CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-323

STATISTICAL REVIEW(S)

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Statistical Review and Evaluation

NDA#	21-323
Submission Date	March 23, 2001
Due Date	January 23, 2002
Sponsor	Forest Laboratories, Inc.
Name of Drug	Escitalopram Oxalate 10 mg and 20 mg Tablets
Indication	Treatment of depression
Documents Reviewed	Study Reports.

Introduction

The sponsor submitted results of two randomized, double-blinded, placebo and active controlled, parallel groups, multicenter pivotal studies to demonstrate the effectiveness of Escitalopram in the treatment of depression. Table 1 lists an overview of the designs of the two studies.

Table 1: An Overview of Designs of the two pivotal Studies.

Study #	Study Design	Randomization criteria
SCT-MD-01	A multicenter, double-blinded randomized fixed dose comparison of the efficacy and safety of Escitalopram 10 mg/day (N=119), Escitalopram 20 mg/day (N=125), Citalopram 40 mg/day (N=125), and placebo (N=122) in the treatment of major depressive disorder. The study consisted of a 1-week single-blind placebo lead-in period followed by 8 weeks of double-blind treatment. The patients were evaluated at the end of weeks 1, 2, 4, 6, and 8 of the double-blind treatment. The study was conducted in 24 US centers .	Patients assigned to Escitalopram 20 mg/day received one week of treatment at an initial dose of 10 mg/day. Patients assigned to Citalopram 40 mg/day received one week of treatment at an initial dose of 20 mg/day
SCT-MD-02	A multicenter, double-blind randomized flexible dose comparison of the efficacy and safety of Escitalopram 10 –20 mg/day (N=125), Citalopram 20-40 mg/day (N=123), and placebo (N=127) in the treatment of major depressive disorder. The study consisted of a 1-week single-blind placebo lead-in period followed by 8 weeks of double-blind treatment. The patients were evaluated at the end of weeks 1, 2, 3, 4, 6, and 8 of the double-blind treatment. The study was conducted in 22 US centers .	Upward titration from 1 to 2 placebo capsules, from 10 to 20 mg/day Escitalopram, and from 20 to 40 mg/day Citalopram was permitted at the end of Week 3 of double-blind treatment, based on clinical response and tolerability. Dosage could be subsequently decreased because of adverse events.

Entry Criteria of the patients in studies SCT-MD-01 and SCT-MD-02:

Male and female outpatients 18 years and older were eligible for participation in the studies. The maximum allowed age was 65 years in SCT-MD-01 and 80 years in SCT-MD-02. Patients were required to meet DSM-IV criteria for a major depressive disorder with an ongoing major depressive episode of at least 4 weeks in duration at baseline. At screening and baseline visits, a minimum total score of 22 on the MADRS and a

minimum score of 2 on item 1 of the HAMD were required. Patients with any principal diagnosis other than major depressive disorder or any clinically significant unstable medical illness were excluded. Patients who were suicidal or met DSM-IV criteria for substance abuse or dependence within 6 months of study start were also excluded from the studies. Women of childbearing potential were required to be using an acceptable method of birth control and not to be pregnant or nursing. Patients with an allergy or hypersensitivity to citalopram, or those who had previously failed to respond to an adequate trial of either SSRI or two non-SSRI antidepressants were also excluded. Concomitant psychotropic treatment (other than Zolpidem for sleep) was not allowed during the study period.

Objectives of the studies:

In both studies, the primary objective was to evaluate the efficacy and safety of escitalopram relative to placebo in the treatment of depression. A secondary objective was to compare the safety and efficacy of citalopram to placebo in the treatment of depression.

Primary and secondary efficacy measures:

In both studies, the primary efficacy measure was the change from baseline to week 8 in the MADRS score. The secondary efficacy measures were the HAMD, the HAMD Depressed Mood Item, the CGI-S score, and the CGI-I score.

