

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-148**

**MEDICAL REVIEW(S)**



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**  
**DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS**

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**ADDENDUM TO CLINICAL REVIEW**

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DATE: June 11, 2008

TO: File, NDA 22-148  
File, NDA 21-427

FROM: Celia Jaffe Winchell, M.D.  
Medical Team Leader  
Division of Anesthesia, Analgesia and Rheumatology Products

RE: Maternal Health Team Recommendations

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Cymbalta (duloxetine) is selective serotonin and norepinephrine reuptake inhibitor (SSNRI) approved initially (August 3, 2004) as an anti-depressant and subsequently for indications of the pain associated with diabetic peripheral neuropathy (DPN), generalized anxiety disorder (GAD) and maintenance treatment of major depression in 2007.<sup>1</sup> The approved application, NDA 21-427, is held by the Division of Psychiatry Products (DPP). The Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) has reviewed a Type 6 NDA (22-148) to add an indication for the management of fibromyalgia.

In anticipation of the approval of Cymbalta for this indication, a condition which primarily affects women of child-bearing potential, DAARP consulted the Maternal Health Team (MHT) to provide advice on the need for and design of the Cymbalta pregnancy registry. In addition, the MHT review recommended language for the Pregnancy and Nursing Mothers subsections of Cymbalta proposed labeling.

MHT makes the following recommendations concerning a pregnancy registry study for Cymbalta:

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There are no human data available on the effects of Cymbalta use during pregnancy. Based on animal data, duloxetine may cause fetal harm. While there are no human data on Cymbalta use during pregnancy, there are numerous case reports and epidemiological studies on the use of SSRIs during pregnancy. There are documented and labeled class effects for SSRIs and SNRIs that involve a withdrawal-like syndrome in the neonatal period. However, current available data on potential embryofetal toxicities are conflicting.

Cymbalta is currently approved for the treatment of MDD, GAD, and Diabetic Peripheral Neuropathic Pain, and is currently under review for the ~~\_\_\_\_\_~~ of FM. MDD, GAD, and FM are all conditions that commonly occur in women of child bearing potential. Even with limited data, the possibility exists that women with these conditions, who are of childbearing potential, may conceive while on Cymbalta therapy, resulting in inadvertent exposure to the drug. During pregnancy, women with these conditions may fail other available therapies. A clinician may choose to prescribe Cymbalta after considering the risks and benefits associated with treatment for both the mother and her embryo/fetus. Therefore, a pregnancy registry is needed to monitor maternal and fetal exposures to Cymbalta during pregnancy and associated pregnancy and fetal outcomes.

The MHT recommends that the sponsor develop and maintain a prospective, observational pregnancy exposure registry conducted in the United States that compares the pregnancy and fetal outcomes of women exposed to duloxetine (for any indication) during pregnancy to an unexposed control population. \_\_\_\_\_

\_\_\_\_\_

The registry should be conducted as a post-marketing requirement for this application. The outcomes of the registry should include major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, and other serious adverse pregnancy outcomes. These outcomes should be assessed throughout pregnancy. Infant outcomes should be assessed through at least the first year of life.

In order to meet statutory requirements for a Post-marketing Requirement (PMR) under the FDA Amendments Act (FDAAA), FDA must find that there is new safety information since approval of the NDA, and that analysis of post-marketing adverse events would be insufficient to assess this risk. Although not described in the clinical reviews for this supplement, I note that the following information was included in Lilly's submission:

Women who were pregnant or breast-feeding and women of childbearing potential not using a medically accepted means of contraception were excluded from participating in all duloxetine clinical studies. [Reviewer's note: Total population, over 27,000.] Nonetheless, a total of 77 pregnancies possibly exposed to duloxetine at various doses were reported in clinical trials since the first patient exposure to duloxetine through May 12, 2007. All exposures were in the first trimester. Eleven (11) women were lost to follow-up, 13 women elected to have therapeutic abortions, and 14 women experienced spontaneous abortions, of which 1 took mifepristone (RU-486) 2 months prior to the loss of the pregnancy, and 1 woman experienced a spontaneous abortion in the first trimester after a rock-climbing accident. In addition to these patients, 3 women had ectopic pregnancies. Twenty-four women delivered apparently normal babies at term. Three

delivered after premature rupture of membranes and/or preterm labor, with none of the infants surviving. One 33-year-old woman experienced placenta previa and pregnancy-induced hypertension, delivering a full term female infant with aortic stenosis and an enlarged left ventricle. ...There are 8 ongoing pregnancies for which Lilly is obtaining follow-up information.

The numbers of natural outcomes were too few to draw conclusions about the effects of duloxetine exposure during pregnancy. For comparison, the frequency of spontaneous abortion in the general population has been found to be at least 15% (Kiely 1991).

I constructed the table below illustrating this data:

Total Pregnancies		77
Lost to Follow-Up		11
Ongoing		8
Pregnancies with Known Outcome		58
Outcomes for Pregnancies With Known Outcome		
	N	% (of 58)
Normal Term Infant	24	41%
Therapeutic Abortion	13	22%
All Spontaneous Adverse Outcomes	21	36%
Specific Adverse Outcomes		
	N	%
Ectopic Pregnancy	3	5%
Spontaneous Abortion	14	24%
Preterm/Stillbirth	3	5%
Congenital anomaly	1	2%

Note that if a rate of adverse outcome is calculated based on the number of pregnancies where the outcome is known *and the pregnancy was not electively terminated*, the rate of spontaneous abortion is 31% and the rate of all adverse outcomes is 47%. This information was not available at the time of initial approval of this NDA.

Furthermore, analysis of post-marketing cases would not be sufficient to assess the risk of adverse reactions in the fetus of pregnant woman and the potential for serious adverse reactions in the nursing infants of women who are receiving Cymbalta as noted in the Pregnancy Registry Guidance:

...some of the well-known limitations of spontaneous reporting are particularly problematic when trying to evaluate drug risks in pregnancy. Limitations include the lack of denominator data, lack of controls, recall bias associated with retrospective reporting, barriers to reporting, and poor case documentation. These limitations can be overcome through use of prospective pregnancy exposure registries, which are recognized as one method for ascertaining major risks associated with a drug exposure during pregnancy.

Therefore, the findings reported in this application, which are new since approval, of adverse pregnancy outcomes occurring with exposure to Cymbalta, along with the observations above concerning the limitations of post-marketing data, meet the FDAAA criteria for a PMR.

DAARP appreciates the input of the MHT concerning revisions of the labeling language. However, these changes will be conveyed to DPP for their consideration and a supplement request letter may be conveyed to Lilly based on these comments, pending concurrence of DPP, which has primary responsibility for this NDA.

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## BACKGROUND

On August 14, 2007, Eli Lilly and Company submitted a new drug application (NDA 22-148) to the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) for Cymbalta (duloxetine hydrochloride) delayed release capsules. The sponsor's proposed indication for NDA 22-148 is for the management of fibromyalgia (FM) \_\_\_\_\_

\_\_\_\_\_ Cymbalta is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) currently approved for the treatment of Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), and Diabetic Peripheral Neuropathic Pain.

Fibromyalgia (FM) is a chronic pain syndrome characterized by musculoskeletal achiness, stiffness, and exaggerated tenderness at eighteen specified tender points.<sup>1</sup> FM occurs in approximately two percent of the U.S. population, but in 3.4% of women.<sup>1</sup> FM is also associated with a variety of other symptoms including fatigue, non-restorative sleep, increased sensitivity to environmental stimuli, backache, headaches, gastrointestinal symptoms, and depression.<sup>2</sup> Many of these symptoms are also commonly encountered in pregnancy. Therefore, when a woman with FM becomes pregnant, she may experience worsening of FM symptoms.<sup>2</sup> These symptoms negatively impact quality of life and an individual's ability to perform activities of daily living.

Because FM is predominantly occurs among women of child bearing potential, DAARP plans to require a pregnancy registry as a post-marketing study for this application to gather data on the use of Cymbalta by pregnant women. DAARP consulted the MHT to provide advice on the need for and design of the Cymbalta pregnancy registry. In addition, this review recommends language for the Pregnancy and Nursing Mothers subsections of Cymbalta proposed labeling.

## RESPONSE TO CONSULT QUESTIONS

This review responds to specific consult questions from DAARP and recommends language for the Pregnancy and Nursing Mothers subsections of Cymbalta proposed labeling. Dr. Celia Winchell's Medical Team Leader review dated May 2, 2008, provides background information on fibromyalgia prevalence, and a summary of Cymbalta safety and efficacy in the management of fibromyalgia \_\_\_\_\_

### Consult Question:

1. Cymbalta (duloxetine) is approved for the treatment of Major Depressive Disorder (MDD), General Anxiety Disorder (GAD), and Neuropathic Pain. Cymbalta is currently under review in DAARP for the \_\_\_\_\_ of Fibromyalgia (FM), a condition that occurs in women of child bearing age. Please provide advice on the need for, and nature of, a post-marketing pregnancy registry.

*MHT Response:* To gather data on Cymbalta use during pregnancy, a PubMed search was performed using the following search terms:

<sup>1</sup> Abeles AM, Pillinger MH, Solitar BM, Abeles M. Narrative review: the pathophysiology of fibromyalgia. *Ann Intern Med.* 2007 May 15;146(10):726-34.

<sup>2</sup> Schaefer KM, Black K. Fibromyalgia and pregnancy: what nurses need to know. *AWHONN Lifelines/Association of Women's Health, Obstetric and Neonatal Nurses.* 2005; 9(3):228-35.

- Cymbalta and pregnancy
- Duloxetine and pregnancy
- Selective serotonin and norepinephrine reuptake inhibitors and pregnancy
- SNRI and pregnancy

In addition, the following sources were used to gather information on Cymbalta and pregnancy:

- TERIS-The Teratogen Information System
- Reprotox
- Shepard's Catalog of Teratogenic Agents

Based on the search described above, there are no human data available on the effects of Cymbalta use during pregnancy. However, in animal studies, duloxetine exposure during pregnancy was associated with decreased pup survival, decreased fetal weight, increased startle response, and decreased habituation of locomotor activity. However no evidence of teratogenicity was observed.

While there are no human data on Cymbalta use during pregnancy, there are data on the effects of selective serotonin reuptake inhibitors (SSRIs) during pregnancy.

As described in class labeling for SSRIs and SNRIs, some neonates exposed to SSRIs late in the third trimester of pregnancy develop complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications may arise immediately upon delivery. Reported clinical findings include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are considered consistent with a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome.<sup>3</sup>

In addition, to the effects described above, Paxil (paroxetine) labeling was updated to include data from two epidemiological studies that showed an increased risk of cardiovascular malformations, primarily ventricular and atrial septal defects (VSDs and ASDs), after first trimester exposure to paroxetine. One study used Swedish National Registry data to evaluate 6,896 infants of women exposed to antidepressants during early pregnancy (5,123 women exposed to SSRIs, 815 were exposed to paroxetine). Infants exposed to paroxetine in early pregnancy had an increased risk of cardiovascular malformations compared to the registry population (OR 1.8; 95% confidence interval 1.1-2.8). The rate of cardiovascular malformations following paroxetine exposure was 2% vs. 1% in the entire registry population. However, no increase in the overall risk for congenital malformations was observed.<sup>4</sup>

Another retrospective cohort study using U.S. United Healthcare data evaluated 5,956 infants of mothers dispensed paroxetine or other antidepressants during the first trimester (n = 815 for paroxetine). As described in Paxil labeling, "this study showed a trend towards an

<sup>3</sup> Cymbalta (duloxetine hydrochloride) FDA approved product labeling dated November 28, 2007.

increased risk for cardiovascular malformations for paroxetine compared to other antidepressants (OR 1.5; 95% confidence interval 0.8-2.9). The prevalence of cardiovascular malformations following first trimester dispensing was 1.5% for paroxetine vs. 1% for other antidepressants. Nine out of 12 infants with cardiovascular malformations whose mothers were dispensed paroxetine in the first trimester had VSDs. This study found a statistically increased risk of overall major congenital malformations (inclusive of the cardiovascular defects) for paroxetine compared to other antidepressants (OR 517 1.8; 95% confidence interval 1.2-2.8). The prevalence of all congenital malformations following first trimester exposure was 4% for paroxetine vs. 2% for other antidepressants.”<sup>4</sup>

More recently, two large case-control studies evaluated the effects of SSRI use during the first trimester of pregnancy. In the National Birth Defects Prevention Study, maternal treatment with SSRIs during early pregnancy was reported more frequently than expected by 214 mothers of infants with anencephaly (odds ratio=2.4, 95% confidence interval 1.1-5.1), 432 mothers of infants with craniosynostosis (odds ratio=2.5, 95% confidence interval 1.5 - 4.0), and 181 mothers of infants with omphalocele (odds ratio=2.8, 95% confidence interval 1.3-5.7).<sup>5</sup> However, another large case-control study conducted by Slone Epidemiology Center found no increased risks among 320 mothers of infants with neural tube defects, 115 mothers of infants with craniosynostosis, or 127 mothers of infants with omphalocele.<sup>5</sup> However, the study identified a statistical association between right ventricular outflow tract obstruction and prenatal paroxetine exposure among 363 infants with this malformation (odds ratio=2.0, 95% confidence interval 1.1-3.6).<sup>5</sup>

Numerous other case reports and small epidemiological studies have evaluated the use of SSRIs during pregnancy. However, current available data provides conflicting evidence on the overall teratogenic risk from SSRI exposure during pregnancy.

Cymbalta is currently approved for the treatment of MDD, GAD, and Diabetic Peripheral Neuropathic Pain, and is currently under review for the ——— of FM. MDD, GAD, and FM are all conditions that commonly occur in women of child bearing potential. Even with limited data, the possibility exists that women with these conditions, who are of childbearing potential, may conceive while on Cymbalta therapy, resulting in inadvertent exposure to the drug. During pregnancy, women with these conditions may fail other available therapies. A clinician may choose to prescribe Cymbalta after considering the risks and benefits associated with treatment for both the mother and her embryo/fetus. Therefore, a pregnancy registry is needed to monitor maternal and fetal exposures to Cymbalta during pregnancy and associated pregnancy and fetal outcomes.

2. **Sponsors Proposed Pregnancy and Nursing Mothers Labeling** - The sponsor’s proposed Pregnancy and Nursing Mothers subsections of labeling are provided below. The MHT recommended revisions to this labeling are provided on pages 8 to 11 of this review.

<sup>4</sup> Paxil (paroxetine hydrochloride) FDA approved product labeling dated August 2, 2007.

<sup>5</sup> TERIS – The Teratogen Information System, information for Fluoxetine and Cymbalta. <http://csi.micromedex.com/DATA/TE/TE5993.htm>

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## DISCUSSION/CONCLUSIONS

Fibromyalgia (FM) is a chronic pain syndrome that occurs primarily in women of child bearing age and is characterized by musculoskeletal achiness, stiffness, and exaggerated tenderness at eighteen specified tender points.<sup>6</sup> Disease symptoms significantly impact daily functioning and quality of life, especially during pregnancy, which can exacerbate many FM-associated symptoms. Treatment of FM during pregnancy may offer significant maternal benefit and may be needed in order for a pregnant woman to fulfill responsibilities at home and/or at work.<sup>2</sup>

There are no human data available on the effects of Cymbalta use during pregnancy. Based on animal data, duloxetine may cause fetal harm. While there are no human data on Cymbalta use during pregnancy, there are numerous case reports and epidemiological studies on the use of SSRIs during pregnancy. There are documented and labeled class effects for SSRIs and SNRIs that involve a withdrawal-like syndrome in the neonatal period. However, current available data on potential embryofetal toxicities are conflicting.

Given extensive use of SSRI and SNRI drugs in women of child bearing age, the possibility exists that women with MDD, GAD, and FM may conceive while on Cymbalta therapy, resulting in inadvertent exposure to the drug. During pregnancy, women with these conditions may fail other available therapies. A clinician may choose to prescribe Cymbalta after considering the risks and benefits associated with treatment for both the mother and her embryo/fetus. Therefore, a pregnancy registry is needed to monitor maternal and fetal exposures to Cymbalta during pregnancy and associated pregnancy and fetal outcomes.

The MHT's recommendations and revisions to the sponsors proposed labeling are provided below.

