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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-427

Statistical Review(s)

9/2/03

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

STATISTICAL REVIEW AND EVALUATION

NDA:	21-427_Responses to Approval Letter
DRUG NAME:	CYMBALTA (duloxetine hydrochloride)
INDICATION:	Major Depressive Disorder
SPONSOR:	Eli Lilly and Company
STATISTICAL REVIEWER:	Ohidul Siddiqui
DATE OF DOCUMENT:	March 25, 2003

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EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

In this submission, the sponsor submitted a complete response to the approval letter for the NDA 21-427. The sponsor also submitted results of two studies to demonstrate the efficacy of 40 mg BID and 60 mg BID. Both studies were conducted in Europe. One study demonstrated the significant efficacy of 40 mg BID and 60 mg BID based on both the LOCF and repeated measures analyses. The second study demonstrated the significant efficacy of the two doses in the repeated measure analyses, but failed to demonstrate significant efficacy of the two doses in the LOCF analyses.

The sponsor also reported the calculated effect sizes of duloxetine 40 mg/day, 60 mg/day based on the primary efficacy measure HAMD17 total score in two studies (HMAT, HMBH). The results of these two studies were originally submitted in NDA 21-427. This reviewer also calculated the effect size of duloxetine 80 mg/day, and 120 mg/day. The effect sizes of different dose levels seem to be not comparable across U.S and Non-U.S studies. Within U.S studies, the effect size of duloxetine 60 mg/day is the highest as compared to the sizes for duloxetine 40 mg/day, and 80 mg/day, and hence, the FDA's recommendation that "Cymbalta should be administered at a dose of 40 to 60 mg/day..." seems to be valid for starting optimal dose range in the treatment of depression.

INTRODUCTION

On November 12, 2001, Lilly submitted a new drug application (NDA 21-427) for the use of duloxetine hydrochloride in the treatment of adult major depressive disorder (MDD). The Division of Neuropharmacological Drug Products subsequently sent an approvable letter on September 13, 2002. In the letter, the division asked the sponsor to address some issues stated in the letter for the final approval. In the submission dated March 25, 2003, the sponsor submitted a Complete Response to that action letter.

One of the issues stated in the approvable letter was that there was no difference in effectiveness between 20 mg twice daily (BID) and 40 mg BID, that efficacy of higher doses of duloxetine (80-120 mg/day) had not been demonstrated, and with the conclusion that "there is no reason to use doses higher than 60 mg/day." FDA recommended to administer at a regimen of 40 to 60 mg/day as starting dose.

The sponsor disagreed with FDA's position at the time of the Approvable Letter. The sponsor has responded that based on the effect sizes, 60 mg/day has greater efficacy overall than 40 mg/day, with similar safety and tolerability. Duloxetine doses of 40 mg/day and 60 mg/day were studied in different protocols. Thus, no direct comparison is possible. Therefore, a comparison of effect sizes of the two doses for the primary efficacy measures clearly indicated superior efficacy for the 60-mg/day dose.

In this submission, the sponsor's original response concerning doses greater than 80 mg/day also has been augmented by inclusion of data from recently completed studies HMAYa and HMAYb. Both of the studies were non-U.S studies (conducted in Bulgaria, Croatia, Romania, Russia, Hungary, Poland, and SK??). In the original NDA (21-427), all of the submitted pivotal studies were conducted in U.S. In this review, the efficacy results of the two studies (HMAYa and HMAYb), and the effect sizes of different dose levels will be calculated and compared across the U.S and Non-U.S studies to recommend the optimal starting dose.

STUDY DESIGN

The two HMAY studies were foreign, multicenter, parallel, double-blind, randomized, placebo- and active comparator-controlled study comparing duloxetine with placebo and paroxetine in the acute and long-term treatment of patients with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)-defined major depressive disorder (MDD).

Each study consisted of three study periods:
•**Study Period I:** A screening phase that lasted 5 to 9 days, during which patients were screened for eligibility.
•**Study Period II:** A 9-week period of acute double-blind treatment. All patients who met entry criteria were enrolled and placed on placebo at Visit 2 (for a period of 1 week). At Visit 3, patients were randomly assigned to one of four treatment groups: duloxetine 60 mg twice daily (BID), duloxetine 40 mg BID, placebo, or paroxetine 20 mg once daily

(QD). At Visit 8, patients either concluded their participation in the study, or continued into Study Period III.

•**Study Period III:** A long-term period (28-week) of continuation double-blind treatment (26 weeks of active treatment; 2 weeks of placebo lead-out). All patients who continued into this phase remained in the same treatment group to which they were randomly assigned at Visit 3. At Visit 15, all patients transitioned to placebo. Patients received placebo from Visit 15 to Visit 16. Figure 1 presents the study design.

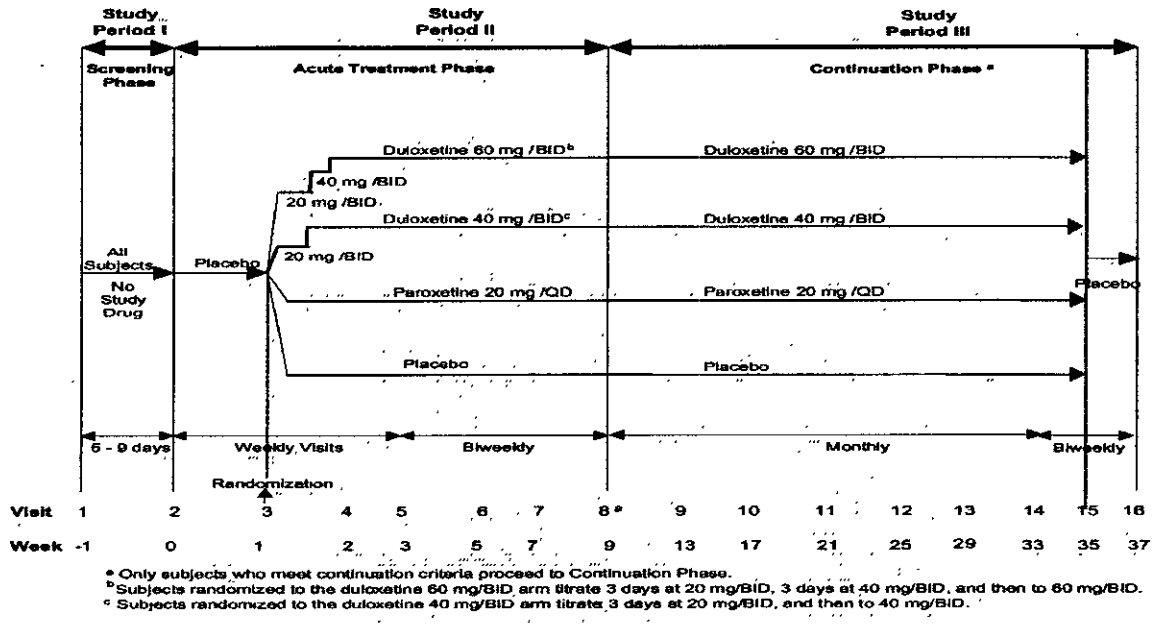

Figure 1: Illustration of study design for studies HMAYA and HMAYB .

STUDY POPULATION

Inclusion Criteria

Male or female patients were included in the study if they were at least 18 years of age with DSM-IV-defined major depression. Patients were required to have 17-item Hamilton Depression Rating Scale (HAMD17) total scores >=15 at Visits 1 and 2, and Clinical Global Impressions of Severity (CGI-Severity) scores >=4 at Visits 1 and 2.

Exclusion Criteria

Patients were excluded from the study if they had any current primary DSM-IV Axis I diagnosis other than MDD; had been diagnosed with dysthymia within the past 2 years; had a previous diagnosis of psychosis, bipolar disorder, or schizoaffective disorder; had any anxiety disorder as a primary diagnosis within the past year; had an Axis II disorder which, in the judgment of the investigator, would have interfered with compliance with the study protocol; had abnormal thyroid-stimulating hormone (TSH) concentrations; had a history of substance abuse or dependence within the past year (excluding nicotine and caffeine); or had a positive urine drug screen for any substances of abuse. Patients judged to be at serious suicidal risk and patients with a serious medical illness were also excluded.

PRIMARY OBJECTIVE

The primary objective of the two studies was to assess the efficacy of duloxetine 60 mg twice daily (BID) compared with placebo in the acute treatment of patients who meet criteria for major depressive disorder (MDD) as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Primary efficacy was evaluated using the mean total scores of the 17-item Hamilton Depression Rating Scale (HAMD17) at endpoint.

STATISTICAL ANALYSIS PLAN

Analyses were conducted on an intent-to-treat sample. An intent-to-treat analysis is an analysis of data by the groups to which patients were assigned by random allocation, even if the patient did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Patients who were discontinued after Visit 2 due to positive urine barbiturate/benzodiazepine results were not included in the analyses.

Multiple Comparisons/Multiplicity

The primary efficacy measure, the HAMD17 total score, was chosen *a priori* to test the efficacy of duloxetine 60 mg BID versus placebo in patients with MDD, and thus the type I error was controlled at the significance level of 0.05 for the primary analysis. The purpose of collecting several secondary efficacy measures was to confirm the findings of the primary measure using different instruments (for example, HAMD17 subscales, patient-reported outcomes), and it was not intended to draw conclusions from these secondary efficacy measures at the same experiment-wise significance level as for the primary measure. Thus, no adjustments for multiplicity were made.

Handling of Dropouts or Missing Data

Patients were included in the efficacy analyses only if they had baseline and at least one postbaseline measures. Total scores (for example, HAMD17 total, HAMD17 subscales) were considered to be missing if any of the item scores were missing.

Table 1: Patients Characteristics by treatment groups.