Statistical Methods to analyze the primary and secondary efficacy measures:

In both studies, the primary analyses were carried out using the last observation carried forward (LOCF) approach, and ANCOVA model with treatment, study center, and the treatment by center interaction as factors, and the baseline score as covariate. The interaction term was dropped from the model if it was not significant at the 10% level. In study SCT-MD-01, pairwise comparisons of escitalopram 10 mg/day versus placebo, and escitalopram 20 mg/day versus placebo were considered only if the overall p-value was significant at significant level 0.05.

The secondary measures HAMD, the HAMD depressed mood item, and CGI-S score were analyzed using the same ANCOVA model as used for the primary efficacy measure. For CGI-I, an analysis of variance (ANOVA) model with treatment, study center, and the treatment by center interaction as factors.

Subgroup analyses (i.e., by gender, race: Caucasian, non-Caucasian, and disease course: single episode, recurrent) on the pooled LOCF dataset were carried out using the primary efficacy measure, change from baseline to week 8 in MADRS. An ANCOVA model with treatment, protocol, and subgroup as main effects, the treatment by subgroup interaction term, and the baseline MADRS score as covariate. The effect of age was analyzed using a similar ANCOVA model with age as a covariate.

Table 2: Disposition of Patients

	SCT-MD-01				SCT-MD-02		
	Placebo	Escitalopram 10 mg/day	Escitalopram 20 mg/day	Citalopram 40 mg day	Placebo	Escitalopram 10-20mg/day	Citalopram 20-40 mg/day
Safety population	122	119	125	125	127	125	123
ITT population	119	118	123	125	125	124	119
Completers	91 (74.6%)	95 (79.8%	94 (74.2%)	93 (74.4%)	105 (82.7%)	96 (76.8%)	99 (80.5%)
Discontinuation	31 (25.4%)	24 (20.2%)	31 (24.8%)	32 (25.6%)	22 (17.3%)	29 (23.2%)	24 (19.5%)
AE	3 (2.5%	5 (4.2%)	13 (10.4%)	11 (8.8%)	4 (3.1%)	11 (8.8%)	5 (4.1%)
Lack of Efficacy	6 (4.9%)	3 (2.5%)	0	1 (0.8%)	1 (0.8%)	2 (1.6%)	1 (0.8%)
Protocol Violation	1 (0.8%)	3 (2.5%)	3 (2.4%)	1 (0.8%)	3 (2.4%)	3 (2.4%)	2 (1.6%)
Withdrawal of consent	10 (8.2%)	2 (1.7%)	6 (4.8%)	3 (2.4%)	6 (4.7%)	5 (4.0%)	6 (4.9%)
Lost to follow-up	10 (8.2%)	11 (9.2%)	8 (6.4%)	15 (12.0%)	6 (4.7%)	7 (5.6%)	10 (8.1%)
Other reasons	1 (0.8%)	0	1 (0.8%)	1 (0.8%)	2 (1.6%)	1 (0.8%)	0

Note: percentages are relative to the safety population

Table 2 lists patient disposition summary by study and treatment group. The safety population includes all patients treated with double-blind study medication. The ITT population includes all patients who received at least one dose of double-blind medication and had at least one post-baseline MADRS assessment. The discontinuation rates and the reasons for discontinuation among the treatment groups with each study are comparable.

Table 3: Patients' baseline Characteristics by treatment groups of each of the two studies.

Study No.	Treatment Group (N)	Mean Age (years) [Range]	# Male (%)	Race (%)
SCT-MD-01	Placebo (N=119)	40.1 [18-63]	48 (40%)	Caucasian : 102 (86%) Non- Caucasian : 17 (14%)
	Escitalopram 10 mg/day (N=118)	40.7 [19-65]	35 (30%)	Caucasian : 102 (86%) Non- Caucasian : 16 (14%)
	Escitalopram 20 mg/day (N=123)	39.6 [19-63]	40 (32%)	Caucasian : 102 (83%) Non- Caucasian : 21 (17%)
	Citalopram 40 mg/day (N=125)	40.0 [18-65]	47 (38%)	Caucasian : 101 (81%) Non- Caucasian : 24 (19%)
SCT-MD-02	Placebo (N=125)	42.3 [18-76]	52 (42%)	Caucasian : 103 (82%) Non- Caucasian : 22 (18%)
	Escitalopram 10 –20 mg/day (N=124)	41.4 [19-73]	60 (48%)	Caucasian : 102 (82%) Non- Caucasian : 22 (18%)
	Citalopram 20-40 mg/day (N=119)	42.0 [19-71]	62 (52%)	Caucasian : 102 (86%) Non- Caucasian : 17 (14%)

Table 3 lists the demographic characteristics of the randomized patients by treatment group. In both studies, the randomization seems to be balanced with respect to the patients' demographic characteristics. Next, the efficacy findings of each of the two studies submitted by the sponsor will be reviewed.