## RECOMMENDATIONS

1. The MHT recommends that the sponsor develop and maintain a prospective, observational pregnancy exposure registry conducted in the United States that compares the pregnancy and fetal outcomes of women exposed to duloxetine (for any indication) during pregnancy to an unexposed control population.

The registry should be conducted as a post-marketing requirement for this application. The outcomes of the registry should include major and minor congenital anomalies, spontaneous

<sup>6</sup> Abeles AM, Pillinger MH, Solitar BM, Abeles M. Narrative review: the pathophysiology of fibromyalgia. *Ann Intern Med.* 2007 May 15;146(10):726-34.

abortions, stillbirths, elective terminations, and other serious adverse pregnancy outcomes. These outcomes should be assessed throughout pregnancy. Infant outcomes should be assessed through at least the first year of life. When submitted, the MHT would be happy to review the sponsor's pregnancy registry protocol.

For guidance on how to establish a pregnancy exposure registry, the sponsor should review the Guidance for Industry on Establishing Pregnancy Exposure Registries available at <http://www.fda.gov/cder/guidance/3626fnl.htm>.

Recommended post-marketing requirement language for Cymbalta action letter:

To develop and maintain a prospective, observational pregnancy exposure registry conducted in the United States that compares the pregnancy and fetal outcomes of women exposed to duloxetine (for any indication) during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, and any serious adverse pregnancy outcomes. These events will be assessed among the women enrolled throughout pregnancy. The events will also be assessed among infants through at least the first year of life.

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Annual interim reports will be submitted until FDA has acknowledged that sufficient data has been collected.

You will conduct this study according to the following timetable:

Protocol Submission: Dates to be determined by Division. MHT recommended date is three months after product approval.

Study Start: Dates to be determined by Division. MHT recommended date is six months after product approval.

Final Report Within six months of FDA notification that sufficient data has been collected.

2. The MHT recommended revisions to the sponsors proposed labeling are provided below. Recommended additions are underlined and deletions are struck-out.

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Draft Labeling

Deliberative Process

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## CLINICAL REVIEW

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Reviewer Name Ricardo E. Dent, M.D.  
Review Completion Date April 22, 2008

Established Name Duloxetine  
(Proposed) Trade Name Cymbalta®  
Therapeutic Class SSNRI  
Applicant Eli Lilly

Priority Designation S

Formulation Oral Capsule  
Dosing Regimen 60-mg QD  
Indication Fibromyalgia  
Intended Population Fibromyalgia

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## **1 EXECUTIVE SUMMARY**

### **1.1 Recommendation on Regulatory Action**

Recommend approving the efficacy supplement with revisions to the proposed label.

### **1.2 Recommendation on Postmarketing Actions**

#### **1.2.1 Risk Management Activity**

No specific risk management steps beyond the product labeling are recommended.

#### **1.2.2 Required Phase 4 Commitments**

Lilly should conduct appropriately-powered studies of the 20 mg/day dose of duloxetine (or, alternatively, 30 mg/day would also be acceptable) in fibromyalgia.

Assessment of the safety of duloxetine in pregnant women should be undertaken.



### **1.3 Summary of Clinical Findings**

#### **1.3.1 Brief Overview of Clinical Program**

Cymbalta (duloxetine hydrochloride) is a selective serotonin and norepinephrine reuptake inhibitor marketed as delayed release capsules (oral) for Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), and Diabetic Peripheral Neuropathic Pain (DPNP). This supplemental application seeks to add an indication for the — of fibromyalgia. Data is provided from six clinical trials (five placebo-controlled) in adults with fibromyalgia, including patients both with and without the co-morbid diagnosis of MDD. A total of 1226 patients were treated with duloxetine (876 in placebo-controlled studies). The overall duloxetine safety database for all indications comprises 27,229 patients.

### 1.3.2 Efficacy

To support the claim of efficacy of duloxetine in the            of fibromyalgia, Lilly submitted one Phase 2 and three Phase 3 placebo-controlled studies, of which one study (HMEF, Phase 3) did not demonstrate efficacy of duloxetine per Lilly's analysis.

The remaining two Phase 3 studies, HMCA and HMCJ, provide evidence of efficacy of duloxetine 60 mg once daily (QD) and 120 mg (either as 120 mg QD or 60 mg BID) in the reduction of pain in patients with fibromyalgia. Supportive evidence for the efficacy of duloxetine 60 mg BID is derived from Phase 2 study HMBO, but this was not a protocol-specified primary analysis and correction for multiple comparisons was not employed.

All studies were double-blind, placebo-controlled, parallel-group studies in adult patients with fibromyalgia (study HMCA enrolled only female patients). Patients were treated with study drug for 3 months (HMCA, HMBO) or 6 months (HMCJ) and were assessed at intervals of approximately 2-4 weeks. Pain intensity using the Brief Pain Inventory (BPI) was assessed at each visit and a functional assessment in both studies, and the Fibromyalgia Impact Questionnaire (FIQ) was repeated approximately biweekly in HMBO and HMCA and approximately monthly in HMCJ. The doses studied in HMCA included placebo, duloxetine (DLX) 60 mg QD, and DLX 60 mg BID. The doses studied in HMCJ included placebo, DLX 20 mg QD (blindly switched to 60 mg QD after the first three months), 60 mg QD, and 120 mg QD. The doses studied in HMBO included placebo and DLX 60 mg BID

Table 1.1 below (from Dr. Buenconsejo's review) illustrates the change in pain score from baseline to the end of three months of treatment in the three studies. Notably, the statistical significance of the results do depend on the imputation method chosen for handling missing data. However, the consistent findings with other endpoints and analyses support the conclusion that the tested doses were effective. Note also that there appears to be little difference in the results across dose groups, suggesting that there is no advantage of the 120 mg/day dose over the 60 mg QD dose, and that even 20 mg QD may potentially be effective.

<b>Table 1.1</b>						
<b>Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint at Endpoint</b>						
<b>All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: HMBO, HMCA, and HMCJ</b>						
<b>Study</b>	<b>Treatment Group</b>	<b>BPI Average Pain Score (BOCF)</b>			<b>BPI Average Pain Score (LOCF/BOCF)</b>	
		<b>Baseline</b>	<b>LSMean Change</b>	<b>p-value</b>	<b>LSMean Change</b>	<b>p-value</b>
<b>HMBO*</b>	Placebo	6.11	-0.7		-0.6	
	Duloxetine 60 mg BID	6.13	-1.2	<b>0.067</b>	-1.2	0.049
<b>HMCA</b>	Placebo	6.52	-0.9		-1.0	
	Duloxetine 60 mg QD	6.37	-2.1	<0.001†	-2.2	<0.001†
	Duloxetine 60 mg BID	6.37	-1.8	0.001	-2.1	<0.001
<b>HMCJ</b>	Placebo	6.58	-1.1		-1.2	
	Duloxetine 20 mg QD	6.77	-1.6	0.135†	-1.9	0.039†
	Duloxetine 60 mg QD	6.49	-1.6	<b>0.065</b>	-1.8	0.036
	Duloxetine 120 mg QD	6.39	-1.7	0.036	-1.8	0.038

\*GLM Model: PGIImp=Treatment+Pool Investigator +Treatment\*Pool Investigator  
 †unadjusted p-value.  
 Dr. Buenconsejo's Table.

Table 1.2 below (also from Dr. Buenconsejo's review) illustrates the effect of duloxetine on patient assessment of global well-being as measured by the PGI-Improvement scale. These findings are consistent with the effects noted above.

Table 1.2 PGI-Improvement at Endpoint All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: HMBO, HMCA, and HMCJ						
Study	Treatment Group	N	PGI Improvement Score (LOCF)		PGI Improvement Score (WOCF)	
			LSMean Change	p-value	LSMean Change	p-value
HMBO*	Placebo	99	3.7		3.8	
	Duloxetine 60 mg BID	95	3.1	0.006	3.2	0.011
HMCA**	Placebo	111	3.8		3.9	
	Duloxetine 60 mg QD	114	3.2	0.005†	3.2	0.002†
	Duloxetine 60 mg BID	111	3.1	0.003	3.2	0.002
HMCJ**	Placebo	139	3.4		3.6	
	Duloxetine 20 mg QD	77	2.9	0.012†	3.1	0.010†
	Duloxetine 60 mg QD	143	3.0	0.026	3.1	0.009
	Duloxetine 120 mg QD	142	2.9	0.004	3.0	0.002

\*GLM Model: PGIImp=Treatment+Pool Investigator +Treatment\*Pool Investigator  
 \*\*GLM Model: PGIImp=Treatment+Pool Investigator  
 †unadjusted p-value.  
 Dr. Buenconsejo's Table.

Table 1.3 below shows the proportion of patients in each treatment group considered responders to treatment, based on either a 30% or a 50% reduction from baseline pain. These results are also consistent with the findings above.

Table 1.3 Responder Analysis of BPI Average Pain Score at Endpoint All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: HMBO, HMCA, and HMCJ						
Study	Treatment Group	N	> 30% Improvement in Pain		> 50% Improvement in Pain	
			n(%)	p-value	n(%)	p-value
HMCA	Placebo	120	24 (20%)		18 (15%)	
	Duloxetine 60 mg QD	118	54 (46%)	<0.001	42 (36%)	<0.001
	Duloxetine 60 mg BID	116	45 (39%)	0.002	36 (31%)	0.003
HMCJ	Placebo	144	37 (26%)		26 (18%)	
	Duloxetine 20 mg QD	79	28 (35%)	<b>0.126</b>	22 (28%)	<b>0.089</b>
	Duloxetine 60 mg QD	150	56 (37%)	0.032	42 (28%)	0.043
	Duloxetine 120 mg QD	147	57 (39%)	0.017	44 (30%)	0.018

Dr. Buenconsejo's Table.

### 1.3.3 Safety

In trials of suitable design and duration, 1226 patients with fibromyalgia were treated with duloxetine during the clinical trial program for this indication. The safety analysis revealed that the adverse event profile in this population is consistent with the already-established profile for duloxetine. Overall, patients with fibromyalgia were more prone to report AEs than patients in the trials for other indications, but this was true equally for those treated with placebo as those treated with duloxetine. The most common adverse events reported in duloxetine-treated patients with fibromyalgia were nausea, headache, dry mouth, insomnia, constipation, fatigue, diarrhea, decreased appetite, dizziness, somnolence, hyperhidrosis, and agitation.

Although withdrawal symptoms have been observed after abrupt discontinuation of duloxetine, data from the fibromyalgia studies demonstrate that these effects occur even after gradual taper. This represents a new safety finding.

#### **1.3.4 Dosing Regimen and Administration**

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Data from the clinical studies confirms that 60 mg, once daily, is an effective dose and that no further benefit derives from using a higher dose. However, comparison of dropout rates suggests that tolerability is improved when titration is used.

#### **1.3.5 Drug-Drug Interactions**

No new drug-drug interaction issues were identified in this application.

#### **1.3.6 Special Populations**

Duloxetine has not been studied in pregnant women and nursing mothers. Because the FM population is overwhelmingly female, this issue should be addressed by Lilly.

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## **2 INTRODUCTION AND BACKGROUND**

### **2.1 Product Information**

Duloxetine hydrochloride is an orally administered serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SNRI) which also has minor inhibition of dopamine reuptake. It is approved and marketed in the United States by Eli Lilly under the brand name Cymbalta® for treatment of major depressive disorder (MDD), generalized anxiety disorder (GAD), and diabetic peripheral neuropathic pain (DPNP). Overseas, duloxetine is also approved for treatment of stress urinary incontinence (SUI) and international names include Yentreve, Xeristar, and Ariclaim.

### **2.2 Currently Available Treatment for Indications**

Fibromyalgia is a syndrome characterized the presence of chronic widespread bilateral musculoskeletal pain, fatigue, disordered sleep, and a variety of nonspecific complaints including depression, cognitive difficulties, dyspepsia, and dysmenorrhea. Although the etiology remains unclear, current hypotheses describe abnormal sensory processing in the central nervous system with subsequent hypothalamic-pituitary (HPA) and autonomic dysfunction. Currently, Pregabalin (Lyrica®) is the only product approved for treatment of fibromyalgia. Off-label, various anxiolytics, antidepressants, muscle relaxants, and anticonvulsants are used to treat fibromyalgia alongside treatment programs that utilize nonpharmacologic therapies such as patient education, low-impact aerobics, and cognitive behavioral therapy (CBT).

In the United States, there are approximately 3 – 6 million individuals afflicted with fibromyalgia. Most of these patients are women between the ages of 30 and 50 years and estimates indicate that up to 30% of all patients with this condition will apply for disability.

### **2.3 Availability of Proposed Active Ingredient in the United States**

Duloxetine is approved and marketed in the United States for treatment of MDD, GAD, and DPNP. Dosage forms include 20, 30, and 60 mg enteric coated capsules.

### **2.4 Important Issues With Pharmacologically Related Products**

Serious adverse events and important issues associated with the use of duloxetine and other SNRIs includes suicidal thinking and behavior in children, adolescents, and young adults (a black box warning for antidepressants), withdrawal symptoms, anxiety, and elevation in blood pressure. All of these issues have been well-described in previous iterations of the product label.

## 2.5 Presubmission Regulatory Activity

In June 2003, the FDA convened an Arthritis Advisory Committee Meeting to discuss the clinical development of programs intended to treat fibromyalgia. The committee's consensus was that improvement in pain was important, but other aspects of this condition such as health-related quality of life and global well being are also important. Due to the chronic nature of fibromyalgia, studies are expected to demonstrate efficacy for a minimum of 3-months. Also, in order to make a claim for \_\_\_\_\_ fibromyalgia syndrome, studies require positive results on the co-primary endpoints of pain, function, and global well being.

### Division Interactions With The Applicant During Product Development

- 1) End of Phase 2 Meeting – 17 October 2002
  - During this meeting, the sponsor was advised that primary endpoints must demonstrate statistical significance before consideration is given to secondary endpoints with respect to potential product labeling. These secondary endpoints must also be prespecified in the protocols.
- 2) End of Phase 2 Meeting – 28 July 2004
  - During this meeting, the sponsor was advised that for a fibromyalgia pain indication, studies need to demonstrate efficacy for pain at 3- and 6-month endpoints. In the 6-month study, there should also be evidence that analgesic effects are present at 3 months (results trending in the right direction). The Division also recommended the Patient Global Impression as a co-primary endpoint in order to address the fact that for a \_\_\_\_\_ pain indication, pain severity alone does not reflect treatment effects adequately. Also, since fibromyalgia is a complicated syndrome, the Division is recommending a third co-primary endpoint of patient-reported physical function outcome.
- 3) Addendum to End of Phase 2 Meeting Minutes – 20 August 2004
  - The Division clarified that all co-primary endpoints had to achieve statistical significance simultaneously; therefore adjustments for multiplicity were not necessary for these primary endpoints. At this time, the Division acknowledged that a gatekeeper strategy was reasonable, but prespecified multiplicity adjustments on secondary endpoints would likely be necessary.
- 4) Response to Sponsor Questions Regarding Protocol Amendment (SN 56) – 9 August 2005
  - The Division notified the Sponsor that Study HMCA would probably not provide pivotal evidence of efficacy due to the fact that male subjects were excluded. Therefore, future studies must include male subjects. Additionally, the Division noted that the Patient's Global Improvement and Fibromyalgia Impact Questionnaires would be considered two additional co-primary endpoints.
- 5) Special Protocol Assessment Meeting (SN 61) – 31 January 2005
  - The co-primary endpoints of BPI pain and PGI-Improvement are adequate to support the indication of \_\_\_\_\_ the pain of fibromyalgia. Additionally, the Division notified the sponsor a reduction in pain intensity both clinically and statistically at the end-of-treatment would be expected and that a 30% improvement in pain relief between baseline and landmark visits would also be expected.

- At this time, it was unclear if positive results from a 6-month study would be required to support proof of efficacy and the Division also noted that the Sheehan Disability Scale may not be validated in fibromyalgia.
  - Also, there were discrepancies regarding the proposed sample size and the handling of missing values in the primary efficacy analysis. The Division recommended that an  $\alpha \geq 0.1$  be used for testing the center-by-treatment interaction and asked the sponsor to provide a rationale for their dose-response analysis.
- 6) Teleconference with Sponsor – 23 June 2006
- The Division notified the sponsor that they would not be required to demonstrate efficacy at 6-months.
- 7) Pre-sNDA Meeting – 13 April 2007
- The Division notified the sponsor that pediatric studies could be deferred until after approval in adults.
- 8) Teleconference with Sponsor – 16 May 2007
- The Division notified the sponsor that the current understanding is that the primary symptom of fibromyalgia is pain and therefore, only 1 indication will be considered, this being '\_\_\_\_\_ of fibromyalgia'. Evaluation of additional endpoints such as disordered sleep and fatigue was encouraged.

