre-NDA meeting held on February 28, 2008. At this meeting it was agreed that this original New Drug Application 22411 for Trazodone Contramid OAD, Extended Release can be filed under section 505(b)(2) for the treatment of Major Depressive Disorder in adults, and the NDA would include 3 PK studies and 1 short-term clinical efficacy and safety study.

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2.2 DATA SOURCES

Data used for review are from the electronic submission received on September 18, 2008. The network path is **\\FDSWA150\NONECTD\N22411\N_000\2008-09-18** in the EDR.

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 OBJECTIVE

The primary objective of this study is to evaluate whether Trazodone Contramid OAD at a flexible dose (titrated up to one of the 4 dosages: 150mg, 225mg, 300mg, or 375mg) once daily demonstrates superior efficacy compared to placebo in patients with unipolar major depression, after 8 weeks of treatment, as evidenced by the change from baseline (randomization [Visit 2]) in the HAMD-17 total score to the final visit (Visit 8, Day 56).

3.1.2 STUDY DESIGN

This was an 8-week multicenter (38 active centers in US and Canada), double-blind, randomized, parallel-group, placebo controlled, Phase III study of the efficacy and safety of Trazodone Contramid OAD at a flexible dose (titrated up to one of the 4 dosages: 150mg, 225mg, 300mg, or 375mg) given once daily as monotherapy in the treatment of patients with unipolar major depressive disorder. The study design is summarized in Table 1. The trial consisted of a Baseline Phase (screening and washout) and a double-blind Randomized Phase (randomization to Trazodone Contramid® OAD or Placebo). The total study duration, including washout of prohibited medications was approximately 11 weeks; the total duration of the randomized treatment phase was 8 weeks (titration: 2 weeks and treatment: 6 weeks). Rescue Medication for MDD was not allowed during the study.

Table 1. Study Flow Chart

	Screening	Randomized Treatment						
		Randomization	Titration		Treatment period			
Visit	1	2	3	4	5	6	7	8
Study Day		1	7	14	21	28	42	56

Source: Corresponds to Figure 9-1 (pg 23), Clinical Study Report 04ACL3-001.

For inclusion in the study, among other criteria, patients had to have MADRS total score of ≥ 26 at screening (Visit 1) and baseline (Visit 2).

3.1.3 PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

This study was conducted at 38 study centers in the United States (US) and Canada. There were 412 patients randomized to either Trazodone Contramid® OAD (flexible dose titrated up to one of the 4 dosages: 150mg, 225mg, 300mg or 375mg) or Placebo (206 patients to each arm); a total of 406 patients received at least one dose of study drug and completed at least one post-baseline HAMD-17 assessment (FA population); a total of 307 (74.5%) patients completed the study.

Table 2. Patient Disposition-All Randomized Patients

	Placebo	Trazodone
Patients		
Randomized	206 (100%)	206 (100%)
Received Study Drug	204 (99.0%)	202 (98.1%)
Discontinued Study	43 (20.9%)	62 (30.1%)
Adverse Event	6 (2.9%)	25 (12.1%)
Lack of Efficacy	9 (4.4%)	8 (3.9%)
Patient Request	9 (4.4%)	11 (5.3%)
Investigator Initiated Discontinuation	19 (9.2%)	16 (7.8%)
Administrative Reason	0 (0.0%)	2 (1.0%)
Completed study	163 (79.1%)	144 (69.9%)

Source: Table 10-1 (pg. 55), Clinical Study Report 04ACL3-001

The patients were between 18 – 80 years of age; 25 patients were 65 years old or older. The mean age of the population was 44 years; 64% were female. The mean total Hamilton Depression Scale (HAMD-17) score at Baseline was 22.4 and 23.2, respectively, for patients randomized to Placebo and Trazodone Contramid® OAD. Table 3 summarizes demographic characteristics (gender, ethnic origin, and age) and HAMD-17 score at randomization for full analysis (FA) population. The two treatment groups were well-matched with respect to demographic characteristics and baseline disease characteristics.