Sponsor's Findings:

Study SCT-MD-01:

The randomized patients had a mean age of 40 years; majority was Caucasian (83.9%), and female (64.9%). Table 3 lists the demographic characteristics by treatment groups. The four treatment groups were comparable with respect to their demographic characteristics.

Table 4: Mean baseline scores and Mean change from baseline to week 8 in MADRS
[Based on ITT Population]

	Mean Baseline Scores							
Measures	Placebo (N=119)		Escitalopram 10 mg/day(N=118)		Escitalopram 20 mg/day (N=123)		Citalopram (N=125)	
MADRS	29.5		28.0		28.9		29.2	
HAMD	25.8		24.3		25.8		25.9	
CGI-S	4.2		4.2		4.3		4.3	
	Mean change from baseline to week 8							
(LOCF analysis)	Placebo		Escitalopram (10 mg/day)		Escitalopram (20 mg/day)		Citalopram	
	N	Mean	N	Mean	N	Mean	N	Mean
MADRS	119	-9.4	118	-12.8	123	-13.9	125	-12.0
P-values (vs. Placebo)				**0.0007**		**<0.0001**		**0.0414**
HAMD	119	-7.6	118	-10.2	123	-11.7	125	-9.9
P-values (vs. Placebo)				**0.0178**		**0.0067**		**0.0518**
CGI-S	119	-0.8	118	-1.3	122	-1.4	125	-1.2
P-values (vs. Placebo)				**0.0002**		**<0.0001**		**0.0266**
(OC analysis)	Placebo		Escitalopram (10 mg/day)		Escitalopram (20 mg/day)		Citalopram	
	N	Mean	N	Mean	N	Mean	N	Mean
MADRS	91	-10.0	95	-14.0	97	-16.1	98	-13.5
P-values (vs. Placebo)				**0.0007**		**<0.0001**		**0.0227**
HAMD	91	-8.2	95	-10.9	97	-13.3	98	-11.0
P-values (vs. Placebo)				**0.0046**		**<0.0001**		**0.0502**
CGI-S	91	-0.9	95	-1.4	96	-1.7	97	-1.4
P-values (vs. Placebo)				0.0002		**<0.0001**		**0.0166**

Table 4 lists the baseline means and the mean changes at week 8 from baseline scores of the primary and secondary efficacy measures. There was no evidence of any statistically significant treatment differences at baseline with respect to the primary (MADRS total score) and secondary efficacy measures. At week 8, the LOCF analysis comparing the mean change from baseline in MADRS in the escitalopram and placebo groups demonstrated a statistically significant overall treatment effect ($p<0.0001$). Pairwise

comparisons demonstrated that the 10 mg/day and 20 mg/day of escitalopram were statistically significantly (p=0.0007 and p<.0001) efficacious as compared to placebo. The treatment by center interaction was not statistically significant (p=0.221) and was dropped from the model.

The OC analyses on the change from baseline to week 8 on the MADRS provided significant results for the both escitalopram groups as compared to the placebo group. Citalopram (the active controlled) treated-patients also showed significant improvement than placebo in the change from baseline to week 8 on the MADRS (p=0.0414 in LOCF and p=0.0227 in the OC analyses).

The response rates (responders defined as a decrease of 50% greater from baseline on MADRS) at week 8 for 10 mg/day and 20 mg/day of escitalopram were significantly higher (p=0.0005, p= 0.0002), as compared to the rate for placebo. The responder rate at week 8 for citalopram group was also significantly higher (p=0.0033), as compared to the rate for placebo.