Protocol No.	Study #	Treatment Group (N)	Mean Age (years) [Range]	Male (%)	Race (%)
F1J-MC-HMAY	A	Placebo (N=93)	43.67 [19-75]	25.8%	100 % Caucasian
		Dulox40BID (N=95)	43.09 [19-65]	26.3%	100 % Caucasian
		Dulox60BID (N=93)	44.72 [20-75]	24.7%	99 % Caucasian
		PRX20QD (N=86)	42.00 [21-62]	32.6%	100 % Caucasian
	B	Placebo (N= 99)	44.67 [22-77]	34.3 %	100 % Caucasian
		Dulox40BID (N=93)	46.47 [21-75]	33.3 %	100 % Caucasian
		Dulox60BID (N=103)	43.99 [20-74]	25.2 %	100 % Caucasian
		PRX20QD (N=97)	45.81 [20-75]	28.9 %	100 % Caucasian

Subgroup analyses were performed considering the subgroups defined either by demographic factors or by baseline disease status as follows: three demographic subgroups were defined as age (<55 or >=55), gender, and racial origin (Caucasian or Other); and four other subgroups were determined by the baseline disease status as 1) Patients with baseline HAMD17 total score of <19 or baseline score >=19; 2) Patients with or without prominent symptoms of anxiety (baseline HAMD17 Anxiety/Somatization subfactor score >=7 or <7); 3) Patients with or without prominent sleep disturbances (baseline HAMD17 sleep subfactor score >=4 or <4); and 4) Patients with or without melancholic features. Subgroup analyses (ANCOVA analysis) were performed on the change score from baseline to endpoint on HAMD17 total score.

SPONSOR'S FINDINGS

EFFICACY FINDINGS

Table 1 lists the patients' demographic characteristics at baseline by treatment groups. No statistically significant differences among treatment groups were observed with regard to age, gender, origin. Patients had a mean age of approximately 43 years in study A and 45 years in study B. In both studies, majority of the patients were females and all patients were Caucasians.

Table 2. Reasons for discontinuation of patients in the Acute Treatment Phase.

Study		PLACEBO N=93	DLX40BID N=95	DLX60BID N=93	PRX20QD N=86
A	Any reason	19%	13%	9.7%	12%
	Adverse event	3.2%	4.2%	3.2%	3.5%
	Lack of efficacy, patient/ MD perception	7.2%	3.2%	2.2%	1.2%
	Personal conflict or other patient decision	2.2%	4.2%	3.2%	3.5%
	Unable to contact patient(lost to follow up)	2.2%	-	-	3.5%
	Sponsor's decision	3.2%	1.1%	-	-
	Protocol violation	1.1%	-	1.1%	-
		PLACEBO N=99	DLX40BID N=93	DLX60BID N=103	PRX20QD N=97
B	Any reason	9.1%	11%	13%	11%
	Adverse event	1.0%	2.2%	1.9%	3.1%
	Lack of efficacy, patient/ MD perception	4%	3.2%	1.9%	3.1%
	Personal conflict or other patient decision	1%	1.1%	1.9%	2.1%
	Unable to contact patient(lost to follow up)	1%	-	-	3.1%
	Sponsor's decision	-	1.1%	.97%	-
	Protocol violation				

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Table 3. Mean Change from Baseline to Endpoint (end of week 9)

TRT (N)	LOCF ANCOVA analysis				Repeated Measure analysis			
	LS Mean change [1]	P-values			LS Mean change [1]	P-values		
		Vs. 1	Vs. 2	Vs. 3		Vs. 1	Vs. 2	Vs. 3
STUDY A								
1) Placebo (N=93)	-8.07				-8.78			
2) Dulox40BID (N=95)	-10.22	**.007**			-11.01	**.001**		
3) Dulox60BID (N=93)	-11.06	**<.001**	.297		-12.08	**<.001**	.122	
4) PRX20QD (N=86)	-10.83	**.001**	.458	.784	-11.68	**<.001**	.347	.569
STUDY B								
		Vs. 1	Vs. 2	Vs. 3		Vs. 1	Vs. 2	Vs. 3
1) Placebo (N= 99)	-10.13				-10.77			
2) Dulox40BID (N=93)	-11.06	.253			-12.14	**.045**		
3) Dulox60BID (N=103)	-11.64	.054	.466		-12.40	**.014**	.698	
4) PRX20QD (N=97)	-10.61	.552	.586	.194	-11.92	.089	.746	.470

[1] Ls mean change from baseline.

LOCF model: In Study A: PROC GLM Model= Trtmnt, Poolinv, and Baseline for Main Effects p- values.

LOCF model: In Study B: PROC GLM Model= Trtmnt, Poolinv, Baseline and Trtmnt* Poolinv for Main Effects p-values.

Repeated Analysis Model: In both studies: Model hamd17= Therapy visit poolinv Therapy* visit basval basval* visit; Cov. Unstructured

Table 2 shows reasons for discontinuation (patient disposition) for the acute treatment phase (Visit 4 to Visit 8). In study A, the rate of discontinuation for any reason in the placebo group was approximately twice that of the duloxetine 60 mg BID group. The percentages of patients who discontinued due to adverse events were similar across the four groups. The discontinuation rate due to perceived lack of efficacy was highest in the placebo group.

In study B, the percentages of patients who discontinued for any reason during the acute treatment phase were similar among the four treatment groups. The percentages of patients who discontinued due to adverse events were similar across the four groups. More patients in the placebo treatment group discontinued for perceived lack of efficacy as compared with the duloxetine 60 mg BID group.

Table 3 lists the sponsor's reported results from repeated measure analysis (protocol specified primary analysis) and LOCF ANCOVA analysis. In study A, both repeated measures analysis and LOCF analysis of the ITT sample demonstrated statistically significant superiority of duloxetine 60 mg BID and 40 mg BID over placebo at visit 8/week 9 (endpoint). Duloxetine 60 mg BID was not statistically significantly (p-value=.297 (LOCF analysis), and p-value=.122 (Repeated analysis) different from 40 mg BID.

In study B, the repeated measures analysis of the ITT sample demonstrated statistically significant superiority of duloxetine 60 mg BID and 40 mg BID over placebo at visit 8/week 9 (endpoint). But the LOCF analysis of the ITT sample demonstrated that none of the treatment duloxetine 60 mg BID and 40 mg BID were statistically significantly superior to placebo. Duloxetine 60 mg BID was marginally statistically significantly (p-value=.054) superior to placebo. Duloxetine 60 mg BID was not statistically significantly (p-value=.466 (LOCF analysis), and p-value=.698 (Repeated analysis) different from 40 mg BID.

SUBGROUP ANALYSIS

In study A, no statistically significant treatment-by-subgroup interactions were observed for the following subgroups: (1) younger and older patient subsets, (2) between male and female patient subsets (there was no non-Caucasian group), (3) baseline HAMD17 total score, (4) the presence of HAMD anxiety, (5) sleep disturbances, and (6) atypical or melancholic features of MDD.

In study B, no statistically significant treatment-by-subgroup interactions for gender, baseline HAMD total score, HAMD anxiety, HAMD insomnia, or melancholic features were observed. There was a statistically significant treatment-by-age interaction. No statistically significant differences were observed among the treatment groups for patients younger than 55. For patients 55 and older, each of the active treatment groups were statistically significantly superior to placebo.

INTERIM ANALYSES

No interim analyses were planned for the two studies.

ADVERSE EVENTS

In study A, there were no deaths during the acute treatment phase of the study. There was 1 serious adverse event. A total of 13 patients discontinued during the acute treatment phase of the study because of adverse events. Of the 367 randomized patients, 170 (46.3%) patients reported at least one treatment-emergent adverse event. Treatment-emergent adverse events were defined as events that first occurred or worsened after randomization (Visit 3) through Visit 8. Duloxetine-treated patients reported treatment-emergent constipation, sweating increased, and somnolence statistically significantly more frequently than placebo-treated patients.

In study B, there were no deaths during the acute treatment phase of the study. There were 3 serious adverse events during the acute treatment phase. Of the 392 randomized patients, 137 (34.9%) reported at least one treatment-emergent adverse event. Treatment-emergent adverse events during the acute treatment phase were defined as events that first occurred or worsened after randomization (Visit 3) through Visit 8. Duloxetine 60 mg twice daily (BID)-treated patients reported treatment-emergent insomnia and nausea

statistically significantly more frequently than placebo-treated patients. A total of 14 patients discontinued during the acute treatment phase of the study because of adverse events.

SPONSOR'S FINAL CONCLUSIONS

In study A, patients treated with duloxetine in both patient treatment groups (40 and 60 mg BID) had statistically significantly greater improvement at the endpoint in the primary efficacy measure (HAMD17 total score) compared with placebo-treated patients in both repeated measures analysis and endpoint LOCF analysis.

In study B, patients treated with duloxetine in both patient treatment groups (40 and 60 mg BID) had statistically significantly greater improvement in the primary efficacy measure (HAMD17 total score) compared with placebo-treated patients, by repeated measures analysis. In the endpoint LOCF analysis, the study is a failed study. In both studies, duloxetine 40 mg BID was not significantly different from duloxetine 60 mg BID with respect to treatment efficacy.

REVIEWER'S ANALYSIS AND COMMENTS

This reviewer did the LOCF (considering as the primary statistical analysis approach) and repeated measure analyses. In both studies, the findings were consistent with the sponsor's reported findings. Study A is a positive study in both LOCF and repeated measure analyses. Study B is a positive study in repeated measure analysis and it is a failed study in LOCF analysis.

OPTIMAL STARTING DOSE

FDA informs the sponsor at the time of the Approvable Letter, that there is no difference in effectiveness between 20 mg twice daily (BID) and 40 mg BID, that efficacy of higher doses of duloxetine (80-120 mg/day) has not been demonstrated. FDA recommends "Cymbalta should be administered at a dose of 40 to 60 mg/day..."

In response to FDA's recommendation, the sponsor informs that 60 mg/day is the optimal starting dose for most patients. The sponsor's argument is based on the evidence showing that 60 mg/day has greater efficacy overall than 40 mg/day, with similar safety and tolerability. The efficacy of 60 mg given once daily is demonstrated definitively and replicated in Studies HMBHa and HMBHb. Duloxetine doses of 40 mg/day and 60 mg/day are studied in different protocols. Thus, no direct comparison is possible. The sponsor presents the effect sizes for the primary efficacy measures to demonstrate the superior efficacy for the 60-mg/day dose (see table 4). The sponsor claims that doses greater than 80 mg/day has shown efficacious based on the recently completed studies HMAYa and HMAYb.