Table 3. Demographic and Baseline characteristics (Full Analysis Population)

Variable	Placebo N=204	Trazodone N=202
Gender, n (%)		
Male	73 (35.8%)	73 (36.1%)
Female	131 (64.2%)	129 (63.9%)
Race		
Caucasian	140 (68.6%)	139 (68.8%)
African American	44 (21.6%)	41 (20.3%)
Asian	3 (1.5%)	4 (2.0%)
Other	17 (8.3%)	18 (8.9%)
Age (years)		
Mean (SD)	44.0 (13.5)	43.8 (12.8)
Median	44.0	44.0
Age category, n (%)		
<65	188 (92.2%)	193 (95.5%)
>=65	16 (7.8%)	9 (4.5%)
HAMD-17 Total Score		
Mean (SD)	22.4 (4.4)	23.2 (4.2)
Median	22.0	23.0

Source: Table 11-1 (pg. 59), Table 11-2 (pg 60) Clinical Study Report 04ACL3-001

3.1.4 STATISTICAL METHODOLOGIES

The primary hypothesis is that Trazodone OAD at a flexible dose (titrated up to one of the 4 dosages: 150mg, 225mg, 300mg, or 375mg) administered once daily demonstrated superior efficacy compared to placebo in patients with unipolar major depression, after 8 weeks of treatment. The primary outcome variable is the change from baseline (randomization) in the (HAMD-17) total score at the final visit. The primary and secondary efficacy analyses were performed on the full analysis (FA) population set. The FA set included all randomized patients who received at least 1 dose of study treatment and who had a randomization (baseline) value and at least one post-randomized HAMD-17 assessment. For the FA population, missing data resulting from patient dropout were imputed using a Last Observation Carried Forward (LOCF) approach with post-baseline data. The primary analysis of change from baseline to final assessment (LOCF) in HAMD-17 total score tested the superiority of Trazodone OAD using an Analysis of Covariance model (ANCOVA) which includes fixed effects of treatment group and pooled study site, and baseline HAMD-17 total score as a covariate.

A supportive secondary analysis model in the FA analysis set, using a mixed model repeated measures (MMRM) approach, was employed to further characterize the treatment effects across 8 weeks of treatment. This approach assumes that missing observations are missing at random (MAR), and utilizes observed data. The model included pooled study site, treatment group, visit, and treatment group-by-visit interaction as factors, baseline HAMD-17 value as covariate, and baseline-by-visit interaction. An unstructured covariance matrix was used for the repeated measures across visits.

A blinded interim analysis was conducted to verify the assumptions used for the sample size calculations in the original protocol. These calculations assumed that that the standard deviation of the change from baseline to Week 8 in HAMD-17 total score was 7.5 and specified a minimum treatment difference of 3. The interim analysis was performed earlier than the originally projected

half of the total enrollment. By the time of the interim analysis, projections from accumulated data indicated that the final early discontinuation rate was more likely to be 15%-20% rather than 30%. The re-estimated standard deviation (7.58) for completers was slightly larger than the value assumed in the protocol's original sample size calculations (7.5). Considering a lower than initially predicted rate of early discontinuation (20% instead of 30%), it was concluded that no increase in sample size was required.

3.1.5   RESULTS OF EFFICACY ANALYSES

Primary Analysis

Table 4 presents the results of the primary efficacy analysis. For the ITT population, LOCF analysis, HAMD-17 total scores decreased for both Trazodone and placebo-treated patients. Based on the ANCOVA model, Trazodone was statistically significantly better than placebo in reducing HAMD-17 total score from baseline to Week 8 with treatment comparison p-value 0.0119. This reviewer also conducted the ANCOVA LOCF analysis of the HAMD-17 totals score mean change from baseline by visit (see Table 5). Numerically, the treatment effect of Trazodone compared with placebo was consistent across the visits.

Table 4. HAMD-17 Total Score LS Mean Change from Baseline to Endpoint Visit (ITT Population)

		Placebo	**Trazodone**
Number of patients	Total number=406	204	202
Baseline HAMD-17	Mean (SD)	22.44 (4.43)	23.16 (4.16)
Change from Baseline	LS Mean (SE)	-9.25 (0.54)	-11.17 (0.55)
Placebo-adjusted difference	LS Mean Change (SE)	NA	-1.93 (0.76)
	95% CI	NA	(-3.42, -0.43)
	P-value	NA	0.0119

Source: Table 12.1.1 and Table 12.3.1

Table 5. HAMD-17 Total score mean change from baseline by visit with missing values imputed by LOCF method (ITT Population).