In the LOCF analyses, both the 10 mg/day and 20 mg/day escitalopram groups showed significant improvements compared to placebo as early as the second week of treatment (p=0.0256 and p=0.0311) and continued to show this difference at every visit through the end of week 8. This significant improvement was also true for the citalopram group. In the OC analyses, significant improvement (p<0.05) in both escitalopram groups was apparent at the end of week 4 and continued through week 8.

For HAMD (secondary measure), the LOCF analyses on the mean change from baseline to week 8 demonstrated that both 10 mg/day and 20 mg/day of escitalopram were statistically significantly efficacious (p=0.0178, p=0.0067), as compared to placebo. Similar results were observed in the OC analyses. By visit wise analyses, both escitalopram dose groups showed efficacious effects, as compared to the placebo group by week 4 and maintained through the end of week 8. For the HAMD depressed mood item, both escitalopram dose groups also showed significant efficacious effect. as compared to the placebo group. Both escitalopram dose groups showed significant efficacious results on CGI-I and CGI-S at week 8. Patients treated with escitalopram 10 mg/day had a significantly improved CGI-I (p=0.0007) and CGI-S (p=0.0002) at week 8 compared to placebo treated patients. Similarly, patients treated with escitalopram 20 mg/day had also significantly better CGI-I (p=0.0001) and CGI-S (p<0.0001) ratings than placebo treated patients at week 8.

No formal interim analyses were planned and done for this study.

Adverse Events:

Seven serious adverse events were reported in 6 patients: 2 in the escitalopram 20 mg/day group (anaphylaxis and suicide attempt), 2 in the citalopram group (accidental overdose and coma in one patient and intestinal fistula in another patient), and 2 in the placebo group (gall bladder stones and non-accidental overdose). Thirty-two patients were

discontinued because of adverse events (Table 2). The incidences of discontinuation for adverse events were 2.5%, 4.2%, 10.4%, and 8.8% for the placebo, escitalopram 10 mg/day, escitalopram 20 mg/day, and citalopram groups, respectively. The most frequent treatment-emergent adverse events were headache, nausea, diarrhea, insomia, mouth dry, and ejaculation disorder (Table 5).

Table 5. Most Frequent Treatment Emergent Adverse Events (>=10%)

	Number (%) of Patients			
	Placebo (N=122)	Escitalopram 10 mg/day (N=119)	Escitalopram 10 mg/day (N=119)	Citalopram (N=125)
Patients with at least 1 TEAE	86 (70.5%)	94 (79.0%)	107 (85.6%)	108 (86.4%)
Headache	30 (24.6%)	18 (15.1%)	26 (20.8%)	31 (24.8%)
Nausea	7 (5.7%)	25 (21.0%)	17 (13.6%)	27 (21.6%)
Diarrhea	9 (7.4%)	12 (10.1%)	17 (13.6%)	14 (11.2%)
Insomnia	4 (3.3%)	12 (10.1%)	17 (13.6%)	14 (11.2%)
Mouth Dry	9 (7.4%)	12 (10.1%)	11 (8.8%)	13 (10.4%)
Ejaculation Disorder[a]	0	3 (8.6%)	5 (12.2%)	2 (4.3%)

[a]: percentages are relative to the number of male patients [placebo(n=50);escitalopram 10 mg/day (N=35); escitalopram 20 mg/day (N=41); and citalopram (N=47)]

Sponsor's Final Conclusion:

The efficacy findings support the conclusion that 10 mg/day and 20 mg/day escitalopram were effective in the treatment of outpatients with major depressive disorder. Escitalopram 10 mg/day and 20 mg/day were also safe and tolerated. The efficacy and safety profile of escitalopram at either dose were similar to that of citalopram.

The escitalopram 20 mg/day was consistently numerically superior to that observed in the escitalopram 10 mg/day. The incidence of discontinuations for adverse events was lower in the escitalopram 10 mg/day, as compared to the rate for escitalopram 20 mg/day. With respect to adverse events rates, escitalopram 20 mg/day was more comparable to citalopram 40 mg/day.