The sponsor noted that while the higher dose in the studies conducted with two doses of duloxetine did not generally show statistically significant superiority over the lower dose, these studies were not designed to do this. The studies were designed and explicitly

powered to compare one dose of duloxetine to placebo, but were not powered to demonstrate statistical differences between doses of an active agent. The result was that, while not statistically different, the numerical advantage consistently favors the higher of the two doses in these studies.

Table 4: Effect Size: Duloxetine vs. Placebo

	U.S Studies			Non U.S study	
	HMAT		HMBH	HMAY	
	Duloxetine 40mg/day (20 mgBID) [1]	Duloxetine 80 mg/day (40 mgBID) [1]	Duloxetine 60 mgQD [2]	Duloxetine 80 mg/day (40 mgBID) [3]	Duloxetine 120 mg/day (60 mgBID) [3]
Change in HAMD17 Total score	.29	.35	.38	.76	.68

[1] Duloxetine 40 mg/day and 80 mg/day came from pooled data from Studies HMATa and HMATb;
[2] Duloxetine 60 mg/day came from pooled data from Studies HMBHa and HMBHb.
[3] Duloxetine 80 mg/day and 120 mg/day came from pooled data from Studies HMAYa and HMAYb;
Non-U.S countries: BG=Bulgaria, HR=Croatia, RO=Romania, RU=Russia, HU=Hungary, PL=Poland, SK=?? .

Reviewer's comments on starting dose

Table 4 lists the effect sizes of different dose regimens across different studies. The sponsor reported the effect sizes for 40mg/day (in study HMAT), and 60 mgQD (in study HMBH) in the complete response letter. This reviewer reproduced the sponsors calculated effect sizes and also calculated the effect sizes for other dose levels as reported in Table 4. The studies HMAT and HMBH were conducted in U.S. The study HMAY was conducted in Bulgaria, Croatia, Romania, Russia, Hungary, and Poland. Both the U.S studies and non-U.S studies had the same inclusion criteria. In the U.S studies the effect sizes are smaller as compared to the effect sizes in the non-U.S study. For example, the effect sizes for Duloxetine 80 mg/day as compared to placebo are .35 and .76 for U.S study (HMAT), and Non-U.S study (HMAY), respectively. The difference between these two effect sizes at the same dose level might be due to some other factors (e.g., cultural, medical facilities, etc). Therefore, a comparison between the effect sizes obtained from the U.S and Non-U.S studies is questionable.

Within the U.S studies, effect sizes for 40 mg/day, 60 mg/day, and 80 mg/day are .29, .38, and .35, respectively. The effect size for 60 mgQD is the highest. Therefore, the FDA recommendation "Cymbalta should be administered at a dose of 40 to 60 mg/day..." seems to be valid.

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

STATISTICAL REVIEW AND EVALUATION

NDA:	21-427
DRUG NAME:	CYMBALTA (duloxetine hydrochloride)
INDICATION:	Major Depressive Disorder
SPONSOR:	Eli Lilly and Company
STATISTICAL REVIEWER:	Ohidul Siddiqui
DATE OF DOCUMENT:	November 13, 2001

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EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

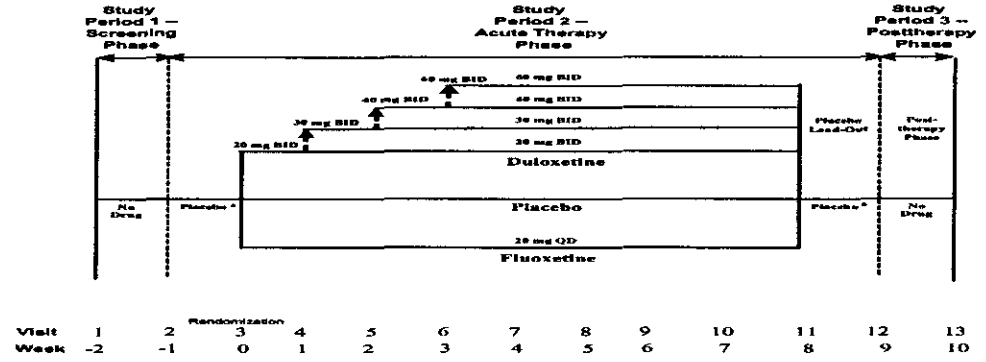
The sponsor submitted results of six adequate and well-controlled clinical trials to support the efficacy of duloxetine in patients who met DSM-IV criteria for major depressive disorder. Evidence of the efficacy of duloxetine in the treatment of depression was claimed by the sponsor in three of these six studies (HMAT(B), HMBH(A), and HMBH(B)) in populations of adult outpatients who were 18 years of age or older and met DSM-IV criteria for major depressive disorder. Based on the endpoint LOCF analyses on the primary outcome measure, the HAMD17 total score, this reviewer also found that duloxetine was statistically significantly superior to placebo in the treatment of depression in these three studies. Two studies (HMBH(A), and HMBH(B)) demonstrated the effectiveness of duloxetine in 60 mg QD and one study (HMAT(B)) demonstrated the effectiveness of duloxetine in 40mg BID dosing regimen. The study HMAT(B) had maximum dose regimen of 40 mg BID. The findings from the three studies (HMAT(B), HMBH(A), and HMBH(B)) demonstrated that duloxetine was effective in the treatment of depression.

INTRODUCTION

The sponsor submitted results of six randomized, double-blinded, placebo controlled studies to demonstrate the efficacy and safety of duloxetine in the treatment of DSM-IV-defined depressive disorder. There were three protocols, and each protocol comprised two identical, independently powered studies. Table 1 and Figures 1-3 list an overview of the designs of the three protocols. Table 2 lists the inclusion criteria of patients in each of the three protocols. Tables 3, 4, and 5 list the primary objectives, the primary and secondary efficacy measures of the studies, and the primary statistical analysis models as specified in the protocols. Table 6 lists the demographic characteristics of the randomized patients by treatment group.

Table 1: Overview of Designs of the six Primary Placebo Controlled Studies.

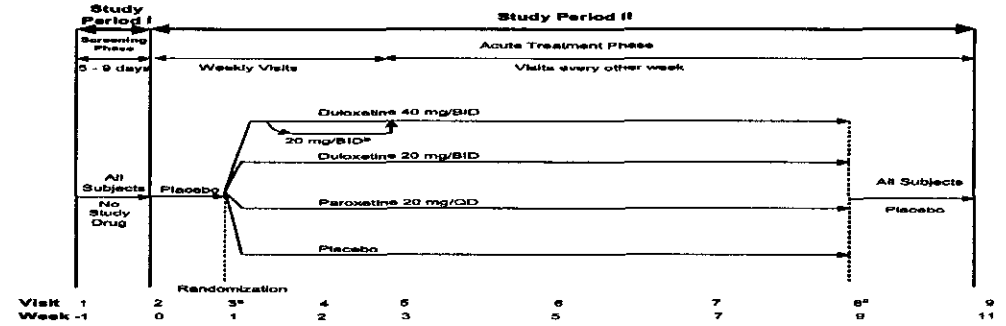
Protocol #	Study Design
F1J-MC-HMAQ	**Phase II,** multicenter, parallel, double-blind, randomized, placebo-controlled, forced-titration trial conducted in the US comparing duloxetine 20 mg to 60 mg twice daily (BID) with placebo and fluoxetine 20 mg once daily (QD) in 8 weeks of acute treatment in male and female patients age 18 to 65 who were diagnosed with DSM-IV–defined major depressive disorder. The research protocol consisted of two identical, independently-powered study groups: F1J-MC-HMAQ(A) was conducted at 8 US sites; and F1J-MC-HMAQ(B) was conducted at 11 US sites.
F1J-MC-HMAT	**Phase III,** multicenter, parallel, double-blind, randomized, placebo-controlled, fixed-dose trial conducted in the US comparing duloxetine 40 mg BID and 20 mg BID with placebo and paroxetine 20 mg QD in 8 weeks of acute treatment in male and female patients at least 18 years of age who were diagnosed with DSM-IV–defined major depressive disorder. The research protocol consisted of two identical, independently-powered study groups: F1J-MC-HMAT(A) was conducted at 22 US sites; and F1J-MC-HMAT(B) was conducted at 22 US sites.
F1J-MC-HMBH	**Phase III,** multicenter, parallel, double-blind, randomized, placebo-controlled, fixed-dose trial conducted in the US comparing duloxetine 60 mg QD with placebo in 9 weeks of acute treatment in male and female patients at least 18 years of age who were diagnosed with DSM-IV–defined major depressive disorder. The research protocol consisted of two identical, independently-powered study groups: F1J-MC-HMBH(A) was conducted at 18 S sites; and F1J-MC-HMBH(B) was conducted at 23 US sites.



= Earliest visit at which dose may be escalated.

* Patients and investigators were told that randomization could occur as early as Visit 2 and as late as Visit 4. All patients were actually given placebo from Visits 2 to 3 with randomization occurring at Visit 3 for all patients.
* Patients and investigators were told that active therapy would continue until Visit 12. All patients actually entered a placebo lead-out from Visit 11 to Visit 12.

Figure 1. Illustration of Study design of F1J-MC-HMAQ



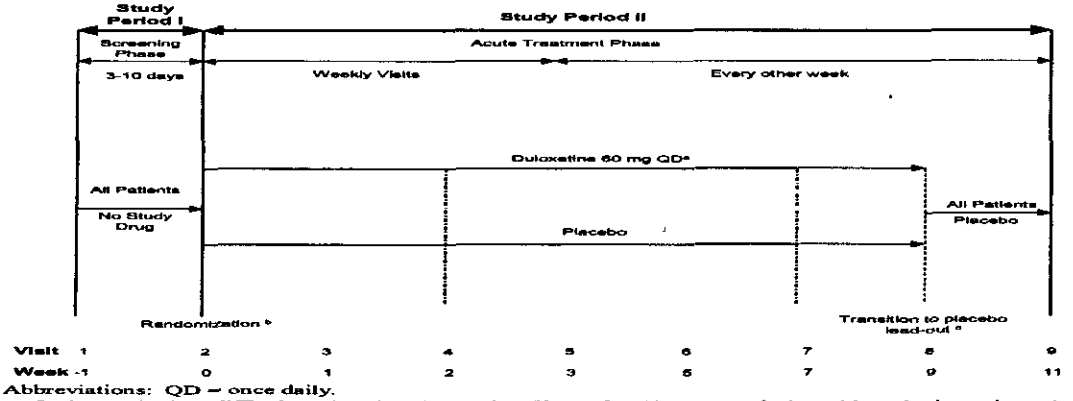
Abbreviations: BID = twice daily, QD = once daily.