	Placebo	**Trazodone**	**Treatment Difference: Trazodone - Placebo**	
Week (Visit)	LS Mean (SE)	LS Mean (SE)	LS Mean (SE)	95% CI
Week 1 (3)	-3.88 (0.35)	-5.29 (0.36)	-1.41 (0.50)	(-2.38, -0.43)
Week 2 (4)	-6.30 (0.42)	-7.69 (0.43)	-1.39 (0.59)	(-2.55, -0.23)
Week 3 (5)	-7.23 (0.45)	-9.82 (0.46)	-2.59 (0.64)	(-3.84, -1.33)
Week 4 (6)	-8.21 (0.49)	-10.38 (0.50)	-2.17 (0.69)	(-3.52, -0.81)
Week 6 (7)	-8.97 (0.49)	-10.95 (0.50)	-1.98 (0.69)	(-3.33, -0.62)
Week 8 (8)	-9.25 (054)	-11.17 (0.55)	-1.93 (0.76)	(-3.42, -0.43)

Source: Reviewer's Results
Note: The reported 95% CIs are nominal and are not adjusted for multiplicity.

Sensitivity Analysis

The reviewer confirmed sponsor's sensitivity analysis on the primary endpoint. Change from baseline in HAMD-17 Total score was analyzed by mixed effect repeated measures model.

The model included study center, treatment group, visit, and treatment group-by-visit interaction as factors, baseline HAMD-17 value as covariate, and baseline-by-visit interaction. An unstructured covariance matrix was used for the repeated measures across visits. The findings support the primary analysis results (see Table 6).

Table 6. HAMD-17 Total Score LS Mean Change from Baseline, Mixed Effects Repeated Measures model (ITT Population).

Day; Visit	Number of Patients		Treatment difference : Trazodone- Placebo	
	Placebo	Trazodone	LS Mean (SE)	95 % CI
Day 7; Visit 3	199	197	-1.40	(-2.38,-0.43)
Day 14; Visit 4	191	179	-1.60	(-2.76, -0.45)
Day 21; Visit 5	186	171	-3.13	(-4.39, -1.87)
Day 28; Visit 6	189	171	-2.67	(-4.03, -1.32)
Day 42; Visit 7	164	153	-2.40	(-3.80,-1.01)
Day 56; Visit 8	163	141	-2.27	(-3.88, -0.67)

Source: Table 11-12 (pg 69), Clinical Study Report 04ACL3-001
Note: The reported 95% CIs are nominal CIs and are not adjusted for multiplicity.

3.1.6   REVIEWER'S COMMENTS.

Trazodone Contramid OAD treatment group (flexible dose titrated up to one of the 4 dosages: 150mg, 225mg, 300mg, or 375mg) was statistically significantly superior to placebo in mean change from baseline to Week 8 in HAMD-17 Total score. The p-value of comparison with placebo obtained from LOCF ANCOVA model with treatment group and pooled study site as factors, and the baseline HAMD-17 total score as a covariate was 0.0119. Several secondary endpoints were analyzed, but none was pre-specified as a key secondary endpoint and no multiple testing procedure was applied to control the overall studywise Type I error rate.

3.2   EVALUATION OF SAFETY

Not evaluated by this reviewer. Please refer to clinical review of this application for a detailed safety evaluation.

4   FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1   GENDER, RACE AND AGE

This reviewer performed exploratory subgroup analyses on the primary efficacy variable, HAMD-17 Total score, using ANCOVA models including fixed effects of treatment group, pooled site, and baseline HAMD-17 total score as a covariate. The subgroups of interest included age (dichotomized by age greater than or equal to 65 versus others), gender and race. For all age and gender subgroups and for the Caucasian race subgroup, the treatment effect appeared to be numerically in favor of Trazodone when compared with placebo. For all racial subgroups other than Caucasian, no numerical advantage of Trazodone versus placebo was observed.