## 2.6 Other Relevant Background Information

For more information on duloxetine worldwide regulatory activity, see Appendix 10.4, Table 7.19.

## 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

### 3.1 CMC (and Product Microbiology, if Applicable)

An environmental assessment is pending at the time of this review. There were no other CMC issues.

### 3.2 Animal Pharmacology/Toxicology

There was no new animal pharmacology/toxicology information included in this supplemental application.

## **4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY**

### **4.1 Sources of Clinical Data**

Clinical data reviewed in support of this NDA submission were generated from the following sources:

- 1) The final study report for Protocol F1J-MC-HMBO, a clinical trial conducted in the United States by the sponsor entitled: Duloxetine Versus Placebo in the Treatment of Fibromyalgia Patients With or Without Major Depressive Disorder.
- 2) The final study report for Protocol F1J-MC-HMCA, a clinical trial conducted in the United States by the sponsor entitled: Duloxetine Versus Placebo in the Treatment of Fibromyalgia Patients With or Without Major Depressive Disorder.
- 3) The final study report for Protocol F1J-MC-HMCJ, a clinical trial conducted in the United States and Puerto Rico by the sponsor entitled: Dose Response Study of Duloxetine Versus Placebo in the Treatment of Fibromyalgia Syndrome.
- 4) The final study report for Protocol F1J-MC-HMEF, a clinical trial conducted in the United States, Germany, Spain, Sweden, and the United Kingdom by the sponsor entitled: Duloxetine 60 to 120 mg Versus Placebo in the Treatment of Fibromyalgia.
- 5) The final study report for Protocol F1J-MC-HMEH, a clinical trial conducted in Argentina, Australia, Brazil, Canada, Mexico, Poland, and Taiwan by the sponsor entitled: A 1-Year Safety Study of Duloxetine in Patients with Fibromyalgia.

### **4.2 Tables of Clinical Studies**

Table 4.1 below lists the studies included in this application. All studies were included in the safety review. Primary attention in the efficacy review was given to the first three studies listed below, HMBO, HMCA, and HMCJ.

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<b>Study ID</b>	<b>Design/ Control type</b>	<b>Primary Endpoint(s)</b>	<b>Number of subjects by arm entered/ completed</b>	<b>Duration</b>	<b>Gender</b>	<b>Test &amp; Control Drug(s) Dose, Route, &amp; Regimen</b>	<b>Diagnosis or Inclusion Criteria</b>
<b>HMBO</b>	Double-blind, randomized, parallel, multicenter, Phase 2 study	Reduction of pain as measured by the Fibromyalgia Impact Questionnaire (FIQ) Pain Item and the FIQ Total Score	Randomized: 104 duloxetine, 103 placebo Completed: 58 duloxetine, 66 placebo	3 months	Male and female patients	Duloxetine 60 mg BID PO Placebo BID PO	Female and male outpatients ≥18 years with primary fibromyalgia (FM), as defined by the ACR, with or without MDD
<b>HMCA</b>	Double-blind, randomized, parallel, multicenter, Phase 3 study	Reduction of pain as measured by the average pain item of the Brief Pain Inventory (BPI)	Randomized: 234 duloxetine, 120 placebo Completed: 148 duloxetine, 68 placebo	3 months	Female patients	Duloxetine 60 mg BID PO Duloxetine 60 mg QD PO Placebo BID PO	Female outpatients ≥18 years with primary FM, as defined by the ACR, with or without MDD
<b>HMCJ</b>	Multicenter, randomized, parallel, double-blind, placebo-controlled, Phase 3 study	Reduction of pain, as measured by the average pain item on the BPI and the PGI-I	Randomized: 376 duloxetine, 144 placebo Completed 3-month therapy phase: 242 duloxetine, 84 placebo Completed 6-month therapy phase: 206 duloxetine, 72 placebo	3 month therapy phase, 3 month continuation phase	Male and female patients	Duloxetine 20 mg QD PO Duloxetine 60 mg QD PO Duloxetine 120 mg QD PO Placebo QD PO	Male or female patients ≥18 years diagnosed with FM, as defined by ACR, with or without MDD.
<b>HMEF</b>	Multicenter, randomized, parallel, double-blind, fixed-dose, placebo-controlled, Phase 3 study	Change in pain severity as measured by the average pain item of the BPI-modified short score and change in patient-reported improvement on the PGI-I scale	Randomized: 162 duloxetine, 168 placebo Completed: 101 duloxetine, 103 placebo	6 months	Male and female patients	Duloxetine 60 mg QD PO Duloxetine 120 mg QD PO Placebo QD PO	Male or female patients ≥18 years diagnosed with FMS, as defined by ACR, with or without MDD.
<b>HMEH</b>	Multicenter, parallel, Phase 3, one year safety study consisting of an 8-week open-label period followed by a 52-week double-blind, randomized period.	Long-term safety and tolerability measures	Randomized: 307 duloxetine Completed: 195 duloxetine (duloxetine 60mg: 71 Duloxetine 120mg: 124)	2 months open label followed by 1 year double-blind	Male and female patients	Duloxetine 30 mg QD Duloxetine 60 mg QD Duloxetine 120 mg QD	Female and male outpatients ≥18 years with diagnosis of FM, as defined by the ACR, and score at least 4 on the average pain item of the BPI-Modified Short Form at Visit 1 and Visit 2

Abbreviations: BID = twice daily; BPI = Brief Pain Inventory; FIQ = Fibromyalgia Impact Questionnaire; HMBO = Study F1J-MC-HMBO; HMCA = Study F1J-MC-HMCA; HMCJ = Study F1J-MC-HMCJ; HMEF = Study F1J-MC-HMEF; HMEH = Study F1J-MC-HMEH; ID = identification; MDD = major depressive disorder; PGI-I = Patient's Global Impressions of Improvement. Source: Clinical study reports for Study HMBO, Study HMCA, Study HMCJ, Study HMEF, and Study HMEH.  
 Applicant's Table, Page 19, Clinical Overview.

### 4.3 Review Strategy

The review of efficacy focused on those studies which the applicant had concluded provided evidence of efficacy. These were Studies HMBO, HMCA, and HMCJ. In addition, study HMEH, which employed a period of double-blind, dose-controlled treatment after a period of open-label run-in, \_\_\_\_\_

The review of safety focused on data from all of the placebo-controlled trials, and also compared these findings to the safety profile of duloxetine in other indications. Special emphasis was given to Study HMCJ for assessment of dose-response data, because this study incorporated a low-dose (20 mg) arm.

### 4.4 Data Quality and Integrity

Following a preliminary review of safety and efficacy, Dr. Joan Buenconsejo and I selected 5 study sites that stood out due to enrollment of a large number of subjects, large number of protocol violations, and high treatment responders. The Investigators at these sites, which were selected for inspection, were Drs. Leslie Arnold, Timothy Smith, Jeffrey Gitt, Richard Weinstein, James Knutson, and Patricia Buchanan.

Sherbet Samuels, R.N., M.P.H., from the Division of Scientific Investigations reviewed the results of the field inspections and determined that data from the inspected sites appeared acceptable for support of the respective indications.

### 4.5 Compliance with Good Clinical Practices

The studies appear to have been conducted in compliance with Good Clinical Practice guidelines.

### 4.6 Financial Disclosures

The only Investigator which reported having Disclosable Information for owning shares of Lilly valued over \$50,000 was \_\_\_\_\_

\_\_\_\_\_ A field investigation of his study site found minor protocol violations related to missed reporting of adverse events. DSI determined that the data from his site appeared acceptable.

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## 5 CLINICAL PHARMACOLOGY

### 5.1 Pharmacokinetics

The following information is taken from the approved Cymbalta package insert:

Duloxetine has an elimination half-life of about 12 hours (range 8 to 17 hours) and its pharmacokinetics are dose proportional over the therapeutic range. Steady-state plasma concentrations are typically achieved after 3 days of dosing. Elimination of duloxetine is mainly through hepatic metabolism involving two P450 isozymes, CYP1A2 and CYP2D6.

**Absorption and Distribution** — Orally administered duloxetine hydrochloride is well absorbed. There is a median 2-hour lag until absorption begins ( $T_{lag}$ ), with maximal plasma concentrations ( $C_{max}$ ) of duloxetine occurring 6 hours post dose. Food does not affect the  $C_{max}$  of duloxetine, but delays the time to reach peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (AUC) by about 10%. There is a 3-hour delay in absorption and a one-third increase in apparent clearance of duloxetine after an evening dose as compared to a morning dose.

The apparent volume of distribution averages about 1640 L. Duloxetine is highly bound (>90%) to proteins in human plasma, binding primarily to albumin and  $\alpha_1$ -acid glycoprotein. The interaction between duloxetine and other highly protein bound drugs has not been fully evaluated. Plasma protein binding of duloxetine is not affected by renal or hepatic impairment.

**Metabolism and Elimination** — Biotransformation and disposition of duloxetine in humans have been determined following oral administration of  $^{14}C$ -labeled duloxetine. Duloxetine comprises about 3% of the total radiolabeled material in the plasma, indicating that it undergoes extensive metabolism to numerous metabolites. The major biotransformation pathways for duloxetine involve oxidation of the naphthyl ring followed by conjugation and further oxidation. Both CYP1A2 and CYP2D6 catalyze the oxidation of the naphthyl ring *in vitro*. Metabolites found in plasma include 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate. Many additional metabolites have been identified in urine, some representing only minor pathways of elimination. Only trace (<1% of the dose) amounts of unchanged duloxetine are present in the urine. Most (about 70%) of the duloxetine dose appears in the urine as metabolites of duloxetine; about 20% is excreted in the feces. Duloxetine undergoes extensive metabolism, but the major circulating metabolites have not been shown to contribute significantly to the pharmacologic activity of duloxetine.

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Dr. Emmanuel O. Fadiran from the Office of Clinical Pharmacology reviewed the current Application and found the submission acceptable. Lilly obtained plasma samples from patients

in Study HMEF to help characterize the clinical pharmacology of duloxetine in patients with fibromyalgia. In his review Dr. Fadiran states that duloxetine PK is similar in healthy subjects and in patients with major MDD, DPNP, SUI, and FM.

With respect to PK, he summarizes that:

- The PK of duloxetine were adequately described by a one compartment model with large interpatient variability (60% to 100%).
- The PK of duloxetine in MDD, SUI, DPNP, and FM patients are similar.
- Body weight, disease condition and dosing regimen did not have any statistically significant effect on duloxetine PK.
- Sex, smoking status, age, ethnic origin, and dose had a statistically significant effect on duloxetine PK. Women and nonsmokers have lower duloxetine oral clearance (CL/F) relative to men and smokers, respectively. Typically, women had 64% higher average duloxetine concentrations at steady state (Cav,ss) than males receiving the same dose of duloxetine. Similarly, nonsmokers had nearly 43% higher Cav,ss than smokers receiving the same dose of duloxetine. The effect of sex and smoking status is likely related to the higher CYP1A2 activity or concentration in men and smokers. The combined effects of sex, smoking, age, dose, and ethnic origin explained only about 8% and 27% of the interpatient variability in CL/F and volume of distribution (V/F), respectively. There remains a high degree of interpatient variability (60 to 100%) unexplained in duloxetine pharmacokinetics. Specific dose recommendations for duloxetine based upon sex, smoking status, age, dose, or ethnic origin are not warranted because the effect of these covariates are small relative to the magnitude of interpatient variability,

## 5.2 Pharmacodynamics

The PK results of Study HMEF were used to explore a PK-PD relationship between baseline-to-endpoint changes in BPI average pain scores and PGI-Improvement. In his review Dr. Fadiran found that:

- A PK-PD relationship was explored between the baseline-to-endpoint change scores for the BPI average pain score and endpoint of PGI-Improvement during the 6-month acute therapy phase in Study HMEF. Linear, Emax and logistic models were examined to investigate the relationship between Cav,ss and the efficacy endpoints. The effect of duloxetine Cav,ss on change in BPI pain score from baseline to endpoint and on AUC pain relief was characterized by a linear PK-PD model. The value of the slope suggests that the effect of duloxetine Cav,ss on change in BPI pain score is very small. There did not appear to be an effect of duloxetine Cav,ss on 30% or 50% reduction in BPI pain score. The probability of a patient reporting an improvement on PGI-Improvement score increased with increasing duloxetine Cav,ss, thus suggesting that increasing the dose for an individual patient may increase the probability of achieving improvement on PGI-I score.

## 5.3 Exposure-Response Relationships

Based on analyses of plasma from Study HMEF, increased serum duloxetine concentrations appear to increase the probability that patients will report better PGI-Improvement scores.

the duloxetine studies included the Patient's Global Impression of Improvement (PGI-Improvement), the Clinical Global Impressions of Severity (CGI-Severity), the Fibromyalgia Impact Questionnaire (FIQ), and the Multidimensional Fatigue Inventory (MFI). A more detailed list of the efficacy measures used in the duloxetine studies can be found in Table 6.1, below.

The development program of duloxetine for the treatment of fibromyalgia was discussed with the Division of Anesthesia, Analgesia, and Rheumatology during meetings from 17 October 2002 through 16 May 2007 under IND 63,615. On 24 October 2004, advice was also provided by the Committees for Medicinal Products for Human Use (CHMP). At the time of the End of Phase 2 Meeting, 28 July 2004, the Applicant had already completed studies HMBO and HMCA; therefore, advice from this meeting was only incorporated into the design of Studies HMCJ, HMEF, and HMEH. Design suggestions that the Applicant incorporated into the studies includes: 1) enrollment of patients of both genders, 2) utilization of coprimary endpoints measuring both pain and global function, 3) collection of long-term data (12-month) for safety and persistence of efficacy, 4) inclusion of lower doses (20 mg QD), 5) stratifying in the randomization for MDD status at baseline, and 6) inclusion of at least one 6-month efficacy study. In subsequent communications with the Applicant, the Division's requirement for a successful 6-month efficacy study was removed. Details about the individual studies may be found in Section 6.1.3, Study Design.