[a] Investigators were told that transition to study drug could occur between Visits 2 and 4. Randomization actually occurred at Visit 3 for all patients.

[b] Patients who had difficulty tolerating duloxetine 40 mg BID could, at the investigator's discretion, have their dose reduced to 20 mg BID. Dose must return to 40 mg BID by Visit 5.

[c] Investigators were told that patients may be switched from active treatment to placebo between Visits 7 and 9. All patients actually transitioned to placebo starting at Visit 8 (Week 9)

Figure 2. Illustration of Study design of F1J-MC-HMAT



Abbreviations: QD = once daily.

[a] Patients who had difficulty tolerating duloxetine 60 mg QD (three capsules) could, at the investigator's discretion, have the number of capsules reduced to the equivalent of 40 mg QD (two capsules) at any time up to Visit 5. Investigator should attempt to escalate dose back to 60 mg QD within about 3 days. Dose must return to 60 mg QD after Visit 5.

[b] Investigators were told that transition to study drug may occur anytime between Visits 2 and 4. Randomization actually occurred at Visit 2 for all patients.

[c] Investigators were told that patients may be switched from active treatment to placebo between Visits 7 and 9. All patients will actually transition to placebo starting at Visit 8 (Week 9).

Figure 3. Illustration of Study design of F1J-MC-HMBH

Table 2: Overview of major Inclusion Criteria among the three protocols.

The following inclusion criteria are common to the six efficacy studies: •Must meet criteria for major depression, as defined by DSM-IV •Must have HAMD17 total score >=15 at Visits 1 and 2 •Must have CGI-Severity score >=4	
The following inclusion criteria are unique to specific studies:	
F1J-MC-HMAQ	**F1J-MC-HMAT & F1J-MC-HMBH**
•Must be male or female outpatients age 18 to 65 years. • Does not specifically require that study participants be "outpatient." •Must have CGI-Severity score >=4 at Visit 1 (does not specify this score at Visit 2).	•Must be male or female outpatients at least 18 years of age. • Must have CGI-Severity score> =4 at Visit 1 and Visit 2.

Note: Majorities of the exclusion criteria were also common to the six studies.

Table 3: Primary objectives of each of the protocols.

Protocol No.	Primary Objectives
F1J-MC-HMAQ	The primary objective was to demonstrate that **duloxetine 20 mg to 60 mg BID** is superior to placebo in the acute treatment of patients with major depression as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).
F1J-MC-HMAT	The primary objective was to demonstrate that **duloxetine 40 mg BID** is superior to placebo in the acute treatment of patients with major depression as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).
F1J-MC-HMBH	The primary objective was to demonstrate that **duloxetine 60 mg QD** is superior to placebo in the acute treatment of patients with major depression as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).

Table 4: Efficacy, Health Outcome, and Somatic/Pain Measures Used in the six Duloxetine Studies

	Measure Used in Study		
Measures	**Studies HMAQa and HMAQb**	**Studies HMATa and HMATb**	**Studies HMBHa and HMBHb**
Efficacy			
$HAMD_{17}$ (Primary measure)	x	x	x
Response and Remission	x	x	x
$HAMD_{17}$ Subscales	x	x	x
MADRS	x	x	
HAMA	x	x	
CGI-Severity	x	x	x
CGI-Improvement	x		
PGI-Improvement	x	x	x
Health Outcomes			
SF-36	x		
QLDS		x	x
Somatic and Pain			
SSI		x	x
VAS		x	x

Abbreviations: CGI-Improvement = Clinical Global Impressions of Improvement; CGI-Severity = Clinical Global Impressions of Severity; HAMA = Hamilton Anxiety Rating Scale; $HAMD_{17}$ = 17-Item Hamilton Depression Rating Scale; MADRS = Montgomery and Asberg Depression Rating Scale; PGI-Improvement = Patient's Global Impressions of Improvement; QLDS = Quality of Life in Depression Scale; SF-36 = Short Form 36 Health Survey; SSI = Somatic Symptom Inventory; VAS = Visual Analog Scales for Pain

Table 5: Protocol specified Statistical analysis plans

Protocol #	Analysis population	Primary efficacy measure	Primary Statistical analysis model	Primary comparison
F1J-MC-HMAQ	ITT	Change from baseline to endpoint (i.e., week 8) on HAMD17	**ANCOVA model**: Change score = Baseline Treatment Investigator	Dulox 20-60mg vs. Placebo (2-sided 0.05 level)
F1J-MC-HMAT	ITT	Change from baseline to endpoint (i.e., week 8) on HAMD17	**MMRM analysis**: Change score = treatment, visit, investigator, baseline score, and interactions of visit with treatment and baseline score	Dulox 40 mg vs. Placebo (2-sided 0.05 level)
F1J-MC-HMBH	ITT	Change from baseline to endpoint (i.e., week 9) on HAMD17	**MMRM analysis**. Change score = treatment, visit, investigator, baseline score, and interactions of visit with treatment and baseline score	Dulox 60 mg vs. Placebo (2-sided 0.05 level)

Table 6: Patients Characteristics by treatment groups of each of the six studies.

Protocol No.	Study #	Treatment Group (N)	Mean Age (years) [Range]	# Male (%)	Race (%)
F1J-MC-HMAQ	A	Dulox (20-60 mg) (N=70)	42.33 [18-63]	37.1%	Caucasian:88.6%
		Placebo (N=70)	41.35 [19-65]	31.4%	Caucasian: 81.4%
		Fluox (N=33)	39.69 [19-61]	42.4%	Caucasian :72.7%
	B	Dulox (20-60 mg) (N=82)	39.86 [19-61]	31.7%	Caucasian:87.8%
		Placebo (N=75)	41.39 [19-65]	33.3%	Caucasian: 90.7%
		Fluoxetine (N=37)	39.65 [18-65]	37.8%	Caucasian :91.9%
F1J-MC-HMAT	A	Dulox20BID (N=91)	43.36 [18-77]	31.9%	Caucasian : 82.4%
		Dulox40BID (N=84)	43.68 [18-78]	39.3%	Caucasian : 81.0%
		Placebo (N=90)	43.18 [18-81]	34.4%	Caucasian : 78.9%
		Paroxetine 20 mg (N=89)	44.43 [19-82]	48.3%	Caucasian : 82.0%
	B	Dulox20BID (N=86)	40.69 [20-71]	44.2%	Caucasian : 83.7%
		Dulox40BID (N=91)	40.89 [18-69]	38.5%	Caucasian : 84.6%
		Placebo (N=89)	40.14 [20-79]	36.0%	Caucasian : 83.1%
		Paroxetine 20 mg (N=87)	40.25 [19-64]	35.6%	Caucasian : 73.6%

F1J-MC-HMBH	A	Dulox60QD (N=123)	42.44 [18-76]	35.0%	Caucasian : 87.0%
		Placebo (N=122)	42.34 [18-78]	32.0%	Caucasian : 84.4%
	B	Dulox60QD (N=128)	40.83 [19-76]	33 6%	Caucasian : 78.1%
		Placebo (N=139)	41.04 [19-83]	28.8%	Caucasian : 78.4%

According to the sponsor's reported findings, the efficacy of duloxetine in the treatment of DSM-IV–defined major depressive disorder had been established in three studies (F1J-MC-HMAT(B), F1J-MC-HMBH(A), F1J-MC-HMBH(B)) out of the six adequate and well-controlled multicenter clinical studies. In this statistical review, the findings of the three positive studies will be reviewed. The sponsor's findings on the primary measures of the three failed studies will be reported at the end of this review.

In each of the three positive studies (F1J-MC-HMAT(B), F1J-MC-HMBH(A), F1J-MC-HMBH(B)), subgroup analyses were performed considering the subgroups defined either by demographic factors or by baseline disease status as follows: three demographic subgroups were defined as age (<55 or >=55), gender, and racial origin (Caucasian or Other); and four other subgroups were determined by the baseline disease status as 1) Patients with baseline HAMD17 total score of <19 or baseline score >=19; 2) Patients with or without prominent symptoms of anxiety (baseline HAMD17 Anxiety/Somatization subfactor score >=7 or <7); 3) Patients with or without prominent sleep disturbances (baseline HAMD17 sleep subfactor score >=4 or <4); and 4) Patients with or without melancholic features. Subgroup analyses (ANCOVA analysis) were performed on the change score from baseline to endpoint on HAMD17 total score.

SPONSOR'S FINDINGS ON STUDY F1J-MC-HMAT(B)

EFFICACY FINDINGS

A total of 353 patients were randomly assigned to one of four treatment groups: placebo (N=89), duloxetine 20 mg BID (N=86), duloxetine 40 mg BID (N=91), or paroxetine 20 mg QD (N=87). No statistically significant baseline differences were observed among the treatment groups with regard to age, gender, origin, or weight. Patients had a mean age of 40.5 years, with the majority being Caucasian (81.3%) and female (61.5%). Table 6 lists the patients' demographic characteristics at baseline by treatment groups.

Patients in this study had a median number of 3 previous episodes of depression. Median duration of current episode of depression was 28.0 weeks. No statistically significant baseline differences were observed among the treatment groups with regard to randomized patients' psychiatric history.

Table 7. Reasons for discontinuation of patients in the double-blind phase.