Table 7. Subgroup Analysis by Age: HAMD-17 Total Score Mean Change from Baseline to Endpoint Visit (ITT population).

		Placebo	Trazodone
Younger than 65 years			
No patients		188	193
Change from Baseline	LS Mean (SE)	-9.41 (0.56)	-11.28 (0.57)
Placebo-adjusted difference	LS Mean (SE)	NA	-1.86 (0.79)
	95% CI	NA	(-3.42, -0.31)
65 years or older			
No patients		16	9
Change from Baseline	LS Mean (SE)	-3.18 (2.67)	-11.14 (3.63)
Placebo adjusted difference	LS Mean (SE)	NA	-7.96 (5.27)
	95% CI	NA	(-19.89, 3.97)

Source: Reviewer's Results

Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

Table 8. Subgroup Analysis by Gender: HAMD-17 Total Score Mean Change from Baseline to Endpoint Visit (ITT population).

		Placebo	Trazodone
Female			
No patients		131	129
Change from Baseline	LS Mean (SE)	-9.22 (0.71)	-11.22 (0.72)
Placebo-adjusted difference	LS Mean (SE)	NA	-2.00 (0.98)
	95% CI	NA	(-3.93, -0.06)
Male			
No patients		73	73
Change from Baseline	LS Mean (SE)	-9.71 (0.90)	-10.92 (0.98)
Placebo adjusted difference	LS Mean (SE)	NA	-1.21 (1.29)
	95% CI	NA	(-3.76, 1.33)

Source: Reviewer's Results

Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

Table 9. Subgroup Analysis by Origin: HAMD-17 Total Score Mean Change from Baseline to Endpoint Visit (ITT population).

		Placebo	Trazodone
Black			
No patients		44	41
Change from Baseline	LS Mean (SE)	-14.19 (1.61)	-13.25 (1.71)
Placebo-adjusted difference	LS Mean (SE)	NA	0.93 (1.96)
	95% CI	NA	(-2.99, 4.85)
White			
No patients		140	139
Change from Baseline	LS Mean (SE)	-7.89 (0.70)	-10.86 (0.73)
Placebo adjusted difference	LS Mean (SE)	NA	-2.97 (0.89)
	95% CI	NA	(-4.73, -1.22)
Other			
No patients		20	22
Change from Baseline	LS Mean (SE)	-10.68 (2.35)	-10.35 (2.38)
Placebo adjusted difference	LS Mean (SE)	NA	0.33 (3.13)
	95% CI	NA	(-6.09, 6.75)

Source: Reviewer's Results

Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

4.2   OTHER SPECIAL/SUBGROUP POPULATIONS

Since all patients were from North America (Canada, USA), this reviewer did not perform subgroup analysis by region.

SUMMARY AND CONCLUSIONS

4.3   STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

Trazodone Contramid OAD treatment group (flexible dose titrated up to one of the 4 dosages: 150mg, 225mg, 300mg, or 375mg) was statistically significantly superior to placebo in mean change from baseline to Week 8 in HAMD-17 Total score. The p-value of comparison with placebo obtained from LOCF ANCOVA model with treatment group and pooled study site as factors, and the baseline HAMD-17 total score as a covariate was 0.0119. Several secondary endpoints were analyzed, but none was pre-specified as a key secondary endpoint and no multiple testing procedure was applied to control the overall studywise Type I error rate.

4.4   CONCLUSIONS AND RECOMMENDATIONS

The sponsor submitted results of one pivotal phase III study (04ACL3-001) in support of efficacy of once daily Trazodone Contramid OAD (flexible dose design with titration to one of the following dosages: 150mg, 225mg, 300mg, or 375mg) versus Placebo for the treatment of Unipolar Major Depressive Disorder.

In the primary analysis of HAMD-17 Total score, adult patients (18 to 80 years of age) with Unipolar Major Depressive Disorder on Trazodone Contramid OAD (flexible dose titrated up to one of the 4 dosages:150mg, 225mg, 300mg, or 375mg) were observed to show statistically significant improvement over patients in the placebo treatment group.

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BIOMETRICS
TL is out of country. Acting TL does not
feel comfortable to sign off since she was
not asked to read the whole review document.
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