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<b>Table 6.1</b>	
<b>Efficacy Measures Used In Fibromyalgia Placebo-Controlled Trials</b>	
<b>HMBO, HMCA, HMCJ, HMEF, and HMEH</b>	
<b>Measure</b>	
	<ul style="list-style-type: none"> <li>• Brief Pain Inventory (BPI) Average Pain Score<sup>a</sup> and Interference: a self-reported scale that measures the severity and of pain and the interference of pain on function. Severity scores range from 0 (no pain) to 10 (pain as bad as you can imagine). Four questions assess the pain severity in the past 24 hours and the pain right now. Interference scores range from 0 (does not interfere) to 10 (completely interferes). The average interference score is the arithmetic mean of the 7 interference questions.               <ul style="list-style-type: none"> <li>○ BPI Worst Pain</li> <li>○ BPI Average Pain Score AUC</li> </ul> </li> <li>• Patient's Global Impressions of Improvement (PGI)-Improvement<sup>b</sup>: a self-administered questionnaire that rates degree of overall improvement at the time of assessment. Score ranges from 1 (very much better) to 7 (very much worse).</li> <li>• Sheehan Disability Scale (SDS) Global Functioning Impairment Total Score: used to assess degree to which symptoms have disrupted work, social, and/or home life. Score ranges from 0 to 30 with a lower score indicating a lower level of disability.</li> <li>• Clinical Global Impression (CGI)-Severity: scale evaluates the severity of illness at the time of assessment from the clinician's perspective. Score ranges from 1 (normal, not at all ill) to 7 (extremely ill).</li> <li>• Fibromyalgia Impact Questionnaire (FIQ) Total Score<sup>c</sup>: a self-administered questionnaire designed to measure the components of health status that are most affected by fibromyalgia. Composed of 20 items, the first 11 measure physical functioning (each rated on 7-point Likert-type-scale). Items 12 and 13 measure number of days patient felt ill. Items 14 – 20 use 11-point Likert-type-scale to measure work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety, and depression. Total score ranges from 0 – 80, with a higher score indicating more negative impact.</li> <li>• Multidimensional Fatigue Inventory (MFI<sup>d</sup>): a 20-item, self-reporting instrument to collect data on general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity.</li> <li>• Mean Tender Point Pain Threshold: assessed for all 18 tender points using a dolorimeter and recorded in kg/cm<sup>2</sup>.</li> <li>• 36-item Short-Form Health Survey (SF-36): consists of 36 questions covering 8 health domains: physical functioning, bodily pain, role limitations due to physical problems, role limitations due to emotional problems, general health perceptions, mental health, social function, and vitality. Each domain is scored from 0 – 100, with higher scores indicating better health status or functioning.</li> <li>• EuroQoL Questionnaire (EQ-5D<sup>d</sup>): a generic, multidimensional, health-related, quality-of-life instrument. Patients rate their health state in the 5 health domains of mobility, self-care, usual activities, pain/discomfort, and mood. Scores between 1 and 3 are generated for each domain and the 5 domains are mapped to a single index through an algorithm. Index ranges between -0.59 and 1 with higher score indicating better health state perceived by the patient.</li> <li>• Response Rate at Endpoint (50%)</li> <li>• Response Rate at Endpoint (30%)</li> <li>• Time to First Response (50%)</li> <li>• Sustained Response</li> <li>• Time to Sustained Response</li> </ul>
<p>Abbreviations: AUC = area under the curve; BID = twice daily; QD = once daily            Note: The following efficacy measures were administered in Study HMEH: BPI average pain score, PGI-Improvement, SDS Global Functioning Impairment Total Score, CGI-Severity, FIQ Total Score, BPI Average Interference, Response Rate at Endpoint (50%), and BPI Worst Pain.            a) Primary efficacy measure in Study FIJ-MC-HMCA, and coprimary efficacy measure in Study FIJ-MC-HMCJ and Study FIJ-MC-HMEF            b) Coprimary efficacy measure in Study FIJ-MC-HMCJ and Study FIJ-MC-HMEF            c) Primary efficacy measure in Study FIJ-MC-HMBO            d) Performed in Study FIJ-MC-HMCJ and Study FIJ-MC-HMEF only            Applicant's Table, Page 23, Clinical Efficacy Summary.</p>	

### 6.1.3 Study Design

Patients in all studies were required to have met criteria for primary fibromyalgia, as defined by the ACR (widespread aching pain in all 4 quadrants of the body and axial skeleton for > 3 months duration and ≥ 11 of 18 tender points under digital palpitation examination with an approximate force of 4 kg/cm<sup>2</sup>). These patients were also required to have a score ≥ 4 on the primary pain severity measures at both screening and baseline suggesting moderately severe disease. Exclusion criteria in all studies included any current Axis I diagnosis other than MDD (except in study HMEH), pain symptoms related to traumatic injury, structural or regional rheumatic disease (such as osteoarthritis, bursitis, and tendonitis), current or previous diagnosis of rheumatoid arthritis, infectious arthritis, or an autoimmune disease, and lastly, use of any medications that could not be discontinued at Visit 1 (excluded medications include narcotics, nonsteroidal anti-inflammatory drugs, tramadol, triptans, anticonvulsants, and antidepressants).

In all studies, the presence or absence of major depression was to be evaluated using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria at baseline using the Mini International Neuropsychiatric Interview (MINI). A summary of major inclusion and exclusion criteria can be found below in Table 6.2.

<b>Table 6.2 Summary of Major Inclusion and Exclusion Criteria for Studies HMBO, HMCA, HMCJ, HMEF, and HMEH</b>					
	HMBO	HMCA	HMCJ	HMEF	HMEH
<b>Inclusion Criteria</b>					
Male and Female outpatients	■		■	■	■
Females outpatients only		■			
Age ≥ 18 years	■	■	■	■	■
Meet ACR criteria for primary fibromyalgia	■	■	■	■	■
Score ≥ 4 on FIQ pain intensity item at baseline	■				
Score ≥ 4 on BPI average pain item at baseline		■	■	■	■
<b>Exclusion Criteria</b>					
Current primary DSM-IV Axis I diagnosis other than MDD	■	■	■	■	■
Diagnosis of dysthymia within the past 2 years	■	■	■	■	■
Previous diagnosis of psychosis, bipolar disorder, or schizoaffective disorder	■	■	■	■	■
Any anxiety disorder within the past year	■	■	■	■	■
Axis II disorder which could interfere with study compliance	■	■	■	■	■
History of substance abuse or dependence within the past year (excluding nicotine and caffeine)	■	■	■	■	■
Positive urine drug screen for any substance of abuse	■	■	■	■	■
Serious suicidal risk	■	■	■	■	■
Pain symptoms related to traumatic injury, structural rheumatic disease (such as osteoarthritis, bursitis, tendonitis), or regional rheumatic disease	■	■	■	■	■
Confirmed or previous diagnosis of rheumatoid arthritis, inflammatory arthritis, or infectious arthritis, or an autoimmune disease	■	■	■	■	■
Abnormal laboratory values for: TSH, CRP, ANA, or RF	■	■	■	■	■
Serious or unstable cardiovascular, hepatic, renal, respiratory, or hematologic illness, symptomatic peripheral vascular disease, or other medical condition that could compromise patient safety	■	■	■	■	■
Treatment with MAOI within 14 days prior to Visit 2 or fluoxetine within 30 days prior to Visit 2	■	■	■	■	■
Total bilirubin > 1 x ULN and/or ALT/AST > 1.5 x ULN	■	■			
Have acute liver injury, uncontrolled seizures, or narrow-angle glaucoma			■	■	■
ACR = American College of Rheumatology, FIQ = Fibromyalgia Impact Questionnaire, BPI = Brief Pain Inventory, DSM IV = Diagnostic and Statistical Manual of Mental Disorders, 4 <sup>th</sup> edition, MDD = major depressive disorder, TSH = thyroid stimulating hormone, CRP = C-reactive protein, ANA = anti-nuclear antibody, RF = rheumatoid factor, ULN = upper limit of normal, ALT = alanine transaminase, AST = aspartate transaminase					

The doses that were to be studied in their five trials included: duloxetine 20 mg daily, 60 mg daily, 60 mg twice daily, and 120 mg once daily (see Table 6.3 below). As mentioned above in the Summary of Interactions with the Sponsor, the addition of a low dose arm (20 mg once daily in Study HMCJ) was added to comply with Division recommendations. Likewise, trial duration recommendations were to be followed to provide a total of two studies of 3-month duration, two studies of 6-month duration, and one long term study of 1-year duration.

**Table 6.3**  
**Summary of Treatment Groups by Study**

Study	Dose				
	Placebo	20 mg QD	60 mg QD	60 mg BID	120 mg QD
HMBO	■			■	
HMCA	■		■	■	
HMCJ	■	■	■		■
HMEF			■		■
HMEH			■		■

**Study HMBO**

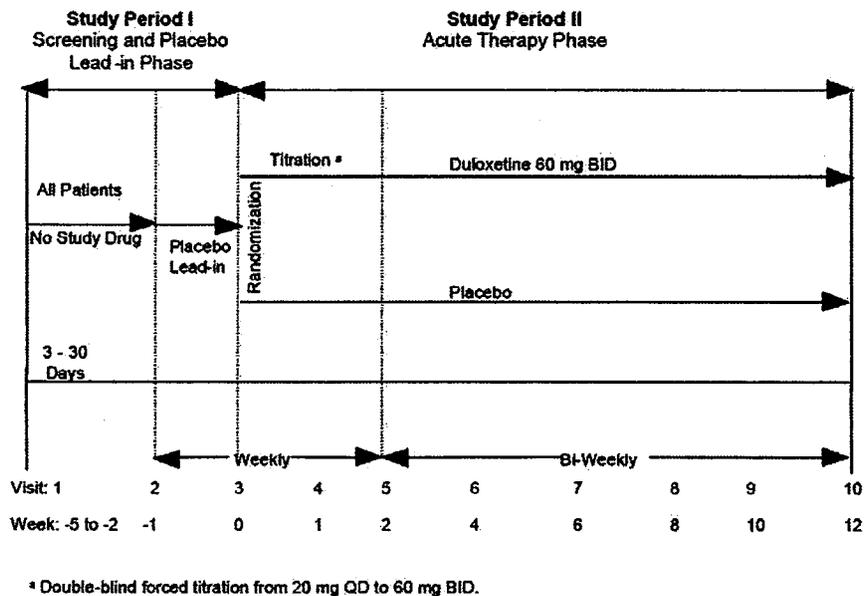
Study HMBO was to be a Phase 2, parallel-group, double-blind, fixed-dose, placebo-controlled study in male and female patients. The primary objective was to assess the efficacy of duloxetine 60 mg BID compared with matched placebo (1:1 ratio) at the end of a 12-week, double-blind therapy phase in reducing pain severity as measured by the FIQ Pain Item and the FIQ Total Score. For more information on the timing of assessments, see Appendix 10.3, Table 6.1.

Study HMBO included a placebo lead-in phase and a 2 week titration. Patients were to be stratified into two groups: those with major depressive disorder (MDD) and those without MDD. Study unblinding did not occur until the reporting database was validated and locked for statistical analysis.

The schematic diagram below illustrates the basic study design.

**Figure 6.1**

**Illustration of Study Design: Study HMBO**



**Figure HMBO.9.1. Illustration of study design for Protocol F1J-MC-HMBO.**

### Patient Disposition

Of the 555 patients screened, 271 met entry criteria and 207 were randomized. One hundred three were randomized to receive placebo and 104 were randomized to duloxetine 60 mg BID. In the placebo arm 66 patients completed the study and 37 discontinued during the acute therapy phase (11 due to AEs, 3 lost to follow-up, 9 due to conflict or personal decision, 1 due to a protocol violation, and 13 due to lack of efficacy). In the duloxetine arm, 58 patients completed the study and 46 discontinued during the acute therapy phase (18 due to AEs, 6 lost to follow-up, 10 due to conflict or personal decision, 1 by physician decision, 2 due to protocol violation, and 9 due to lack of efficacy). This discontinuation rate and the reasons for discontinuation are reasonable and unlikely to adversely affect the efficacy results.

	<b>Placebo N = 103</b>	<b>DLX 60 BID N = 104</b>
Completed acute phase	66 (64%)	58 (56%)
Discontinued		
Adverse Event	11 (11%)	18 (17%)
Patient decision	9 (9%)	10 (10%)
Physician decision		1 (1%)
Lost to follow-up	3 (3%)	6 (6%)
Protocol Violation	1 (1%)	2 (2%)
Lack of Efficacy	13 (13%)	9 (9%)
Exclusion Criteria		

### Study Endpoints

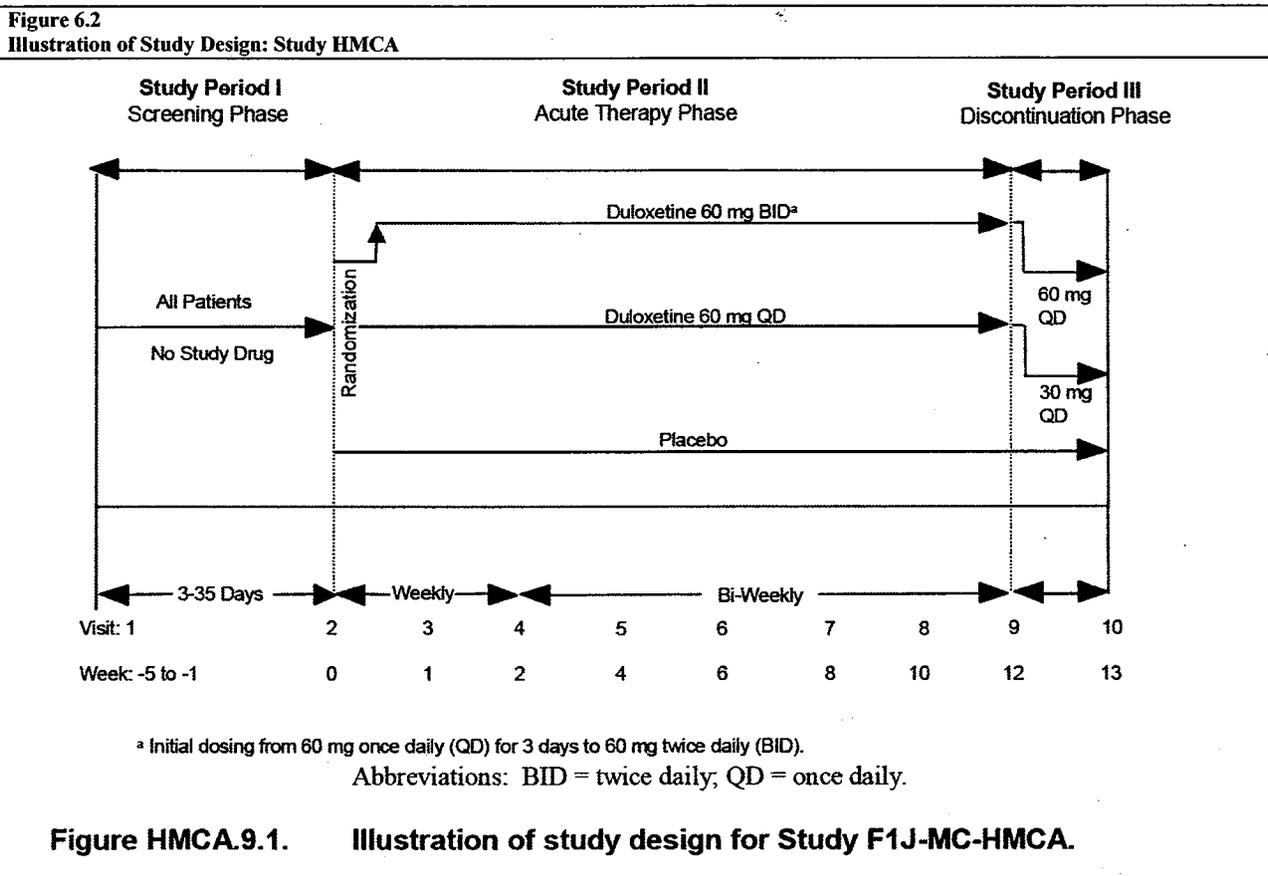
- Efficacy
  - Primary: Fibromyalgia Impact Questionnaire (FIQ) Pain Item and FIQ Total Score
  - Mean Tender Point Pain Threshold
  - FIQ Items: Fatigue, Rest, and Stiffness
  - Clinical Global Impression of Severity (CGI-Severity)
  - Patient Global Impressions of Improvement (PGI-Improvement)
  - Brief Pain Inventory (BPI)
  - Beck Depression Inventory-II (BDI-II) scale
  - Beck Anxiety Inventory (BAI) scale
- Health Outcomes
  - Interference portion of the Brief Pain Inventory (BPI)
  - Sheehan Disability Scale (SDS)
  - Quality of Life in Depression Scale (QLDS)
  - Medical Outcomes Study Short Form-36 (SF-36)

**Study HMCA**

Study HMCA was to be a Phase 3, parallel-group, double-blind, placebo-controlled study in women treated with either duloxetine 60 mg BID or 60 mg QD (1:1:1 ratio). The primary objective was to assess the efficacy of duloxetine 60 mg BID compared with placebo on the reduction of pain severity as measured by the average pain item of the BPI during a 12-week, double-blind, placebo-controlled therapy phase. For more information on the timing of assessments, see Appendix 10.3, Table 6.2.

Study HMCA included a 3 day titration for the higher dose (60 mg BID) and one-week taper phase at the end of 12 weeks. Patients were also stratified into two groups (with and without MDD). Unblinding did not occur until the reporting database was validated and locked.

The schematic diagram below illustrates the basic study design.