	PLACEBO N= 89	DLX20BID N= 86	DLX40BID N= 91	PRX20QD N= 87
Any reason	42%	36%	42%	44%
Lack of efficacy, patient/ MD perception	26%	12%	6.6%	13%
Adverse event	9.0%	12%	15%	9.2%
Personal conflict or other patient decision	3.4%	5.8%	9.9%	6.9%
Unable to contact patient(lost to follow up)	2.2%	3.5%	3.3%	8.0%
Protocol violation		3.5%	5.5%	5.75
Physician decision	1.1%		1.1%	1.1%

Table 7 shows patient disposition/reasons for discontinuation for the acute therapy phase of this study. The overall discontinuation rate in this study was 41%. The percentages of patients who discontinued for any reason were similar among the four treatment groups. The percentages of patients who discontinued due to perceived lack of efficacy were lower in the duloxetine 20 mg BID, duloxetine 40 mg BID, and paroxetine treatment groups as compared to the percentage in the placebo treatment group. The incidence of discontinuation due to lack of efficacy was lower in the duloxetine 40 mg BID group than in the paroxetine treatment group.

Tables 3, 4, and 5 list the primary objective, the primary and secondary efficacy measures, and the protocol specified statistical analysis plan of the study. The primary analysis was based on an Intent-to-treat (ITT[1]) sample. Table 8 lists the sponsor's reported results from repeated measure analysis (protocol specified primary analysis) and LOCF ANCOVA analysis. Both repeated measures analysis and LOCF analysis of the ITT sample demonstrated statistically significant superiority of duloxetine 40 mg BID over placebo [p-value=.002 (MMRM), .003 (LOCF)] at visit 8/week 9 (endpoint). The observed case analysis of the HAMD17 total score results were consistent with the repeated measures and LOCF analyses.

In both endpoint LOCF and repeated measures analyses, duloxetine 40 mg BID demonstrated statistically significant superiority compared with placebo on the secondary efficacy measure HAMD item# 3.

Except for the subgroups determined by baseline HAMD17 total score and the presence of anxiety symptoms, no statistically significant treatment-by-subgroup interactions were observed for the subgroups. In patients with baseline HAMD17 total score <19, the mean changes in HAMD17 total score were smaller, as compared to the mean changes of HAMD17 total score in the patients with baseline HAMD17 total scores >=19. Comparisons between treatment groups within subgroups yielded consistent results to those of the overall efficacy analysis.

[1] Among the randomized patients, who have baseline measure and atleast one post-baseline measure.

INTERIM ANALYSES

The study data was monitored in a sequential fashion using the triangular test. Boundaries for the triangular test were computed as described by Whitehead (1992). These boundaries indicated that a decision on the effectiveness of the treatment could be made with the appropriate significance level and power specified for this study. The study was not to be stopped early due to positive efficacy results (if duloxetine was statistically superior to placebo) based on interim data. Thus, no adjustment to the significance level at the final analysis was made.

Table 8. Mean Change from Baseline to Endpoint (end of week 9)

Scale	TRT (N)	Repeated Measure analysis				LOCF ANCOVA analysis			
		LS Mean change [1]	P-values			LS Mean change	P-values		
HAMD17 total score			Vs. 1	Vs 2	Vs. 3		Vs. 1	Vs. 2	Vs. 3
	1)PLACEBO (89)	-4.99				-3.67			
	2)DLX20BID (86)	-7.42	.034			-6.08	.022		
	3)DLX40BID (91)	-8.61	**.002**	.293		-6.77	**.003**	.508	
	4)PRX20QD (87)	-6.22	.285	.293	.037	-5.18	150	.395	.129
SECONDARY MEASURES									
HAMD Item 1 (Depressed Mood)	1)PLACEBO (89)	-.89				-.604			
	2)DLX20BID (86)	-1.15	.174			-.935	.053		
	3)DLX40BID (91)	-1.16	.152	.932		-.919	.064	.926	
	4)PRX20QD (87)	-1.11	.255	.835	.771	-.869	.122	.700	.769
HAMD Item 3 (Suicide)	1)PLACEBO (89)	-.11				-.060			
	2)DLX20BID (86)	-.40	.005			-.325	.005		
	3)DLX40BID (91)	-.40	**.004**	.949		- 297	**.011**	.769	
	4)PRX20QD (87)	-.18	.508	.033	.028	-.118	.540	.0307	.059
CGI-Severity	1)PLACEBO (89)	-1.10				-0.77			
	2)DLX20BID (86)	-1.36	.242			-1.05	.135		
	3)DLX40BID (91)	-1.42	.153	.785		-1.10	.078	.799	
	4)PRX20QD (87)	-1.25	.507	.625	.450	-0.98	.262	.713	.530
PGI-Improvement	1)PLACEBO (89)	2.87				3.24			
	2)DLX20BID (86)	2.74	.522			2.93	.162		
	3)DLX40BID (91)	2.52	.093	.290		2.86	.079	.727	
	4)PRX20QD (87)	2.80	.743	.761	.180	2.99	.253	.799	.545

[1] Ls mean change from baseline.

Note: The primary objective of the study is to compare duloxetine 40 mg BID (DLX40BID) vs. PLACEBO).

The sponsor did not report the LOCF analyses on HAMD item 1 and item 3. This reviewer reported the results on HAMD item 1 and item 3 based on his own analyses.

ADVERSE EVENTS

There were no deaths. Only two patients had serious adverse events; these were judged by investigators to be unrelated to study drug. Discontinuations due to adverse events did not differ significantly across treatment groups, although there was a numeric dose-related increase in adverse events among duloxetine-treated patients. Statistically significantly higher incidences of treatment-emergent adverse events reported for duloxetine-treated patients compared with placebo-treated patients included nausea, insomnia, somnolence, dizziness, dry mouth, sweating, anorexia, and accidental injury.

SPONSOR'S FINAL CONCLUSIONS ON STUDY F1J-MC-HMAT(B)

Both repeated measures and LOCF analyses demonstrated that the duloxetine 40 mg BID treatment group was statistically significantly superior to placebo on the protocol-defined primary efficacy measure (HAMD17 total score). The duloxetine 40 mg BID treatment group also demonstrated statistically significantly superior efficacy on most secondary outcome measures (HAMD17 subscales, MADRS, HAMA, QLDS, and VAS-Overall Pain).

The percentage of patients who discontinued due to perceived lack of efficacy was statistically significantly lower in the duloxetine 40 mg BID group, as compared to the placebo treatment group.

The results of Study F1J-MC-HMAT(B) demonstrated that duloxetine at 40 mg BID is efficacious in the acute treatment of patients with DSM-IV–defined major depressive disorder.

REVIEWER'S ANALYSIS AND COMMENTS ON STUDY F1J-MC-HMAT(B)

Based on the letter issued by the Agency to the sponsor (dated January 11, 2002), this reviewer considered the LOCF analysis as the primary statistical analysis to evaluate the efficacy of duloxetine. This reviewer did the LOCF and OC analyses. The findings were consistent with the sponsor's reported findings. An exploratory analysis on the primary efficacy measure had also been done to compare the dropout patients versus non-dropouts at each week with respect to their HAMD17 total score.

Table 9 lists the LOCF and OC analyses by visit. Both LOCF and OC analyses on the primary efficacy measure HAMD17 total score showed that Duloxetine 40 mg BID was statistically significant effective from Visit 5 through Visit 8 (Endpoint), as compared to Placebo.

Tables 10 and 11 show the percentages of patients who were present in the study at each visit, and the observed mean of HAMD17 total score at the last available visit for the dropout and the corresponding mean for the non-dropout patients. The percentages of patients who continued the study were similar among the four treatment groups. In each treatment group, the observed means of HAMD17 total score for the dropout patients were higher (although, not true at every visit), as compared to the means for the continued patients. The observed means by dropout status at each visit were very similar among the treatment groups.

Table 9. LOCF and OC analyses on HAMD17 by visit

Primary measure	Treatment	L.S mean change from baseline in HAMD17				
		Visit 4/ WK 2	Visit 5 /WK 3	Visit 6 Wk 5	Visit 7 /Wk 7	Visit 8/ WK 9
HAMD17 (LOCF analysis)	PLACEBO (89)	-1.34	-1.93	-2.71	-3.42	-3.67
	DLX20BID (86)	-1.14	-3.07	-4.70	-5.79	-6 07
	DLX40BID (91)	**-1.85**	**-4.06**	**-5.14**	**-6.69**	**-6.77**
	PRX20QD (87)	-1.84	-3.59	-5.37	-5.58	-5.17
	P-values					
	DLX20BID vs. PLACEBO	0.762	0.162	0.031	0.017	0.022
	DLX40BID vs. PLACEBO	**0.441**	**0.009**	**0.008**	**0.001**	**0.003**
	PRX20QD vs. PLACEBO	0.455	0.042	0.004	0.029	0.149
		OC Analysis				
HAMD17 (OC analysis)	PLACEBO (89)	-1.34	-2.13	-3.42	-4.64	-6.28
	DLX20BID (86)	-1.14	-3.42	-5.12	-6.92	-7.65
	DLX40BID (91)	**-1.85**	**-4.56**	**-5.96**	**-8.69**	**-8.90**
	PRX20QD (87)	-1.84	-3.70	-6.01	-6.61	-6.69
	P-values					
	DLX20BID vs. PLACEBO	0.762	0.136	0.083	0.023	0.226
	DLX40BID vs. PLACEBO	**0.442**	**0.005**	**0.009**	**0.0001**	**0.022**
	PRX20QD vs. PLACEBO	0.455	0.070	0.008	0.050	0.717

Table 10. Percentages of subjects were present at each Visit.

Treatment	Visit 3/ WK 2 / Baseline	Visit 4/ Wk 2	Visit 5 / WK 3	Visit 6 / Wk 5	Visit 7 / Wk 7	Visit 8/ Wk 9 (OR Completers)
PLACEBO	89 (100%)	98.88%	91 01%	85.39%	73.03%	60.67%
DLX20BID	86 (100%)	97.67%	90.70%	84.88%	74.42%	67.44%
DLX40BID	91(100%)	94.51%	85.71%	78.02%	71.43%	60.44%
PRX20QD	87 (100%)	96.55%	86.21%	80.46%	71.26%	62.07%

Note: The percentages of completers/dropouts are not consistent between Table 7 and table 10. Sixteen patients (6 from DLX20BID, 3 from DLX40BID, 2 from PLACEBO, and 5 from PRX20QD) who have complete data, were considered as discontinued patients by the sponsor in Table 7

Table 11. Observed mean score of HAMD17 total score by subjects' dropout status.