Reviewer's Analysis and comments:

This reviewer reanalyzed the data set according to the statistical plan specified in the protocol. The findings were consistent with the sponsor's reported findings on the primary and secondary efficacy measures.

Study SCT-MD-02:

The randomized patients had a mean age of 42 years; majority was Caucasian (83%), and female (53%). Table 3 lists the demographic characteristics by treatment groups. The three treatment groups were comparable with respect to their demographic characteristics.

Table 6: Mean baseline scores and Mean change from baseline to week 8 in MADRS
[Based on ITT Population]

Measures	Mean Baseline Scores					
	Placebo (N=125)		Escitalopram (N=124)		Citalopram (N=119)	
MADRS	28.8		28.7		28.3	
HAMD	25.0		24.8		25.0	
CGI-S	4.3		4.3		4.3	
	Mean change from baseline to week 8					
(LOCF analysis)	Placebo		Escitalopram		Citalopram	
	N	Mean	N	Mean	N	Mean
MADRS	125	-11.2	124	-12.9	119	-13.0
P-values (vs. Placebo)			**0.251**		**0.151**	
HAMD	125	-9.6	124	-10.4	119	-11.4
P-values (vs. Placebo)			**0.506**		**0.068**	
CGI-S	125	-1.1	124	-1.3	119	-1.5
P-values (vs. Placebo)			**0.439**		**0.024**	
(OC analysis)	Placebo		Escitalopram		Citalopram	
	N	Mean	N	Mean	N	Mean
MADRS	108	-11.8	98	-15.1	102	-14.1
P-values (vs. Placebo)			**0.032**		**0.050**	
HAMD	108	-10.2	98	-12.3	102	-12.4
P-values (vs. Placebo)			**0.100**		**0.027**	
CGI-S	108	-1.2	98	-1.5	102	-1.7
P-values (vs. Placebo)			**0.061**		**0.005**	

Table 6 lists the baseline means and the mean changes at week 8 from baseline scores of the primary and secondary efficacy measures. There was no evidence of any statistically significant treatment differences at baseline with respect to the primary (MADRS total score) and secondary efficacy measures. At the end of week 8, the escitalopram and citalopram groups showed numerically greater decreased as compared to the baseline score on the MADRS than the decreased for the placebo group, but the differences were not statistically significant in the LOCF analysis. The treatment by center interaction was not statistically significant (p=0.106) and was dropped from the model. For the OC analyses at week 8, the mean change from baseline on MADRS score for the escitalopram group was significantly higher (p=0.032), as compared to the change for the placebo group. Citalopram treated patients also showed significantly greater improvement (p=0.050) than placebo in the week 8 OC analysis.

The response rate on the MADRS (Responders defined as a decrease of 50% or greater from baseline) in the week 8 LOCF analysis was 41% in the placebo group, 46% in the escitalopram and 51% in the citalopram group.

In the by-visit LOCF analyses, there were no significant differences between either escitalopram or citalopram treatment and placebo treatment at any visit. However, both escitalopram and citalopram groups produced numerically grater improvement than placebo at each week in both LOCF and OC analyses.

There were no significant differences between either escitalopram or citalopram treatment and placebo treatment with respect to the secondary measures (HAMD and CGI-S) in the by-visit LOCF analyses. However, both escitalopram and citalopram groups produced numerically grater improvement than placebo at each week in both LOCF and OC analyses.

No formal interim analyses were planned and done for this study.

Adverse Events:

Serious adverse events, all of which were classified as unrelated to study drug by the investigator, were reported in 3 patients: 2 patients in the escitalopram group (suicidal tendency and suicide attempt in one and non-accidental overdose, suicide attempt, and tachycardia in the other) and 1 in the citalopram group (cholestasis intrahepatic and dehydration). Twenty patients were discontinued because of adverse events (Table 2). The incidences of discontinuation for adverse events were 8.8%, 4.1%, and 3.1% for the escitalopram, citalopram, and placebo groups, respectively. The most frequent treatment-emergent adverse events were headache, nausea, ejaculation disorder, insomia, fatigue, mouth dry, and somnolence (Table 7). No deaths occurred during the conduct of the study.