### Patient Disposition

Of the 746 patients screened, 354 met entry criteria and were randomized. One hundred twenty were randomized to receive placebo, 118 were randomized to duloxetine 60 mg QD, and 116 were randomized to duloxetine 60 mg BID. In the placebo arm 68 patients completed the study and 52 discontinued during the acute therapy phase (14 due to AEs, 4 lost to follow-up, 1 due to conflict or personal decision, 1 due to noncompliance, 1 due to a protocol violation, 13 due to withdrawal of informed consent, and 18 due to lack of efficacy). In the duloxetine 60 mg QD arm, 77 patients completed the study and 41 discontinued during the acute therapy phase (25 due to AEs, 1 lost to follow-up, 3 due to conflict or personal decision, 1 by physician decision, 3 due to noncompliance, 1 due to withdrawal of informed consent, and 7 due to lack of efficacy). In addition to these discontinuations, 1 patient discontinued during the discontinuation phase due to an AE. In the duloxetine 60 mg BID arm, 71 patients completed the study and 45 discontinued during the acute therapy phase (27 due to AEs, 5 lost to follow-up, 4 due to conflict or personal decision, 1 due to noncompliance, 4 due to withdrawal of informed consent, and 4 due to lack of efficacy). This discontinuation rate and the reasons for discontinuation are reasonable and unlikely to adversely affect the efficacy results.

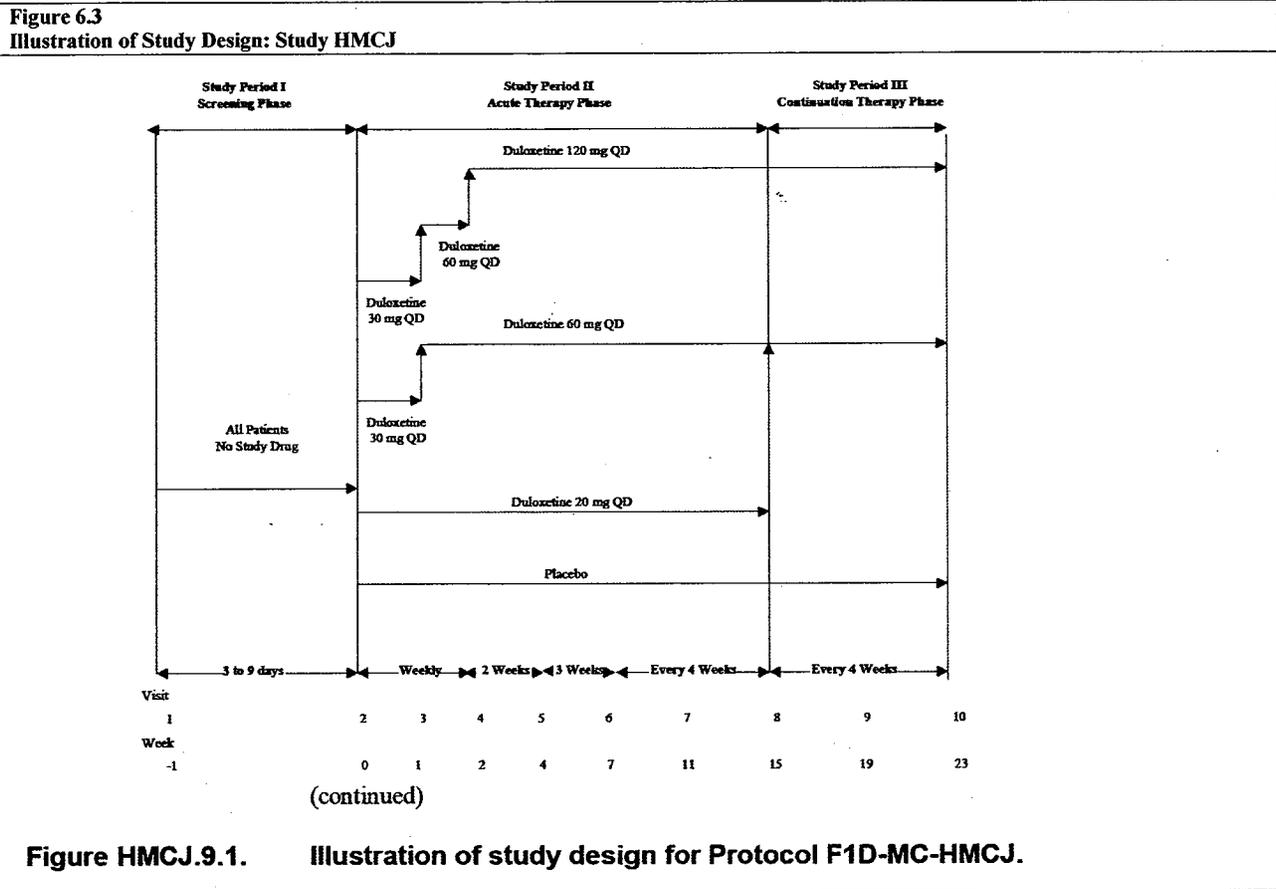
	<b>Placebo</b> N = 120	<b>DLX 60 QD</b> N = 118	<b>DLX 60 BID</b> N = 116
Completed acute phase	68 (57%)	77 (65%)	71 (61%)
Discontinued			
Adverse Event	14 (12%)	25 (21%)	27 (23%)
Patient decision	4 (3%)	1 (1%)	4 (4%)
Physician decision		1 (1%)	
Noncompliance	1 (1%)	3 (3%)	1 (1%)
Protocol Violation	1 (1%)		
Lack of Efficacy	18 (15%)	7 (6%)	4 (3%)

### Study Endpoints

- Efficacy
  - BPI average pain score
  - Fibromyalgia Impact Questionnaire (FIQ)
  - BPI severity and interference scores
  - Mean tender point pain thresholds
  - Clinical Global Impressions of Severity (CGI-Severity) rating
  - Patient's Global Impressions of Improvement (PGI-Improvement) rating
  - 17-item Hamilton Depression Scale total score
- Health Outcomes:
  - Short Form-36 (SF-36) scale
  - Quality of Life in Depression Scale (QLDS)
  - Sheehan Disability Scale (SDS)

**Study HMCJ**

Study HMCJ was to be a Phase 3, randomized, multi-center, double-blind, parallel-group, fixed dose, placebo-controlled study in male and female patients. Duloxetine treated patients were to receive one of 3 doses versus matched placebo: 20 mg QD, 60 mg QD, or 120 mg QD (1:2:2:2 ratio). Patients were to be assessed after 3 months of treatment and again after 6 months of treatment (patients in the 20 mg QD were titrated to 60 mg QD after 3 months). For more information on the timing of assessments, see Appendix 10.3, Table 6.3. The schematic diagram below illustrates the basic study design.



The primary objective of this study was to assess the efficacy of duloxetine 120 mg QD compared with placebo on the treatment of pain in patients with ACR-defined primary fibromyalgia, in the 3-month therapy phase of the study. This objective was to be evaluated from 2 perspectives: reduction in pain severity (average pain item on the BPI) and patient-reported improvement (PGI-Improvement).

This study also intended to use a gatekeeper strategy for sequential testing of the secondary objectives. These objectives included:

- A comparison between duloxetine 60 mg QD and placebo on the change from baseline to endpoint on the average pain item on the BPI and the endpoint of PGI-Improvement (3-month comparison)
- A comparison between duloxetine 60 mg QD, 120 mg QD, and placebo on the change from baseline to endpoint on the average pain item of the BPI and the endpoint of PGI-Improvement (6-month comparison)
- A comparison between duloxetine 60 mg QD, 120 mg QD, and placebo on the change from baseline to endpoint as measured by the Sheehan Disability Scale (SDS) total score (3-month comparison)
- A comparison between duloxetine 60 mg QD, 120 mg QD, and placebo on the change from baseline to endpoint on the SDS total score (6-month comparison)

Study HMCJ included a 2-week titration for the 120 mg QD group and a 1-week titration for the 60 mg QD group. Patients were again stratified by presence or absence of MDD. Due to serious adverse events, a total of 9 patients were unblinded during the study.

### Patient Disposition

A total of 520 patients were randomized to either placebo (n=144), duloxetine 20 mg QD (n=79), duloxetine 60 mg QD (n=150), and duloxetine 120 mg QD (n=147) for the first 3-month part of the study. At 3-months, in the placebo group, 84 patients completed that part of the study, and 60 patients discontinued (17 due to AEs, 14 due to lack of efficacy, 10 due to personal decision, 13 were lost to follow-up, 5 due to protocol violations, and 1 due to physician decision). In the duloxetine 20 mg QD group, 49 patients completed 3-months and 30 patients discontinued (8 due to AEs, 8 due to lack of efficacy, 8 due to subject decision, 3 were lost to follow-up, 1 due to protocol violation, 1 due to physician decision, and 1 due to entry criteria exclusion). In the duloxetine 60 mg QD group, 97 patients completed 3-months and 53 patients discontinued (22 due to AEs, 11 due to lack of efficacy, 9 due to subject decision, 7 were lost to follow-up, 3 due to protocol violation, and 1 due to physician decision). In the duloxetine 120 mg QD group, 95 patients completed 3-months and 52 patients discontinued (32 due to AEs, 6 due to lack of efficacy, 5 due to subject decision, 7 were lost to follow-up, and 2 due to protocol violation).

	<b>Placebo N = 144</b>	<b>DLX 20 QD N = 79</b>	<b>DLX 60 QD N = 150</b>	<b>DLX 120 QD N = 147</b>
Completed acute phase	84 (58%)	49 (62%)	97 (65%)	95 (65%)
Discontinued				
Adverse Event	17 (12%)	8 (10%)	22 (15%)	32 (22%)
Patient decision	10 (7%)	8 (10%)	11 (7%)	6 (4%)
Physician decision	1 (1%)	1 (1%)	1 (1%)	
Lost to follow-up	13 (9%)	3 (4%)	7 (5%)	7 (5%)
Protocol Violation	5 (3%)	1 (1%)	3 (2%)	2 (1%)
Lack of Efficacy	14 (10%)	8 (10%)	9 (6%)	5 (3%)
Exclusion Criteria		1 (1%)		

At 6-months all patients in the duloxetine 20 mg QD arm were titrated to 60 mg QD. In the placebo group, 72 patients completed the 6-months and 72 patients discontinued (19 due to AEs, 16 due to lack of efficacy, 12 due to subject decision, 18 were lost to follow-up, 6 due to protocol violation, and 1 due to physician decision). In the duloxetine 20/60 mg QD group, 44 patients completed 6-months and 35 patients discontinued (9 due to AEs, 8 due to lack of efficacy, 10 due to subject decision, 4 were lost to follow-up, 1 due to protocol violation, 2 due to physician decision, and 1 due to entry criteria exclusion). In the duloxetine 60 mg QD group, 82 patients completed 6-months and 68 patients discontinued (23 due to AEs, 15 due to lack of efficacy, 12 due to subject decision, 10 were lost to follow-up, 5 due to protocol violation, and 3 due to physician decision). In the duloxetine 120 mg QD group, 79 patients completed 6-months and 68 patients discontinued (39 due to AEs, 7 due to lack of efficacy, 10 due to subject decision, 8 were lost to follow-up, 2 due to protocol violation, 1 due to physician decision, and 1 due to sponsor decision). These discontinuation rates and the reasons for discontinuation at both 3- and 6-months appear reasonable and unlikely to adversely affect the efficacy results.

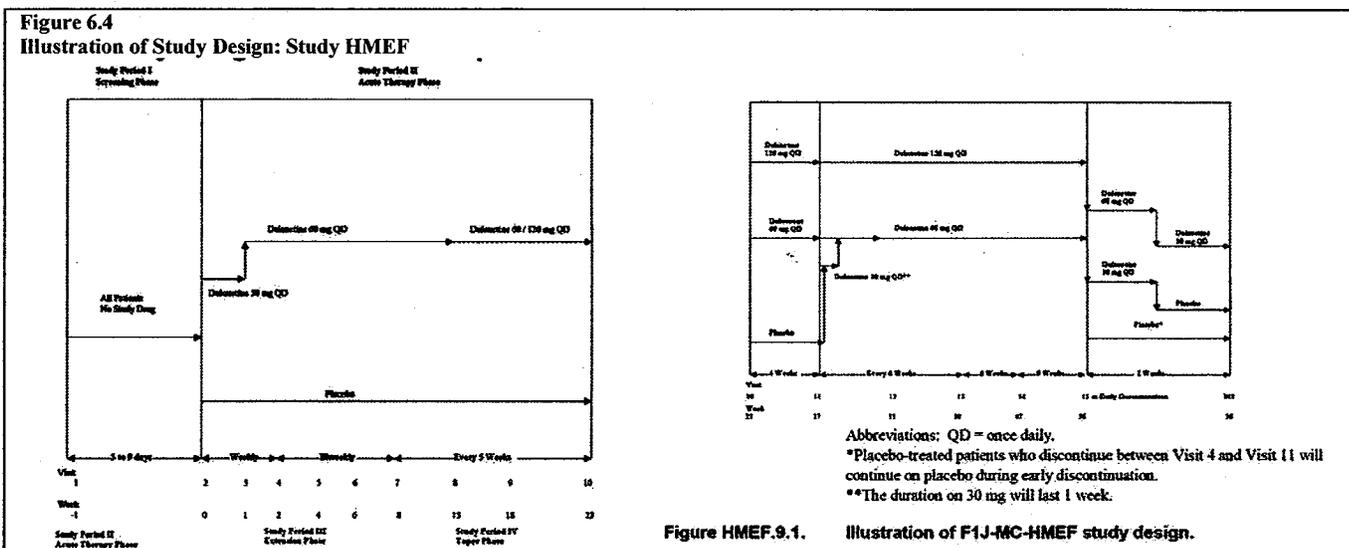
	Placebo N = 144	DLX 20/60 QD N = 79	DLX 60 QD N = 150	DLX 120 QD N = 147
Completed acute phase	72 (50%)	44 (56%)	82 (55%)	79 (54%)
Discontinued				
Adverse Event	19 (13%)	9 (11%)	23 (15%)	39 (27%)
Patient decision	12 (8%)	10 (13%)	12 (8%)	10 (7%)
Physician decision	1 (1%)	2 (3%)	3 (2%)	1 (1%)
Lost to follow-up	18 (13%)	4 (5%)	10 (7%)	8 (5%)
Protocol Violation	6 (4%)	1 (1%)	5 (3%)	2 (1%)
Lack of Efficacy	16 (11%)	8 (10%)	15 (10%)	7 (5%)
Exclusion Criteria		1 (1%)		
Sponsor Decision				1 (1%)

### Study Endpoints

- Efficacy
  - The Brief Pain Inventory (BPI) – Modified Short Form (Severity and Interference scores)
  - The Patient’s Global Impressions of Improvement (PGI-Improvement) scale
  - The Fibromyalgia Impact Questionnaire (FIQ)
  - The Clinical Global Impressions of Severity (CGI-Severity) scale
  - The Tender Point Pain Threshold
  - The Multidimensional Fatigue Inventory (MFI)
  - 17-item Hamilton Depression Rating Scale (HAMD17)
  - Patient’s Global Impressions of Severity (PGI-Severity)
- Health Outcomes
  - The patient-rated Sheehan Disability Scale (SDS)
  - The patient-rated 36-item Short Form Health Survey (SF-36)
  - The EuroQoL Questionnaire – 5 Dimension (EQ-5D)

### Study HMEF

Study HMEF was to be a Phase 3, parallel-group, double-blind, placebo-controlled, flexible-dose study in male and female patients. Duloxetine-treated patients initially received a dose of 60 mg QD for 12 weeks, after which they could be titrated up to a dose of 120 mg QD if the patient had a < 50% reduction in BPI (1:1 ratio). For more information on the timing of assessments, see Appendix 10.3, Table 6.4. The schematic diagram below illustrates the basic study design.



The primary objective of this study was to assess the efficacy of duloxetine 60/120 mg QD compared with placebo on treatment of pain in patients with ACR-defined fibromyalgia, during the 6-month therapy phase of the study. Co-primary measures included average pain item of the BPI and patient-reported improvement as measured by the PGI-Improvement scale.

A gatekeeper strategy for sequential testing of secondary objectives was also to be used in this study. The secondary gatekeeper objective for the study was to evaluate the efficacy of duloxetine 60/120 mg QD compared with placebo during the 6-month therapy phase using the change from baseline to endpoint on the SDS total score.