Treatment	Mean at Baseline		Mean at Visit 4		Mean at Visit 5		Mean at Visit 6		Mean at Visit 7	
	Drop at Visit 4	Present at Visit 4	Drop at Visit 5	Present at Visit 5	Drop at Visit 6	Present at Visit 6	Drop at Visit 7	Present at Visit 7	Drop at Visit 8	Present at Visit 8
PLACEBO	18.00	17.20	19.28	15.37	21.00	13.86	13.00	12.69	19.45	10.48
DLX20BID	23.50	18.63	19.83	16.57	12.00	14.11	14.55	11.50	17.00	9.74
DLX40BID	14.40	18.06	20.25	15.25	14.42	12.15	20.66	9.61	7.60	7.76
PRX20QD	22.67	17.65	14.66	15.44	17.00	12.68	16.50	9.43	15.37	8.57

SPONSOR'S FINDINGS ON STUDY F1J-MC-HMBH (A)

EFFICACY FINDINGS

A total of 341 patients entered the screening phase of the study. Of these 341 patients, a total of 96 patients failed to meet entry criteria or declined to participate in the study. The remaining 245 patients were randomized to one of two treatment groups: placebo (N=122) or duloxetine (N=123) at Visit 2.

No statistically significant differences between the two treatment groups with respect to age, gender, origin, weight, or height were observed. Patients had a mean age of 42 years, with the majority being Caucasian and Female. Table 6 lists the patients' demographic characteristics at baseline by treatment groups.

Patients in this study had a median number of 4 previous episodes of depression. Median duration of current episode of depression was 38.0 weeks. No statistically significant baseline differences were observed among treatment groups with regard to randomized patients' psychiatric history.

Table 12. Reasons for discontinuation of patients in the double-blind phase.

	PLACEBO N= 122	DLX60QD N= 123
Any reason	29.5%	35%
Lack of efficacy, patient/ MD perception	8.2%	3.3%
Adverse event	2.5%	13.8%
Personal conflict or other patient decision	7.4%	8.1%
Unable to contact patient(lost to follow up)	7.4%	6.5%
Protocol violation	3.3%	2 4%
Physician decision	.8%	.8%

Table 12 shows patient disposition/reasons for discontinuation for the acute therapy phase of this study. The overall discontinuation rate in this study was 31.2%. More patients in the duloxetine group discontinued because of adverse events, as compared to the placebo group.

Tables 3, 4, and 5 list the primary objective, the primary and secondary efficacy measures, and the protocol specified statistical analysis plan for the study. The primary analysis was based on an Intent-to-treat (ITT) sample. Table 13 lists the sponsor's reported results from repeated measure analysis (protocol specified primary analysis) and LOCF ANCOVA analysis. Both repeated measures analysis and LOCF analysis of the ITT sample demonstrated statistically significant superiority of duloxetine 60 mg QD over placebo [p-value <.001 (MMRM), <.001 (LOCF)] at visit 8/week 9 (endpoint). The observed case analysis of the HAMD17 total score results were consistent with the repeated measures and LOCF analyses.

In both endpoint LOCF ANCOVA and repeated measures analyses, duloxetine 60 mg QD demonstrated statistically significantly superior compared with placebo on the

following secondary efficacy measures: HAMD item# 1, item# 3, CGI severity, and PGI Improvement. Duloxetine 60 mg was also statistically significant superior over placebo on HAMD17 response and remission rates, all of the protocol specified subfactors of the HAMD17 , and the VAS measures of overall pain, back pain, shoulder pain, interference of overall pain with daily activities, and amount of time awake in pain. There was also marginally statistically significant superiority for duloxetine over placebo on the SSI assessment. Patients treated with duloxetine also showed statistically significantly greater improvement than did placebo-treated patients on the Quality of Life in Depression scale. In summary, the consistency of results across all of these measures demonstrates duloxetine's robust efficacy profile.

No statistically significant treatment-by-subgroup interactions were observed for the subgroups. This observation indicates that the efficacy of duloxetine in improving HAMD17 total score from baseline to endpoint was consistent between younger and older patients, between male and female patient subsets, and between Caucasian and other racial origin subsets. This observation also implies that baseline HAMD17 total score, the presence of anxiety, sleep disturbances, and atypical or melancholic features of major depressive disorder did not statistically significantly affect treatment-group differences.

INTERIM ANALYSES

No interim analysis was conducted and there was no Data Monitoring Board.

Table 13. Mean Change from Baseline to Endpoint (end of week 8)

Scale	TRT (N)	Repeated Measure analysis		LOCF ANCOVA analysis	
		LS Mean change	P-value: Placebo vs. DLX60QD	LS Mean change	P-value: Placebo vs. DLX60QD
HAMD17 total score	PLACEBO (122)	-6.05		-5.67	
	DLX60QD (123)	-10.91	**<.001**	-9.47	**<.001**
SECONDARY MEASURES					
HAMD Item 1	PLACEBO (122)	-.95		-.830	
	DLX60QD (123)	-1.62	**<.001**	-1.372	**<.001**
HAMD Item 3	PLACEBO (122)	-.29		-.237	
	DLX60QD (123)	-.56	**.004**	-.490	**.005**
CGI-Severity	PLACEBO (122)	-.97			
	DLX60QD (123)	-1.87	**<.001**	-.90	
				-1.62	**<.001**
PGI-Improvement [2]	PLACEBO (122)	3.27		3.09	
	DLX60QD (123)	2.48	**<.001**	2.00	**<.001**

[1] *Ls mean change from baseline.*
[2] *Improvement mean score*

ADVERSE EVENTS

There were no deaths. Three patients reported four serious adverse events; all were in the placebo treatment group. Discontinuations due to adverse events were reported significantly more frequently by duloxetine patients than by placebo patients (Table 12). Duloxetine patients had short-term dose reductions significantly more frequently than placebo patients. Statistically significantly higher incidences of treatment-emergent adverse events reported by duloxetine-treated patients compared with placebo-treated patients included nausea, dry mouth, dizziness, somnolence, diarrhea, insomnia, anorexia, constipation, vomiting, palpitation, amblyopia, vasodilation, and weight loss. Adverse events were generally mild or moderate in severity.

SPONSOR'S FINAL CONCLUSIONS ON STUDY F1J-MC-HMBH (A)

Duloxetine was effective in the treatment of outpatients with DSM-IV–defined major depressive disorder at a fixed dose of 60 mg QD. Duloxetine was also safe and well-tolerated when administered at this dose for up to 9 weeks. Patients treated with duloxetine showed statistically significantly greater decreases on change in the HAMD17 total score from baseline to Visit 8, than did patients treated with placebo.

REVIEWER'S ANALYSIS AND COMMENTS ON STUDY F1J-MC-HM(A)

Based on the letter issued by the Agency to the sponsor (dated January 11, 2002), this reviewer considered the LOCF analysis as the primary statistical analysis to evaluate the efficacy of duloxetine. This reviewer did the LOCF and OC analyses. The findings were consistent with the sponsor's reported findings. An exploratory analysis on the primary efficacy measure had also been done to compare the dropout patients versus non-dropouts at each week with respect to their HAMD17 total score.

Table 14 lists the LOCF and OC analyses by visit. Both LOCF and OC analyses on the primary efficacy measure HAMD17 total score showed that Duloxetine 60 mg QD was statistically significant effective at Visit 4 through Visit 8 (Endpoint), as compared to Placebo.

Tables 15 and 16 show the percentages of patients who were present in the study at each visit, and the observed mean of HAMD17 total score at the last available visit for the dropout and the corresponding means for the continued patients. The percentages of patients who continued the study were similar between the two treatment groups. In each treatment group, the observed means of HAMD17 total score for the dropout patients were higher (although, not true at each visit), as compared to the means for the continued patients. The observed means by dropout status at each visit were very similar between the treatment groups.

Table 14. LOCF and OC analyses on HAMD17 by visit

Primary measure	Treatment	L.S. mean change from baseline in HAMD17					
		LOCF Analysis					
		Visit 3 /Wk 1	Visit4/ Wk 2	Visit 5/ Wk 3	Visit 6/ Wk 5	Visit 7/ Wk 7	Visit 8 / Wk 9
HAMD17 (LOCF analysis)	PLACEBO (122)	-2.48	-3.25	-4.31	-5.51	-5.48	-5.67
	DLX60QD (123)	-2.88	-5.45	-6.92	-8.17	-8.86	-9.47
		P-values					
	DLX60QD vs. PLACEBO	**.427**	**.001**	**<.001**	**.001**	**<.001**	**<.001**
		OC Analysis					
HAMD17 (OC analysis)	PLACEBO (122)	-2.48	-3.26	-4.71	-6.19	-6.26	-6.75
	DLX60QD (123)	-2.88	-5.71	-7.54	-9.31	-10.68	-11.78
		P-values					
	DLX60QD vs. PLACEBO	**.427**	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**

Table 15. Percentages of subjects were present at each Visit.

Treatment	Visit 2/ Baseline	Visit 3/ WK 1	Visit 4/ Wk 2	Visit 5 / WK 3	Visit 6 / Wk 5	Visit 7 / Wk 7	Visit 8/ Wk 9 (Completers)
PLACEBO	122 (100%)	94.25%	90.15%	84.43%	82.79%	76.23%	72.95%
DLX60QD	123 (100%)	98.57%	91.06%	85.37%	81.30%	73.98%	68.29%

Table 16. Observed mean score of HAMD17 total score by subjects' dropout status.

Treatment	Mean at Baseline		Mean at Visit 3		Mean at Visit 4		Mean at Visit 5		Mean at Visit 6	
	Drop at Visit 3	Present at Visit 3	Drop at Visit 4	Present at Visit 4	Drop at Visit 5	Present at Visit 5	Drop at Visit 6	Present at Visit 6	Drop at Visit 7	Present at Visit 7
PLACEBO	22 00	21.08	22.60	18.53	20.57	17.50	20.50	16.30	18.87	14.93
DLX60QD	17.00	21`.49	19.67	18.58	15.71	15.75	18.60	13.93	20.78	11.70

Mean at Visit 7	
Drop at Visit 8	Present at Visit 8
20.25	14.74
10.71	10.73

SPONSOR FINDINGS ON STUDY F1J-MC-HMBH (B)

EFFICACY FINDINGS

Originally, the study F1J-MC-HMBH (B) was conducted in 21 centers. In the middle of the study period, the sponsor realized that the enrollment rate of patients in the study was low, and the enrollment rate in FIJ-MC-HMBH(A) was high. To make the enrollments as expected in the study HMBH(B) protocol, the sponsor reallocated two centers (Centers # 101 & 122) with the largest number of patients from Study F1J-MC-HMBH (A) to study F1J-MC-HMBH (B). The sponsor confirmed that there were no interim analyses performed, no data monitoring via interactive voice recognition, and no unblinding

before the database was locked (June 8, 2001). Therefore, there were 23 centers in the study F1J-MC-HMBH (B).