Table 7. Most Frequent Treatment Emergent Adverse Events (>=10%)

	Number (%) of Patients		
	Placebo (N=127)	Escitalopram (N=125)	Citalopram (N=123)
Patients with at least 1 TEAE	96 (75.6%)	99 (79.2%)	100 (81.3%)
Headache	23 (18.1%)	27 (21.6%)	28 (22.8%)
Nausea	16 (12.6%)	20 (16.0%)	18 (14.6%)
Ejaculation Disorder [b]	0	9 (15.0%)	10 (15.9%)
Insomnia	8 (6.3%)	17 (13.6%)	14 (11.4%)
Fatigue	3 (2.4%)	15 (12.0%)	5 (4.1%)
Mouth Dry	15 (11.8%)	13 (10.4%)	8 (6.5%)
Somnolence	6 (4.7%)	13 (10.4%)	9 (7.3%)
Diarrhea	11 (8.7%)	12 (9.6%)	18 (14.6%)

[b]: percentages are relative to the number of male patients [placebo(n=53); escitalopram (N=60); and citalopram (N=63)]

Sponsor's Final Conclusion:

Neither escitalopram nor citalopram treatment produced significant improvement (although numerically superior) as compared to placebo treatment in the protocol specified primary efficacy analysis, an analysis of the change from baseline to week 8 in the MADRS using LOCF approach. So the study is considered as a failed study. The OC analysis on MADRS demonstrated statistically significant improvement for escitalopram and citalopram treatment as compared to placebo treatment.

Reviewer's Analysis and comments:

This reviewer reanalyzed the data set according to the statistical plan specified in the protocol. The findings were consistent with the sponsor's reported findings on the primary and secondary efficacy measures.

Subgroup Analyses:

The sponsor did subgroup analyses on the primary efficacy measure, change from baseline to week 8 in the MADRS, using the pooled LOCF dataset from both clinical trials. Controlling sex, race, age, and disease course, the subgroup analyses were done. The subgroup analyses indicated that the mean changes from baseline were similar in magnitude in escitalopram treated patients. There was no significant effect of any subgroup, or treatment-by-subgroup interaction effect.

Reviewer's Overall Conclusion:

In this new drug application, the sponsor submitted two randomized trials' results to support the efficacy of escitalopram for treatment of major depressive disorder. The sponsor analyzed the data sets according to the protocol-specified models. The study designs of the two studies were identical (except study SCT-MD-01 was a fixed dose study and study SCT-MD-02 was a flexible dose study). The fixed dose study demonstrated the efficacy of escitalopram for treatment of major depressive disorder. The flexible dose study was a failed study and was failed with respect to the study drug escitalopram, as well as with respect to the active controlled drug citalopram. The sponsor claimed that the failure of the flexible dose study could be attributed to the magnitude of the placebo response.

Before submitting this NDA, the sponsor made an agreement (a response letter from FDA, dated April 22, 1998) with FDA that one well designed and conducted efficacy study should be sufficient to support the efficacy of escitalopram in the treatment of depression. In this NDA submission, the sponsor demonstrated the efficacy of escitalopram based on the fixed dose study (study SCT-MD-01). Both Escitalopram 10 and 20 mg/day doses were effective in the treatment of outpatients with major depressive disorder. The doses were also safe and tolerated. The efficacy and safety profiles of escitalopram at either dose were similar to that of citalopram.

Ohidul Siddiqui, Ph.D
Mathematical Statistician

Concur: Dr. Kun Jin

Dr. George Chi

CC:
Arch NDA # 21-323
HFD-120/Dr. Katz
HFD-120/Dr. Laughren
HFD-120/Dr. Brugge
HFD-120/Mr. David
HFD-710/Dr. Chi
HFD-710/Dr. Jin
HFD-710/Dr. Siddiqui
HFD-700/Dr. Anello

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/s/

Ohidul Siddiqui
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Kun Jin
11/16/01 10:08:53 AM
BIOMETRICS

George Chi
11/19/01 03:09:48 PM
BIOMETRICS