Study HMEF included a 2 week titration and a 2 week taper. Patients were again stratified into two groups by presence or absence of MDD. With respect to blinding, the acute therapy phase was to remain blinded until it was validated and locked. The unblinded treatment assignments would not be provided to the investigators after the acute phase therapy database was locked. All Eli Lilly personnel that had direct contact with the study sites during the extension phase and taper phase would remain blinded to patient treatment assignments, except for creating one-page patient summaries for the acute therapy phase clinical study report. After the acute therapy database was locked, access to unblinded data was provided to the following disciplines: pharmacokinetics, clinical pharmacology, CSA statistical analysts, project statisticians, and regulatory scientists. Results from the acute therapy phase that were shared with investigators would not contain patient, site, or country information.

### Patient Disposition

A total of 330 patients were randomized to either placebo (n=168) or duloxetine (n=162). For the first 3-months patients in the duloxetine arm received 60 mg QD and for the second 3-months they received up to 120 mg QD depending on their clinical response and product tolerability. At the end of the 6-months, 103 patients in the placebo group completed the study and 65 patients discontinued (19 due to AEs, 25 due to lack of efficacy, 9 due to subject decision, 5 due to protocol violation, 6 were lost to follow-up, and 1 due to physician decision). In the duloxetine 60/120 mg QD group, 101 patients completed the study and 61 patients discontinued (30 due to AEs, 12 due to lack of efficacy, 5 due to subject decision, 8 due to protocol violation, 4 were lost to follow-up, 1 due to physician decision, and 1 due to sponsor decision. These discontinuation rates and the reasons for discontinuation appear reasonable and unlikely to adversely affect the efficacy results.

	<b>Placebo N = 168</b>	<b>DLX 60/120 QD N = 162</b>
Completed acute phase	103 (61%)	101 (62%)
Discontinued		
Adverse Event	19 (11%)	30 (19%)
Patient decision	9 (5%)	5 (3%)
Physician decision	1 (1%)	1 (1%)
Lost to follow-up	6 (4%)	6 (4%)
Protocol Violation	5 (3%)	
Lack of Efficacy	25 (15%)	12 (7%)
Exclusion Criteria		

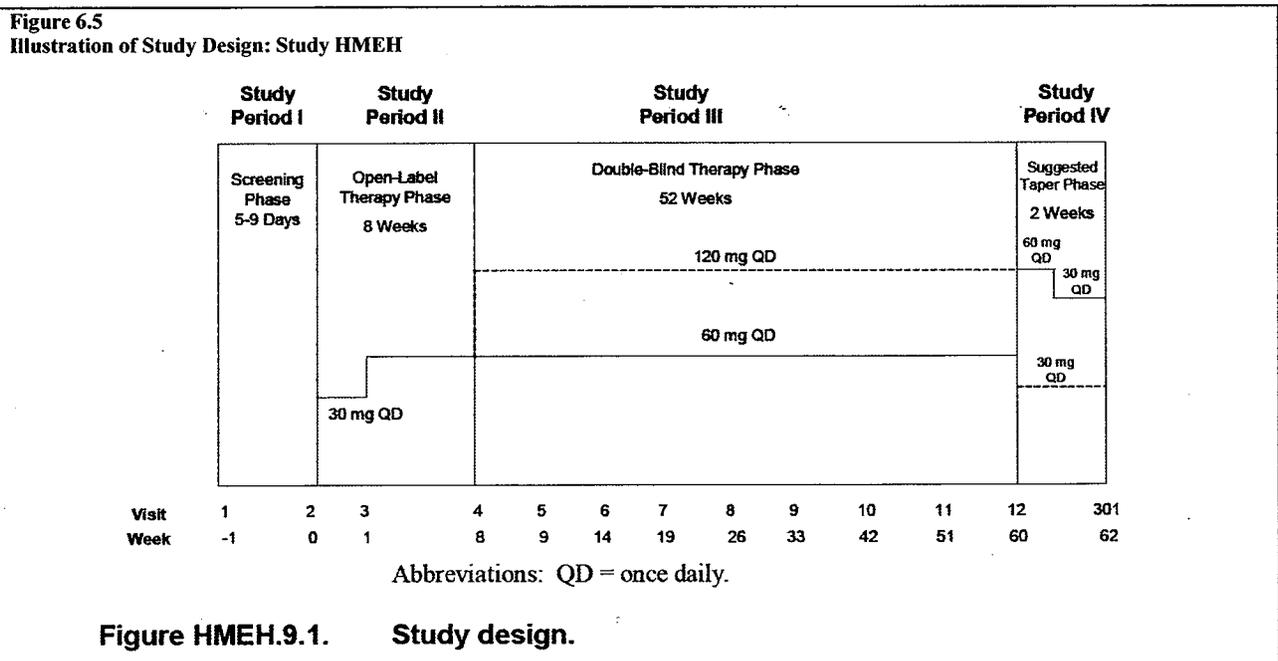
### Study Endpoints

- Efficacy
  - Brief Pain Inventory (BPI-Modified Short Form) Severity (worst pain, least pain, average pain, and pain
  - right now) and average interference score
  - Patient's Global Impressions of Improvement
  - Fibromyalgia Impact Questionnaire (FIQ)
  - Clinical Global Impressions of Severity (CGI-Severity)
  - Tender Point Pain Threshold
  - Area under the curve (AUC) of pain relief, based on the BPI average pain score
  - Multidimensional Fatigue Inventory (MFI) Dimensions
  - 17-item Hamilton Depression Rating Scale (HAMD17)
  - Beck Depression Inventory-II (BDI-II)
- Health Outcomes
  - Sheehan Disability Scale (SDS)
  - 36-item Short Form Health Survey
  - EuroQoL Questionnaire – 5 Dimension

**Study HMEH**

Study HMEH was to be a 1-year safety study consisting of an 8-week open-label period, followed by a 52-week double-blind, randomized period. The primary objective was to assess long-term safety and tolerability of duloxetine at doses up to 120 mg QD for up to 60 weeks in patients with ACR-defined primary fibromyalgia. Additionally, patients who complete the 60 mg open-label phase and were randomized to again receive 60 mg QD would be assessed for persistence of efficacy at this dose. For more information on the timing of assessments, see Appendix 10.3, Table 6.5.

Study HMEH included a 1-week titration and 2-week taper. The schematic diagram below illustrates the basic study design.



**Patient Disposition**

In total, 350 patients entered the original open-label study phase and 43 patients discontinued duloxetine 60 mg QD (26 due to AEs, 1 due to lack of efficacy, 9 due to patient decision, 3 due to protocol violation, and 4 were lost to follow-up). Three hundred seven continued onto the double-blind study phase and 104 were randomized to duloxetine 60 mg QD and 203 to duloxetine 120 mg QD. In the duloxetine 60 mg QD arm 71 patients completed the study and 33 patients discontinued (14 due to AEs, 8 due to lack of efficacy, 5 due to physician decision, 4 due to protocol violation, and 2 were lost to follow-up). In the duloxetine 120 mg QD arm, 124 patients completed the study and 79 patients discontinued (34 due to AEs, 20 due to lack of efficacy, 19 due to physician decision, 2 due to protocol violation, 3 were lost to follow-up, and 1 due to sponsor decision). This discontinuation rate and the reasons for discontinuation are reasonable and unlikely to adversely affect the efficacy results.

<b>Table 6.9</b>		
<b>HMEH: Patient Disposition (At study completion; 1 year)</b>		
	<b>DLX 60 QD</b> N = 104	<b>DLX 120 QD</b> N = 203
Completed acute phase	71 (68%)	124 (61%)
Discontinued		
Adverse Event	14 (13%)	34 (17%)
Physician decision	5 (5%)	19 (9%)
Lost to follow-up	2 (2%)	3 (1%)
Protocol Violation	4 (4%)	2 (1%)
Lack of Efficacy	8 (8%)	20 (10%)
Sponsor Decision		1 (1%)

## Study Endpoints

- Efficacy
  - The Brief Pain Inventory (BPI) – Modified Short Form (Severity and Interference scores)
  - The Fibromyalgia Impact Questionnaire (FIQ) scores
  - The Patient’s Global Impressions of Improvement (PGI-Improvement) ratings
  - The Clinical Global Impressions of Severity (CGI-Severity) ratings
  - Tender Point Pain Threshold measures
- Health Outcomes
  - Sheehan Disability Scale (SDS) scores

### 6.1.4 Efficacy Findings

As mentioned above, the clinical development program of duloxetine for of fibromyalgia consisted of 4 placebo-controlled studies of 3 – 6 month duration (HMBO, HMCA, HMCJ, and HMEF) and one long-term, study (HMEH) of 1-year duration. Studies HMCA and HMCJ were phase 3, fixed-dose, and used the same primary efficacy objective of efficacy of duloxetine on pain severity as measured by the average pain item on the Brief Pain Inventory (BPI), therefore emphasis is placed on their analysis. Study HMCJ used a co-primary objective of improvement in Patient Global Impression of Improvement (PGI-Improvement). As mentioned previously, HMCA did not enroll any male patients. Study HMBO, the phase 2 study, was similarly designed and contained comparable efficacy measures (see Table 6.10 Primary Efficacy Variable(s) by Study). HMBO assessed pain severity via the Fibromyalgia Impact Questionnaire (FIQ) Pain Item and the BPI was a secondary outcome measure, therefore the results could be pooled for help in describing the effect of subgroups (such as the effect of duloxetine on male patients). As mentioned previously, study HMEF was of 6-month duration and the requirement for efficacy at this length of time was waived during late stage product development discussions with the Applicant.

<b>Table 6.10</b>				
<b>Primary Efficacy Variable(s) by Study</b>				
Study	Analysis	Endpoints	Comparison	Method
HMBO	Co-Primary	(1) FIQ Pain Item Score (2) FIQ Total Score	Duloxetine 60 mg BID versus placebo	Mixed model repeated measures analysis that included fixed categorical effects of treatment, investigator, visit, and treatment-by-visit interaction, as well as continuous fixed covariates of baseline score and baseline-by-visit interaction. The unstructured covariance structure was used in the analysis.
	Secondary	Includes but not limited to: (1) BPI average pain severity score (2) Patient Global Impression of Improvement		Repeated measures analysis as described above with the additional terms of the baseline MDD group and the treatment-by-group interaction.
HMCA	Primary	BPI average pain score	Duloxetine 60 mg BID versus placebo	Analysis of covariance model with the terms of treatment, investigator, treatment-by-investigator interaction, and baseline scores.
HMCJ	Co-Primary	(1) BPI average pain (2) PGI Improvement at 3-month acute therapy phase	Duloxetine 120 mg QD versus placebo	Analysis of covariance model with terms of treatment, investigator, treatment-by-investigator interaction, and baseline BPI pain scores for the analysis on changes on BPI average pain. Analysis of variance model with the terms of treatment, investigator, treatment-by-investigator interaction, and baseline PGI-severity at baseline for the analysis on the endpoint of PGI.

Table from Dr. Joan Buenconsejo's Statistical Review.

### ***Handling of Missing Data***

The Applicant's review of efficacy used the Last Observation Carried Forward (LOCF) imputation method. Mixed-effects repeated measures modeling (MMRM) was used to provide comparisons between groups by visit.

### ***Handling of Multiple Comparisons***

Treatment effects were evaluated using pairwise comparisons between duloxetine and placebo, based on 2-sided tests with a significance level of 0.05. As mentioned above, a gatekeeper strategy was used in Study HMCJ which sequentially tested the secondary hypotheses. If the primary hypothesis was found statistically significant, the second gatekeeper hypotheses were tested. No multiplicity adjustments were made for Studies HMBO, HMCA, and HMEH.

### ***Patient Characteristics***

Within all studies, treatment groups were comparable with respect baseline characteristics such as age, sex (except HMCA which was only females), race, weight, height, presence or absence of major depressive disorder (MDD), and presence or absence of anxiety disorders. The total number of males enrolled in all of the studies was approximately 5% of the total number of patients. This is slightly below the number expected male to female ratio in fibromyalgia, which is approximately 1:9. As expected, the majority of the patients were Caucasian and the mean age was approximately 50 years (minimum age was 18 years and maximum was 83). Studies HMBO, HMCA, and HMCJ were conducted entirely in the United States, whereas studies HMEF and HMEH included patients from North and South America, Europe, and Asia. With respect to disease severity, BPI score ranged from 6.1 – 6.5 and FIQ scores from 49 – 52 indicating moderate pain and impact from fibromyalgia.

In Study HMBO, the majority of the patients were Caucasian (87%) and female (89%). Patient age ranged from 19 to 80 years with a median of 50. Thirty eight percent of the patients suffered from MDD and 20% from anxiety disorders. Mean baseline BPI was 6.1 and mean FIQ was 49.

In Study HMCA, all patients were female, 90% were Caucasian with ages ranging from 20 to 80 years and a median of 51 years. Twenty six percent had MDD and 10% had anxiety disorders. Mean baseline BPI was 6.4 and mean FIQ was 52.

In Study HMCJ, 95% of the patients were female and 84% Caucasian. Ages ranged from 19 to 77 years with a median of 53 years. Twenty four percent had history of MDD and 6% anxiety disorders. Mean baseline BPI was 6.5, mean FIQ 52, and mean PGI-severity was 4.

In Study HMEF, 93% of the patients were female and 91% Caucasian. Ages ranged from 20 to 83 years with a median of 51 years. Twenty two percent had diagnosis of MDD and 2% of anxiety disorders. Mean baseline BPI was 6.5, mean FIQ 50, and PGI-severity was 3.9.

In Study HMEH, 96% of the patients were female and 61% Caucasian. Ages ranged from 18 to 84 years with a median of 50 years. Mean baseline BPI was 6.7, mean FIQ was 54, and mean PGI-Severity was 4.

#### ***Exposure to Study Medication***

In Study HMBO, 67% of all enrolled patients in the placebo group and 59% in the duloxetine group received at least 63 days (9 weeks) of study medication during the acute therapy phase. Median duration of exposure was similar across treatment groups with 81 days for placebo and 79 for duloxetine 60 mg BID. At the end of the study (Week 12), compliance was approximately 62% in the placebo group and 54% in the duloxetine group. A patient was considered compliant if the compliance rate (percentage of capsules taken between visits divided by the total number of capsules prescribed for that treatment interval) was between 80% and 120% at that visit.

In Study HMCA, 61% of the patients in the placebo group, 69% of patients in the duloxetine 60 mg QD group, and 66% of the patients in the duloxetine 60 mg BID group study medication for the full 63 days of the acute therapy phase. Median duration of exposure was 86 days for placebo, 88 days for duloxetine 60 mg QD, and 88 days for duloxetine 60 mg BID. Compliance for the placebo group at the end of the acute therapy phase (Week 12) was 55%, for duloxetine 60 mg QD it was 63%, and for duloxetine 60 mg BID it was 61%.

In Study HMCJ, 39% of patients in the placebo group, 53% of patients in the duloxetine 20 mg QD group, 40% of patients in the duloxetine 60 mg QD group, and 47% of patients in the duloxetine 120 mg QD group received at least 105 days for therapy during the 3-month acute therapy phase. Median duration of exposure was 103 days for placebo, 105 days for duloxetine 20 mg QD, 104 days for duloxetine 60 mg QD, and 104 days for duloxetine 120 mg QD. Compliance for the placebo group was 60% (end of Week 12), for duloxetine 20 mg QD it was 70%, for duloxetine 60 mg QD it was 69%, and for duloxetine 120 mg QD it was 69%.

In Study HMEF, 39% of patients in the placebo group, 36% of patients in the duloxetine 60/120 mg QD group received at least 189 days for therapy during the 6-month therapy phase. Median duration of exposure was 187 days for placebo and 188 days for duloxetine 60/120 mg QD. Compliance for the placebo group was 78% for placebo and 77% for duloxetine 60/120 mg.

In Study HMEH, the median duration of exposure was 56 days for all enrolled patients during the 8-week open-label phase. During the double-blind phase, median duration of exposure as 364 days for the duloxetine 60 mg QD group and 362 days for the duloxetine 120 mg QD group. During the double-blind and taper phases of the study, there was a higher incidence of noncompliance in the 120 mg QD group when compared to the 60 mg QD group.