The issue of reallocation of centers from Group A to Group B of Study HMBH had been brought to the Division's attention in February, 2001. FDA met internally to discuss the plan but was unable to provide feedback to Lilly prior to the implementation.

A total of 367 patients entered the screening phase of the study. Of these 367 patients, a total of 100 patients failed to meet entry criteria or declined to participate in the study. The remaining 267 patients were randomized to one of two treatment groups: placebo (N=139) or duloxetine 60 mg QD (N=128) at Visit 2.

No statistically significant differences between the two treatment groups in age, gender, origin, weight, or height were observed. Patients had a mean age of 41 years, with the majority being Caucasian and female. Table 6 lists the patients' demographic characteristics at baseline by treatment groups.

Patients in this study had a median number of 4 previous episodes of depression. Median duration of current episode of depression was 26 weeks. No statistically significant baseline differences were observed among treatment groups with regard to randomized patients' psychiatric history.

Table 17. Reasons for discontinuation of patients in the double-blind phase.

	PLACEBO N= 139	DLX60QD N= 128
Any reason	35.3%	39.1%
Lack of efficacy, patient/ MD perception	13.7%	5.5%
Adverse event	4.3%	12.5%
Personal conflict or other patient decision	5.8%	4.7%
Unable to contact patient(lost to follow up)	9.4%	9.4%
Protocol violation	2.2%	7.0%
Patients completed the study	64.7%	60.9%

Table 17 shows patient disposition/reasons for discontinuation for the acute therapy phase of this study. The overall discontinuation rate in this study was 37.1%. More patients in the duloxetine group discontinued because of adverse events compared with the placebo group. The discontinuation rate due to lack of efficacy in the duloxetine group was lower as compared to the rate in the placebo group.

Tables 3, 4, and 5 list the primary objective, the primary and secondary efficacy measures, and the protocol specified statistical analysis plan for the study. The primary analysis was based on an Intent-to-treat (ITT) sample. Table 18 lists the sponsor's reported results from repeated measure analysis (protocol specified primary analysis) and LOCF ANCOVA analysis. Both repeated measures analysis and LOCF analysis of the ITT sample demonstrated statistically significant superiority of duloxetine 60 mg QD over placebo (p-value =.024 (MMRM), p-value =.047 (LOCF)) at visit 8/week 9

(endpoint). The observed case analysis of the HAMD17 total score at visit 8 was not statistically significant (p-value=.130).

In both ANCOVA endpoint and repeated measures analyses, duloxetine 60 mg QD demonstrated statistically significant superiority compared with placebo on the following secondary efficacy measures: HAMD Item# 1, Item# 3, and PGI Improvement. Duloxetine 60 mg was also statistically significant superior over placebo on HAMD17 response, the Core Factor, Maier, and Retardation subfactors of the HMAD17, and the Quality of Life in Depression scale.

Except for the subgroups determined by the presence of insomnia symptoms and melancholic features of major depressive disorder, no statistically significant treatment-by-subgroup interactions were observed for the subgroups. A statistically significant treatment-by-subgroup interaction was observed for the subgroup determined by the presence of insomnia symptoms. Duloxetine was statistically significantly superior to placebo for patients without insomnia, whereas placebo had a small numerical superiority for patients with insomnia. Another statistically significant treatment-by-subgroup interaction was observed for the subgroup determined by the presence of melancholic features of major depressive disorder. Duloxetine was statistically significantly superior to placebo for patients without melancholic features, whereas placebo had a small numerical superiority for patients with melancholic features.

INTERIM ANALYSES

No interim analyses were conducted and there was no Data Monitoring Board.

Table 18. Mean Change from Baseline to Endpoint (end of week 8)

Scale	TRT (N)	Repeated Measure analysis		LOCF ANCOVA analysis	
		LS Mean change	P-value: Placebo vs. DLX60QD	LS Mean change	P-value: Placebo vs. DLX60QD
HAMD17 total score	PLACEBO (122)	-8.29		-7.02	
	DLX60QD (123)	-10.46	**.024**	-8.75	**.047**
SECONDARY MEASURES					
HAMD Item 1	PLACEBO (122)	-1.14		-.89	
	DLX60QD (123)	-1.64	**.001**	-1.32	**.001**
HAMD Item 3	PLACEBO (122)	-.25		-.20	
	DLX60QD (123)	- 45	**.030**	-.37	**.043**
CGI-Severity	PLACEBO (122)	-1.51		-1 22	
	DLX60QD (123)	-1.74	**.150**	-1.40	**.222**
PGI-Improvement [2]	PLACEBO (122)	3.00		3.23	
	DLX60QD (123)	2.59	**.014**	2.87	**.025**

[1] Ls mean change from baseline.
[2] Improvement mean score

ADVERSE EVENTS

There were no deaths. Two patients reported two serious adverse events. Both patients were in the duloxetine treatment group, but they were not considered to be related to duloxetine by the investigators. Discontinuations due to adverse events were reported statistically significantly more frequently by duloxetine-treated patients than by placebo-treated patients. However, only 12.5% of duloxetine-treated patients discontinued due to adverse events during the acute therapy phase, and no single adverse event was reported as a cause for discontinuation by more than 2 duloxetine-treated patients. Duloxetine patients had short-term dose reductions significantly more frequently than placebo patients did, but the great majority of duloxetine-treated patients (91.2%) tolerated the dose without a reduction. Statistically significantly higher incidences of treatment-emergent adverse events reported by duloxetine-treated patients compared with placebo-treated patients included nausea, dry mouth, constipation, and dizziness. Adverse events were generally mild or moderate in severity.

SPONSOR'S FINAL CONCLUSIONS ON STUDY F1J-MC-HMBH (B)

Duloxetine was effective in the treatment of outpatients with DSM-IV–defined major depressive disorder at a fixed dose of 60 mg QD. Duloxetine was also safe and well-tolerated when administered at this dose for up to 9 weeks. Patients treated with duloxetine showed statistically significantly greater decreases on the primary efficacy outcome, change in the HAMD17 total score from baseline to Visit 8, than did patients treated with placebo.

REVIEWER'S ANALYSIS AND COMMENTS ON STUDY F1J-MC-HMBH (B)

Based on the letter issued by the Agency to the sponsor (dated January 11, 2002), this reviewer considered the LOCF analysis as the primary statistical analysis to evaluate the efficacy of duloxetine. This reviewer did the LOCF and OC analyses. The findings were consistent with the sponsor's reported findings. An exploratory analysis on the primary efficacy measure had also been done to compare the dropout patients versus non-dropouts at each week with respect to their HAMD17 total score.

Table 19 lists the LOCF and OC analyses by visit. LOCF analyses on the primary efficacy measure HAMD17 total score showed that Duloxetine 60 mg QD was statistically significantly effective at Visit 7 and Visit 8 (Endpoint), as compared to Placebo. The observed case analyses of the HAMD17 total score showed that duloxetine 60-mg QD was marginally significant as compared to placebo at visit 7.

Tables 20 and 21 show the percentages of patients who were present in the study at each visit, and the observed mean of HAMD17 total score at the last available visit for the dropout and the corresponding means for the non-dropout patients. The percentages of patients who continued the study were similar among the two treatment groups. The

observed means of HAMD17 total score for the dropouts and non-dropout patients within each treatment group were similar at each visit. The observed means at each visit were very similar between the two treatment groups.

Table 23 lists the LOCF ANCOVA and OC ANCOVA analyses by visit after excluding the patients belonged to Center # 101 and 122 from the data set. The LOCF analyses on the primary efficacy measure HAMD17 total score showed that Duloxetine 60 mg QD was statistically significant effective at Visit 7 (p-value=.027) and Visit 8 (p-value=.039), as compared to Placebo. The observed case analyses of the HAMD17 total score showed that duloxetine 60 mg QD was not statistically significantly different from placebo at any visit.

Table 19. LOCF and OC analyses on HAMD17 by visit

Primary measure	Treatment	L.S mean change from baseline in HAMD17					
		LOCF Analysis					
		Visit 3 /Wk 1	Visit4/ Wk 2	Visit 5/ Wk 3	Visit 6/ Wk 5	Visit 7/ Wk 7	Visit 8 / Wk 9
HAMD17 (LOCF analysis)	PLACEBO (139)	-2.68	-4.04	-5.59	-6.64	-6.77	-7.02
	DLX60QD (128)	-2.94	-4.97	-6.16	-7.65	-8.60	-8.75
	P-values						
	DLX60QD vs. PLACEBO	**.589**	**.117**	**.404**	**.197**	**.033**	**.047**
		OC Analysis					
HAMD17 (OC analysis)	PLACEBO (139)	-2.68	-4.08	-5.77	-7.11	-8.67	-9.41
	DLX60QD (128)	-2.94	-5.15	-6.57	-8.36	-10.37	-10.83
	P-values						
	DLX60QD vs. PLACEBO	**.589**	**.085**	**.264**	**.136**	**.051**	**.130**

Table 20. Percentages of subjects were present at each Visit.

Treatment	Visit 2/ Baseline	Visit 3/ WK 1	Visit 4/ Wk 2	Visit 5 / WK 3	Visit 6 / Wk 5	Visit 7 / Wk 7	Visit 8/ Wk 9 (Completers)
PLACEBO	139 (100%)	97.84%	92.81%	87.77%	79.86%	69.78%	64.75%
DLX60QD	128 (100%)	96.09%	85.94%	84.38%	75.78%	69.53%	63.28%

Table 21. Observed mean score of HAMD17 total score by subjects' dropout status.

	Mean at Baseline		Mean at Visit 3		Mean at Visit 4		Mean at Visit 5		Mean at Visit 6	
Treatment	Drop at Visit 3	Present at Visit 3	Drop at Visit 4	Present at Visit 4	Drop at Visit 5	Present at Visit 5	Drop at Visit 6	Present at Visit 6	Drop at Visit 7	Present at Visit 7
PLACEBO	19.00	20.49	17.14	17.88	16.42	16.09	13.90	14.50	19.07	12.53
DLX60QD	21.6	20.27	16.76	17.51	17.00	14.80	13.09	13.61	19.75	11.20

Mean at Visit 7	
Drop at Visit 8	Present at Visit 8
14.14	12.10
9.12	9.82

Table 22. Mean Change from Baseline to Endpoint (Excluding the two centers (Center # 101, and 122).

Scale	TRT (N)	Repeated Measure analysis		LOCF ANCOVA analysis	
		LS Mean change	P-value: Placebo vs. DLX60QD	LS Mean change	P-value: Placebo vs. DLX60QD
HAMD17 total score	PLACEBO (122)	-8.12		-7.17	
	DLX60QD (123)	-9.97	**.062**	-9.02	**.040**
SECONDARY MEASURES					
HAMD Item 1	PLACEBO (122)	-1.12		-.88	
	DLX60QD (123)	-1.166	**.002**	-1.43	**<.001**
HAMD Item 3	PLACEBO (122)	-.16		-.12	
	DLX60QD (123)	- 38	**.043**	-.27	**.112**
CGI-Severity	PLACEBO (122)	-1.46		-1.21	
	DLX60QD (123)	-1.68	**.209**	-1.43	**.189**
PGI-Improvement [2]	PLACEBO (122)	2 99		3.21	
	DLX60QD (123)	2.58	**.037**	2.80	**.032**

[1] Ls mean change from baseline.
[2] Improvement mean score

Table 23. LOCF and OC analyses on HAMD17 by visit (excluding the two centers # 101, and 122).

Primary measure	Treatment	L.S mean change from baseline in HAMD17					
		Visit 3 /Wk 1	Visit4/ Wk 2	Visit 5/ Wk 3	Visit 6/ Wk 5	Visit 7/ Wk 7	Visit 8 / Wk 9
HAMD17 (LOCF analysis)	PLACEBO (139)	-2.88	-3.92	-5.43	-6.64	-6.94	-7.17
	DLX60QD (128)	-3.14	-4.67	-6.00	-8.03	-8.87	-9.02
	P-values						
	DLX60QD vs. PLACEBO	**.632**	**.243**	**.412**	**.086**	**.027**	**.039**
		OC Analysis					
HAMD17 (OC analysis)	PLACEBO (139)	-2.88	-3.84	-5.38	-6.66	-8.33	-8.96
	DLX60QD (128)	-3.14	-4.70	-6.22	-8.35	-9.69	-10.21
	P-values						
	DLX60QD vs. PLACEBO	**.632**	**.190**	**.252**	**.055**	**.147**	**.215**

FAILED STUDIES

According to the sponsor's report, studies F1J-MC-HMAQa, F1J-MC-HMAQb, and F1J-MC-HMATa were failed studies with respect to LOCF endpoint analyses on the primary efficacy measure HAMD17 total score. Table 24 lists the least square mean change from baseline to endpoint in HAMD17 total score and the p-values comparing the least square mean difference between duloxetine and placebo.

TABLE 24: LOCF Primary Efficacy Analysis Results of the three Failed studies

Study #	Primary measure	TRT (N)	LOCF ANCOVA analysis	
			LS Mean Change	P-values
F1J-MC-HMAQa	HAMD17 total score			Vs. Placebo
		1)PLACEBO (57)	-6 53	
		2)DLX (56)	-8.49	0.146
		3) Fluoxetine (n=27)	-7.07	0.750
F1J-MC-HMAQb	HAMD17 total score			
		1)PLACEBO (72)	-5.73	
		2)DLX (81)	-6.17	0.681
		3) Fluoxetine (n=37)	-6.30	0.673
F1J-MC-HMATa	HAMD17 total score			
		1)PLACEBO (89)	-4.14	
		2)DLX20BID (90)	-5.30	0.222
		3)DLX40BID (81)	-5.59	0.138
		4)PRX20QD (87)	-5.96	0.058

DLX=Duloxetine

REVIEWER'S OVERALL CONCLUSION

In this new drug application, the sponsor submitted results of six adequate and well-controlled clinical trials to support the efficacy of duloxetine in patients who met DSM-IV criteria for major depressive disorder. Evidence of the efficacy of duloxetine in the treatment of depression was claimed in three of these six studies (HMAT(B), HMBH(A), and HMBH(B)) in populations of adult outpatients who were 18 years of age or older and met DSM-IV criteria for major depressive disorder. Based on the endpoint LOCF analyses on the primary outcome measure, the HAMD17 total score, this reviewer also found that duloxetine was statistically significantly superior to placebo in the treatment of depression in these three studies. Two studies (HMBH(A), and HMBH(B)) demonstrated the effectiveness of duloxetine in 60 mg QD and one study (HMAT(B)) demonstrated the effectiveness of duloxetine in 40mg BID dosing regimen. The study HMAT(B) had maximum dose regimen of 40 mg BID.

In study HMAT (B), duloxetine 40 mg BID was statistically significantly superior to placebo on the secondary measures: HAMD17 Item #3 (Suicide). In studies HMBH(A), and HMBH(B), duloxetine 60 mg QD was statistically significantly superior to placebo on the secondary measures: HAMD17 Item # 1 and Item # 3, and PGI-Improvement. In study HMBH(A), duloxetine 60 mg QD was also statistically significantly superior to placebo on CGI-Severity.

The findings from the three studies (HMAT(B), HMBH(A), and HMBH(B)) demonstrated that duloxetine was effective in the treatment of depression.

In study HMAT (B), the sponsor monitored the data in a sequential fashion using triangular test. The sponsor noted in the protocol that the study would not be stopped early due to positive efficacy results based on the interim looks. Therefore, the sponsor did not make any alpha adjustment at the final analysis. This reviewer did not find any

document where the sequential interim analysis was approved by the agency. In this study, the conclusion would not be changed if an alpha adjustment was made.

Monitoring the data in a sequential fashion may introduce potential changes in conducting the study design. Therefore, monitoring the data in a sequential fashion without the agency's approval may not be an acceptable practice in the future NDA reviews.

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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: September 12, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Additional Comments on Approvable Action for
Cymbalta (duloxetine) capsules for the treatment of major depressive disorder

TO: File NDA 21-427, and Robert Temple, M.D.
[**Note:** This overview should be filed with the 11-12-01
original submission.]

Please refer to my 9-3-02 memo for my summary comments supporting an approvable action for this NDA. This memo is intended to comment on questions and comments of Dr. Temple on our draft of labeling for this product. Thus, my comments are directed to Dr. Temple, and include new data not previously available.

I have incorporated your changes, with few exceptions, as noted below, and I've tried to answer your questions and respond to other comments:

p.3: Absolute bioavailability: There was a 2 patient study that wasn't informative; however, both Ray and Ron think that the mass balance study suggests that the bioavailability is likely very high (80-90%).

p.4: I've tried to separate important from unimportant interactions, as proposed.

p.7: The suicide statement is standard language for antidepressants, even those not particularly risky in overdose;

pp.9-11: I've tried to separate important from unimportant interactions, as proposed. I have combined the language for antiacids and antidiarrheals into one paragraph.

pp.11-12: We've changed the MRHD ratios to match the new maximum recommended dose of 60 mg/day. The pharm/tox is ok with these margins.

p.15: Yes, [redacted] column comes out.

p.17: Potential for Liver Toxicity

Our draft of labeling included, under "Laboratory Changes," the following statement: [redacted] In your mark-up of labeling, you noted that a memo by Dr. Katz indicated otherwise. There were 2 patients in question, E00301 and A09505, both, to my understanding, from the Japanese database. Dr. Andreason had not included actual transaminase values for these patients (in his summary on pp.36-37 of his review), however, he has subsequently been able to retrieve the actual laboratory data, and I will summarize these here.

Patient E00301:

This patient apparently began taking duloxetine 10 mg on 2-26-00, and later ([redacted]) developed tremor that worsened over several days. The patient was hospitalized for worsening depression on [redacted], at which time drug was stopped. Laboratory findings relevant to hepatic function were as follows:

Lab Test	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SGOT	27	25	21	16	16
SGPT	36	47	38	24	21
Total bilirubin	0.4	1.4	1.4		0.3

Patient A09505:

This patient apparently began taking duloxetine 30 mg on about 8-11-00, and was noted to have markedly elevated transaminases and a clearly abnormal total bilirubin on [redacted] We have very little information on this patient, other than that the patient may also have taken a variety of other medications in the meantime, presumably in addition to duloxetine, including antidepressants, anxiolytics, and hypnotics. Duloxetine was stopped on [redacted] Laboratory findings relevant to hepatic function were as follows:

Lab Test	[redacted]	[redacted]	[redacted]	[redacted]
SGOT	29	33	2837	23
SGPT	18	37	2362	55
Total bilirubin	0.4	0.7	2.3	11.1

No more laboratory data were reported for this patient, however, it was noted that on [redacted] almost 1 year later, the patient was reported to have suspected "drug hepatopathy." No other relevant information is available on this patient.

Comment on Liver Findings:

-The SGPT increase for patient E00301 is quite small, and of questionable significance, however, the bilirubin change seems real, but is also marginal (but above the ULN). On the other hand, the changes, both transaminases and bilirubin, for patient A09505 are quite striking and of considerable concern. We have asked the sponsor to provide whatever additional followup information they can obtain on both cases. In the meantime, we have deleted the statement [ ]

-While I continue to feel that an approvable action is appropriate, we need more information about these cases, and labeling may need to be further modified with regard to hepatotoxicity depending on what further information we can obtain.

cc:
Orig NDA 21-427
HFD-120
HFD-120/TLaughren/RKatz/PAndreason/DBates
HFD-101/RTemple

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/s/

Thomas Laughren
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MEDICAL OFFICER