**Summary of Results**

***Evaluation of Primary Efficacy Endpoints: Brief Pain Inventory, Patient Global Improvement, and Fibromyalgia Impact Questionnaire***

The Applicant’s efficacy analyses were conducted using patients who had at least 1 post-baseline measure which they called the intent-to-treat (ITT) population, but I will refer to as the modified-intent-to-treat population (mITT). For missing values, the Applicant used the last observation carried forward (LOCF) approach, whereas our Statistics Reviewer, Dr. Joan Buenconsejo, used several imputation methods including LOCF, baseline observation carried forward (BOCF), and an LOCF/BOCF hybrid. Despite using different data imputation methods, the results of Dr. Buenconsejo for the most part concur with the Applicant’s results, as we will see below.

In Dr. Buenconsejo’s reanalysis of the submitted datasets (e.g. patient disposition, demographics, baseline characteristics, and primary and secondary endpoint analyses), she identified several areas that required further exploration. To ensure comparability between treatment groups, a re-analysis of the data using the ITT population instead of the mITT population was performed. The resultant discrepancies were small and unlikely to affect the overall study conclusions (see Table 6.11 below).

<b>Table 6.11 Treatment Groups by Study</b>						
<b>Study</b>	<b>Population</b>	<b>Dose</b>				
		<b>20 mg QD</b>	<b>60 mg BID</b>	<b>60 mg QD</b>	<b>120 mg QD</b>	<b>Placebo</b>
<b>HMBO</b>	mITT		100			102
	ITT		103			102
<b>HMCA</b>	mITT		114	116		118
	ITT		116	117		120
<b>HMCJ</b>	mITT	77		144	142	139
	ITT	79		150	147	144

Dr. Buenconsejo’s Table.

As mentioned above, the Applicant used the LOCF method to impute missing data in all placebo-controlled trials. This approach tends to exaggerate the treatment effect if dropouts occur primarily due to drug-related adverse events, in which case, the dropouts are actually non-responders and should actually be represented by their BOCF. In Dr. Buenconsejo's re-analysis of the data, she used the entire ITT population and BOCF and hybrid LOCF/BOCF methods to evaluate the BPI average pain scores. Using the hybrid method, patients who drop out due to adverse events are assigned their baseline score and patients who drop out for other reasons are assigned their last observation BPI score for the missing variables. Worst observation carried forward was applied to missing data in the PGI-Improvement rating score.

Studies HMBO, HMCA, and HMCJ were all of 3-month duration and explored multiple secondary endpoints. Study HMCJ was the only study with a gatekeeper strategy to adjust for multiplicity and this strategy did not include all of the secondary endpoints. Because of this, it is difficult to draw conclusions regarding their statistical significance, much less their clinical relevance or validity. Issues regarding secondary endpoints are discussed in more detail in Section 9.4, Labeling Review. In her statistical review, Dr. Buenconsejo discusses several options the Applicant could have used to evaluate secondary objectives more rigorously.

Tables 6.12 and 6.13 below summarize the results for the efficacy variables of Brief Pain Inventory Average Score (BPI) and Patient Global Impression of Improvement (PGI-Improvement). As we can see, using the LOCF/BOCF hybrid for BPI average pain score (Table 6.12), all three studies (HMBO, HMCA, and HMCJ) demonstrate statistically significant p-values across all treatment doses at 3-months. However, in study HMBO, BPI average pain score was a secondary endpoint and did not adjust for multiplicity. Using BOCF, Study HMBO at duloxetine 60 mg BID and study HMCJ at 60 mg QD did not demonstrate a statistically significant improvement in BPI average pain score.

Table 6.12 Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint at Endpoint All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: HMBO, HMCA, and HMCJ						
Study	Treatment Group	BPI Average Pain Score (BOCF)			BPI Average Pain Score (LOCF/BOCF)	
		Baseline	LSMean Change	p-value	LSMean Change	p-value
HMBO*	Placebo	6.11	-0.7		-0.6	
	Duloxetine 60 mg BID	6.13	-1.2	0.067	-1.2	0.049
HMCA	Placebo	6.52	-0.9		-1.0	
	Duloxetine 60 mg QD	6.37	-2.1	<0.001†	-2.2	<0.001†
	Duloxetine 60 mg BID	6.37	-1.8	0.001	-2.1	<0.001
HMCJ	Placebo	6.58	-1.1		-1.2	
	Duloxetine 20 mg QD	6.77	-1.6	0.135†	-1.9	0.039†
	Duloxetine 60 mg QD	6.49	-1.6	0.065	-1.8	0.036
	Duloxetine 120 mg QD	6.39	-1.7	0.036	-1.8	0.038

\*GLM Model: PGIImp=Treatment+Pool Investigator +Treatment\*Pool Investigator  
 †unadjusted p-value.  
 Dr. Buenconsejo's Table.

**Table 6.13**  
**PGI-Improvement at Endpoint**  
**All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: HMBO, HMCA, and HMCJ**

Study	Treatment Group	N	PGI Improvement Score (LOCF)		PGI Improvement Score (WOCF)	
			LSMean Change	p-value	LSMean Change	p-value
HMBO*	Placebo	99	3.7		3.8	
	Duloxetine 60 mg BID	95	3.1	0.006	3.2	0.011
HMCA**	Placebo	111	3.8		3.9	
	Duloxetine 60 mg QD	114	3.2	0.005†	3.2	0.002†
	Duloxetine 60 mg BID	111	3.1	0.003	3.2	0.002
HMCJ**	Placebo	139	3.4		3.6	
	Duloxetine 20 mg QD	77	2.9	0.012†	3.1	0.010†
	Duloxetine 60 mg QD	143	3.0	0.026	3.1	0.009
	Duloxetine 120 mg QD	142	2.9	0.004	3.0	0.002

\*GLM Model: PGIImp=Treatment+Pool Investigator+Treatment\*Pool Investigator  
\*\*GLM Model: PGIImp=Treatment+Pool Investigator  
†unadjusted p-value.  
Dr. Buenconsejo's Table.

As described above, the LOCF/BOCF hybrid attributes the BOCF to patients who drop out due to AEs. In study HMCJ, there were 24 patients (placebo = 3, DLX20QD = 9, DLX60QD = 4, and DLX120QD = 8) who discontinued at Visit 8 (Month 3) and of these, 11 dropped out due to adverse events. For this reason, the hybrid strategy likely results in p-values <0.05.

With respect to PGI-Improvement Scores (Table 6.13), it appears as though all doses (duloxetine 20 mg QD, duloxetine 60 mg QD, duloxetine 60 mg BID, and duloxetine 120 mg QD) in all studies (HMBO, HMCA, and HMCJ) demonstrated a statistically significant p-value compared to placebo when either the last observation was carried forward or the worst observation was carried forward to describe missing data. However, in studies HMBO and HMCA, PGI-Improvement was not a primary endpoint and did not adjust for multiplicity.

For Study HMBO, none of the primary endpoints (i.e. FIQ Total Score and FIQ pain item) were significant and there were multiple secondary endpoints. Therefore, evidence of a treatment group difference between duloxetine 60 mg BID and placebo cannot be established in this study based on the aforementioned p-values.

In Study HMCJ, the duloxetine 20 mg QD dose was added to establish 60 mg QD as the lowest effective dose. In the Applicant's analysis of efficacy, duloxetine 20 mg QD did not beat placebo at 3 months with respect to BPI-average pain score. However, Dr. Buenconsejo's analysis using BOCF and BOCF/LOCF hybrid indicates that this dose may have in fact had a similar treatment effect when compared to duloxetine 60 mg QD and 120 mg QD with respect to both BPI average pain score and PGI-Improvement score. For this reason, it hard to establish that there is a treatment difference between duloxetine at doses between 20 mg QD and 120 mg QD.

In her analysis of the data, Dr. Buenconsejo created continuous responder curves for Studies HMCA and HMCJ (see Figures 6.6 and 6.7 below). For these plots, all dropouts were considered non-responders. The x-axis shows percent reduction in pain from baseline (i.e. improvement) to end of study and the y-axis shows the percentage of patients achieving pain reduction. Because there was no treatment effect seen in Study HMBO, this study was not explored further.

In Study HMCA, there appears to be a distinct separation in the curves of duloxetine 60 mg QD and duloxetine 60 mg BID when either is compared to placebo at 3-months. In Study HMCJ, duloxetine 20 mg QD, duloxetine 60 mg QD, and duloxetine 120 mg QD are all separate from placebo for the 3-months duration. However, only 60 mg QD in Study HMCA and 120 mg QD in Study HMCJ were separated from placebo for the entire 3-months. It appears as though this separation is maintained even when response criteria is set to > 70% improvement in pain, clearly suggesting that higher doses lead to a larger improvement in pain.

There also appears to be evidence that in Study HMCA duloxetine 60 mg BID and in Study HMCJ duloxetine 60 mg QD both have a higher proportion of responders when compared to placebo. However, when multiplicity adjustments are applied to HMCA, the difference is not statistically significant. Duloxetine 20 mg QD in Study HMCJ also appears to have a similar response when compared to both duloxetine 60 mg QD and duloxetine 120 mg QD.

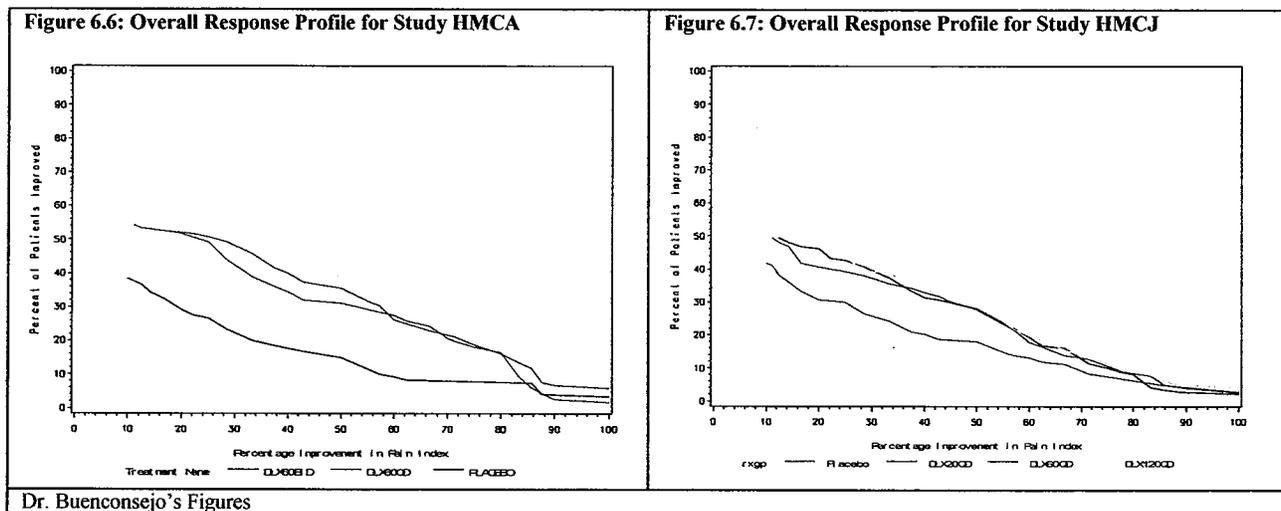


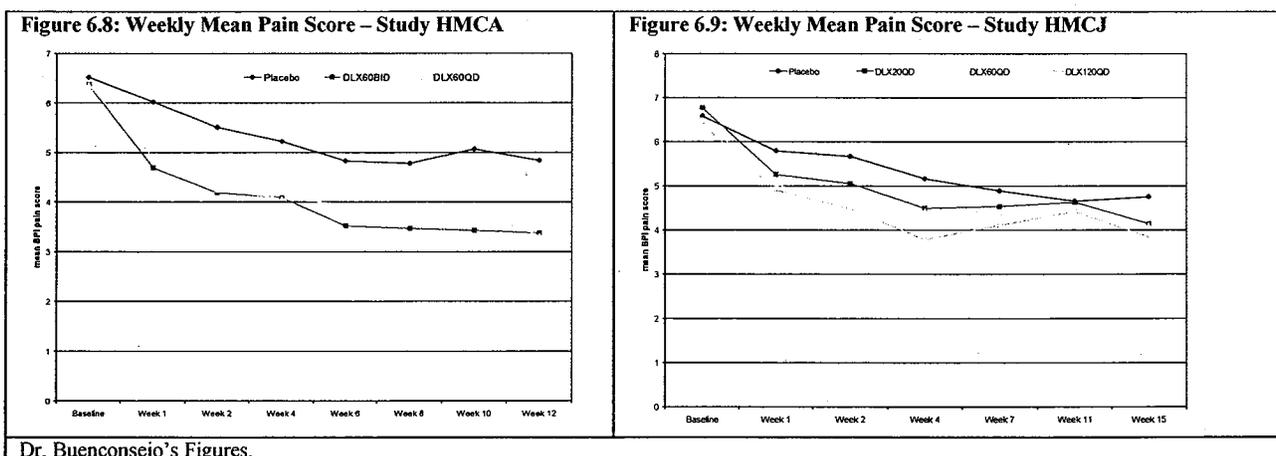
Table 6.14 explores the proportion of patients who had at least a 30% or 50% improvement in pain. In Study HMCA duloxetine 60 mg QD and 60 mg BID had statistically significant p-values for both 30% and 50% improvement in pain whereas in Study HMCJ statistically significant p-values were only seen for duloxetine 60 mg QD and 120 mg QD, but not 20 mg QD for both 30% and 50% improvement in pain. These p-values, to a certain extent, provide some support for a dose-response effect.

**Table 6.14**  
**Responder Analysis of BPI Average Pain Score at Endpoint**  
**All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: HMBO, HMCA, and HMCJ**

Study	Treatment Group	> 30% Improvement in Pain			> 50% Improvement in Pain	
		N	n(%)	p-value	n(%)	p-value
HMCA	Placebo	120	24 (20%)		18 (15%)	
	Duloxetine 60 mg QD	118	54 (46%)	<0.001	42 (36%)	<0.001
	Duloxetine 60 mg BID	116	45 (39%)	0.002	36 (31%)	0.003
HMCJ	Placebo	144	37 (26%)		26 (18%)	
	Duloxetine 20 mg QD	79	28 (35%)	0.126	22 (28%)	0.089
	Duloxetine 60 mg QD	150	56 (37%)	0.032	42 (28%)	0.043
	Duloxetine 120 mg QD	147	57 (39%)	0.017	44 (30%)	0.018

Dr. Buenconsejo's Table.

In her review of the raw data from Study HMCA, Dr. Buenconsejo found that average pain over time was reduced in patients treated with duloxetine 60 mg QD or 60 mg BID. This improvement was seen as early as Week 1 and seemed to reach a plateau around Week 4 for duloxetine 60 mg QD and Week 6 for duloxetine 60 mg BID. In Study HMCJ, a similar improvement trend was seen for duloxetine at doses of 60 mg QD and 120 mg QD. However, in Study HMCJ placebo-treated patients who completed the study also had some improvement in their pain scores. For a plot of these pain scores, see Figures 6.8 and 6.9 below.

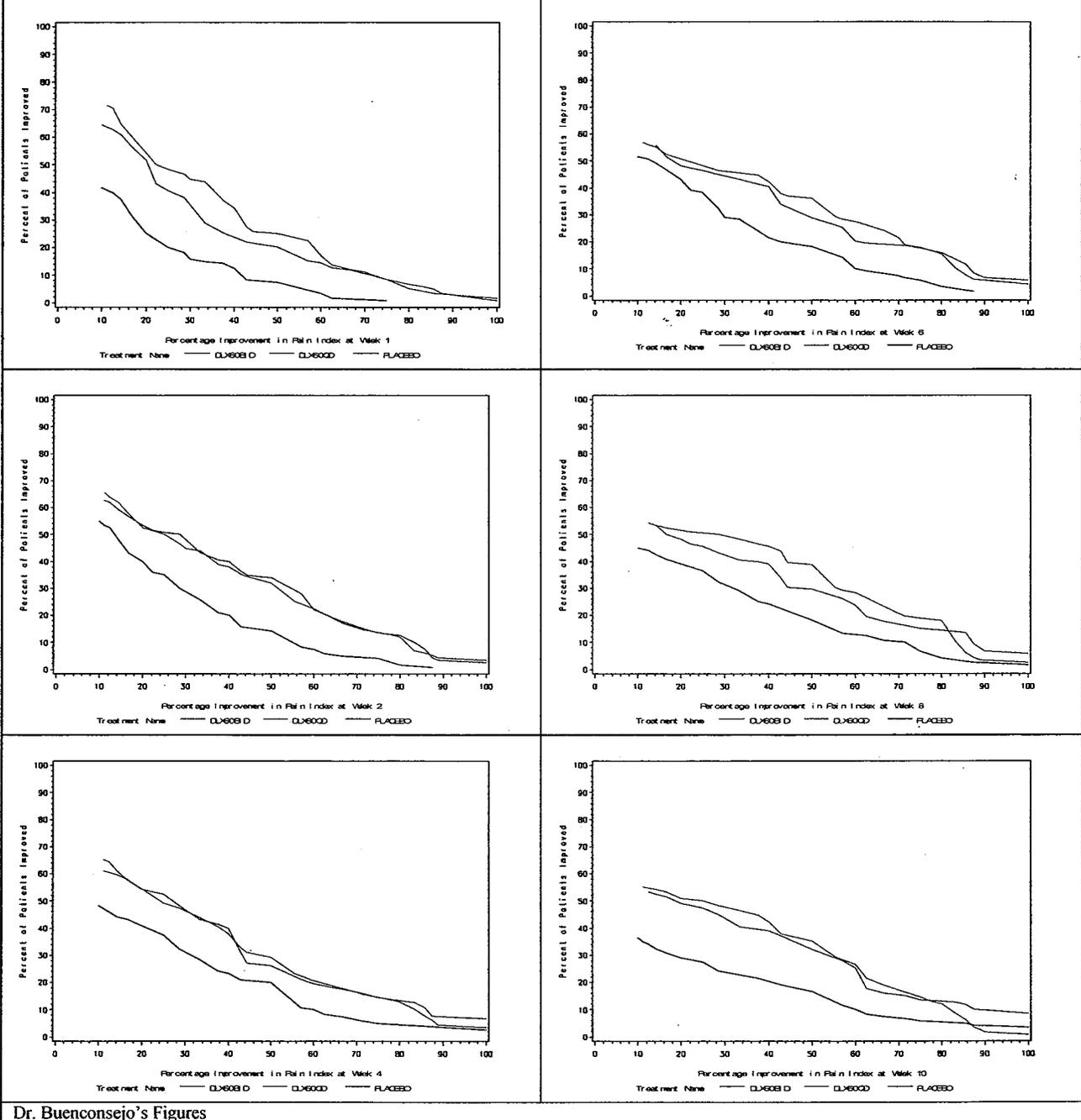


Continuous responder analyses can be useful in providing a visual display of the relative effect of different doses. Figures 6.10 and 6.11 were created by Dr. Buenconsejo for her statistical review. In these plots, all discontinuations are considered non-responders. The x-axis shows percent reduction in pain from baseline and the y-axis shows the corresponding percentage of patients achieving that level of pain reduction or greater.

From these plots, we see that in Study HMCA there is evidence that patients treated with duloxetine at doses of both 60 mg QD and 60 mg BID had a better response than placebo-treated patients throughout the entire length (12 weeks) of the study. In Study HMCJ, the only duloxetine dose that clearly differentiated itself from placebo throughout the treatment period was 120 mg QD. Duloxetine 60 QD appears to achieve a higher level of pain reduction at many time points, but this response was not consistent. Note that the duloxetine 60 mg QD and 120 mg QD groups were receiving the same dose of duloxetine through Week 2 and that in the

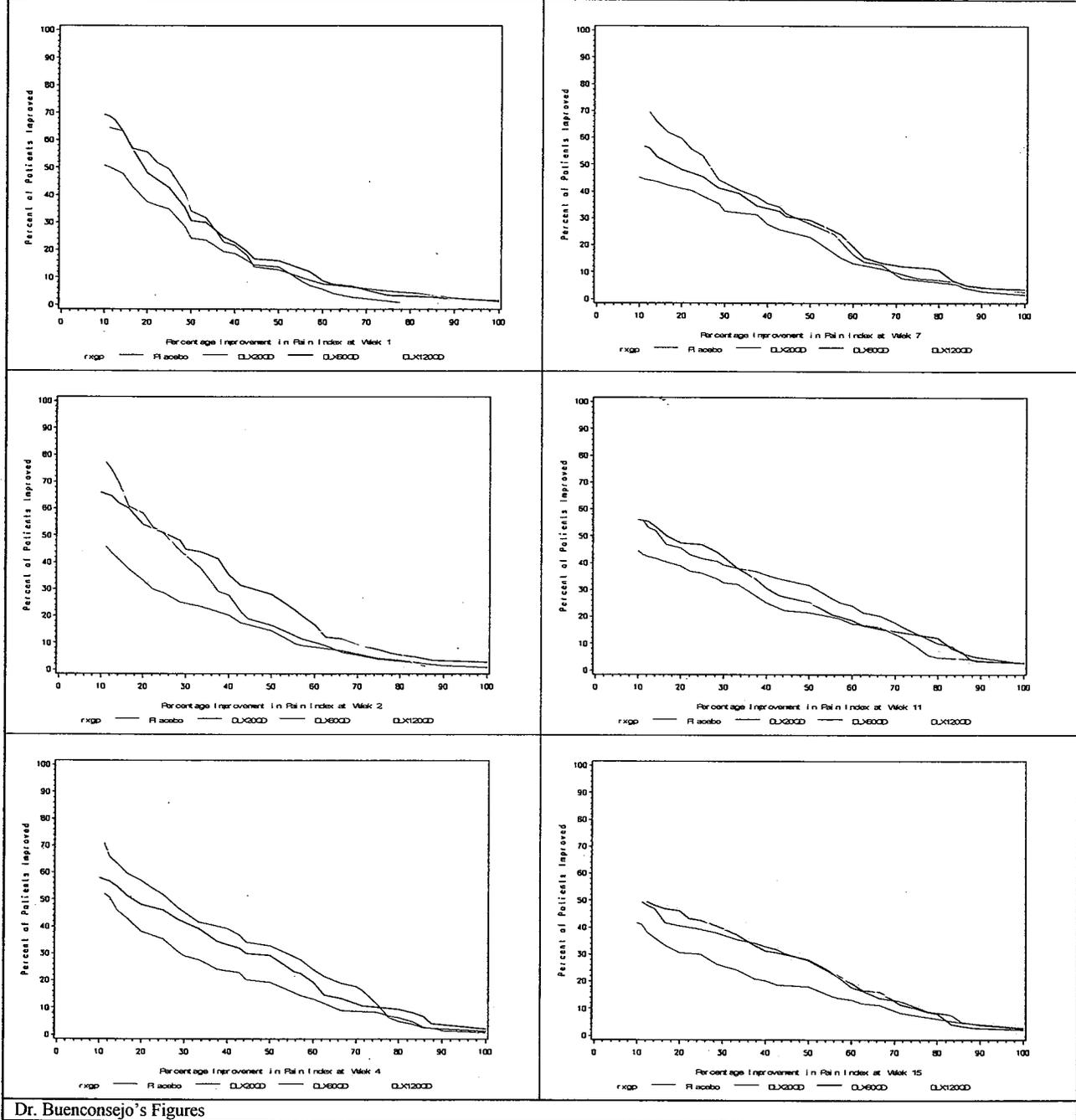
duloxetine 60 mg QD arm there were 14 male patients out of a total of 28 who dropped before week 12.

Figure 6.10: Continuous Responder Analysis by Week – Study HMCA



Dr. Buenconsejo's Figures

Figure 6.11: Continuous Responder Analysis by Week – Study HMCJ



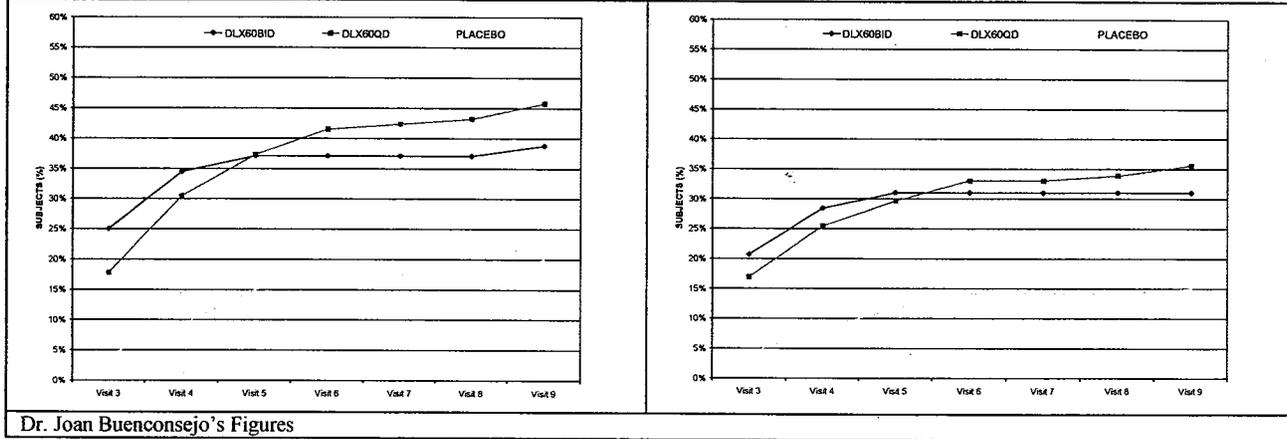
Dr. Buenconsejo's Figures

Another way to evaluate the treatment effect is to look at patients who completed the studies and met 30% and 50% response criteria. In both Studies HMCA and HMCJ it appears as though all doses of duloxetine achieved a better pain response than placebo in study completers (see Figures 6.12 and 6.13). In Study HMCA, 133 patients completed the study and had a 30% reduction in pain from baseline whereas 96 six patients completed the study and had a 50% reduction in pain. Both duloxetine 60 mg QD and 60 mg BID appear to have elicited a response

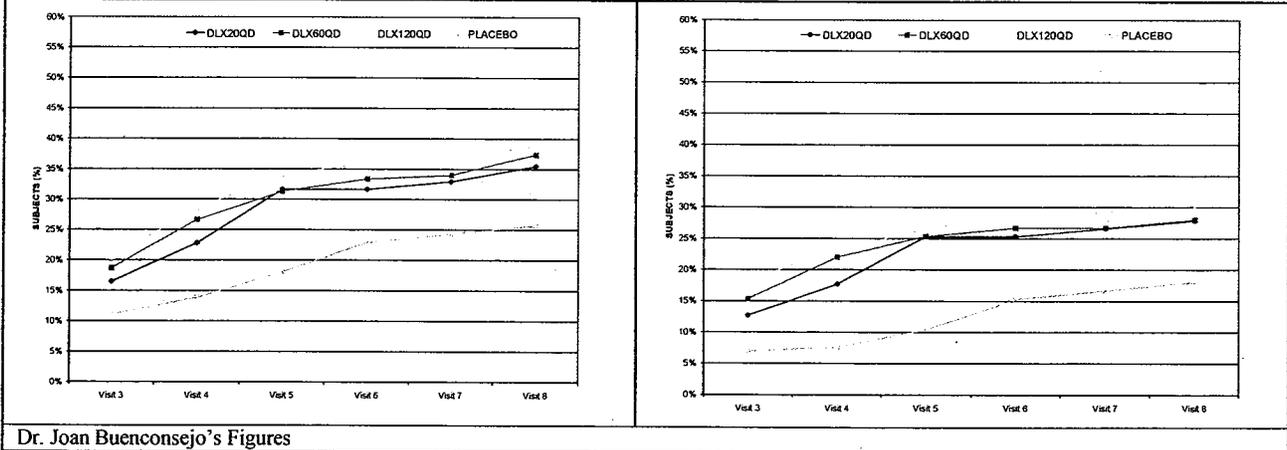
better than placebo, however it is not clear if one of these doses was superior as their plots nearly overlap.

A similar situation is seen in Study HMCJ. In this study, 178 patients completed and had a 30% response and 134 patients completed and had a 50% response. In this study it is once again difficult to see a difference in the treatment effect between the duloxetine doses (20 mg QD, 60 mg QD, and 120 mg QD).

**Figure 6.12**  
 Study HMCA: Proportion of Responders by Week – 30% and 50%



**Figure 6.13**  
 Study HMCJ: Proportion of Responders by Week – 30% and 50%



Studies HMCJ and HMEF evaluated the efficacy of duloxetine for up to 6 months. Study HMCJ, which has been described above and had positive results at 3-months, was divided into an original 3-month assessment window and a 3-month continuation phase. Study HMEF did not have positive results and was not analyzed by Dr. Buenconsejo in her Statistical Review. As mentioned previously, the requirement for proof of efficacy at 6-months was waived during the development process. Both studies used gatekeeper strategies for secondary endpoints, as described above.

During the second 3-months of Study HMCJ, duloxetine 60 mg QD and 120 mg QD were compared to placebo (all patients on duloxetine 20 mg QD were increased to 60 mg QD). For the 6-month therapy phase, the Applicant's Review of BPI average pain score and PGI-Improvement used LOCF to handle missing data. Using this method, the Applicant concluded that there was a significant difference in BPI average pain score for all doses of duloxetine (20/60 mg QD, 60 mg QD, and 120 mg QD) when compared to placebo. For PGI-Improvement, the Applicant concluded that there was only a significant difference between placebo and duloxetine 20/60 mg QD and 120 mg QD, but not for 60 mg QD.

Dr. Buenconsejo's review, which again used BOCF and LOCF/BOCF hybrid (see Table 6.15 below) did not reveal a statistically significant difference for BPI average pain score between placebo and duloxetine 60 mg QD or 120 mg QD. However, there was a statistically significant difference between placebo and duloxetine 20/60 mg. Because statistical significance was not demonstrated for duloxetine 60 mg QD and 120 mg QD, Dr. Buenconsejo did not explore PGI-Improvement at 6 months.

**Table 6.15**  
**Study HMCJ: Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint at 6-Months**  
**All Randomized Patients**

Treatment Group	BPI Average Pain Score (BOCF)			BPI Average Pain Score (LOCF/BOCF)		BPI Average Pain Score (LOCF/BOCF)*	
	Baseline	LSMean Change	p-value	LSMean Change	p-value	LSMean Change	p-value
Placebo	6.58	-1.1		-1.2		-1.2	
Duloxetine 20 mg QD/60 mg QD	6.77	-1.9	<b>0.018</b>	-2.2	0.003	-2.2	<b>0.004</b>
Duloxetine 60 mg QD	6.49	-1.4	0.391	-1.7	0.048	-1.7	0.057
Duloxetine 120 mg QD	6.39	-1.4	0.251	-1.7	0.093	-1.6	0.121

\*Eight patients who dropped out at Visit 11 retained their Visit 11 score.  
 Dr. Buenconsejo's Table.

The secondary endpoints of FIQ Total Score and Clinical Global Impression of Severity were examined by the Applicant; however no adjustments were made for multiplicity. Using the BOCF and BOCF/LOCF hybrid method of data imputation, Studies HMCA and HMCJ indicate that duloxetine doses of 60 mg QD, 60 mg BID, and 120 mg QD may have an effect on FIQ Total Score (see Tables 6.16 and 6.17 below). For CGI Improvement, duloxetine at doses of 60 mg QD, 60 mg BID, and 120 mg QD all show a numerical improvement over placebo.

**Table 6.16**  
**Fibromyalgia Impact Questionnaire Total Score Change from Baseline to Endpoint\***  
**All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: HMCA and HMCJ**

Study	Treatment Group	FIQ Total Score (BOCF)			FIQ Total Score (LOCF/BOCF)	
		Baseline	LSMean Change	p-value†	LSMean Change	p-value†
HMCA	Placebo	53.1	-6.7		-7.6	
	Duloxetine 60 mg QD	51.4	-13.6	<b>0.001</b>	-14.2	<b>0.002</b>
	Duloxetine 60 mg BID	52.5	-12.9	<b>0.003</b>	-14.3	<b>0.002</b>
HMCJ	Placebo	53.0	-8.0		-9.1	
	Duloxetine 20 mg QD	54.0	-11.1	0.130	-13.3	0.053
	Duloxetine 60 mg QD	51.7	-12.1	<b>0.017</b>	-12.9	<b>0.032</b>
	Duloxetine 120 mg QD	51.7	-11.7	<b>0.030</b>	-12.7	<b>0.048</b>

\*negative implies improvement  
 †unadjusted p-value  
 Dr. Buenconsejo's Table.

**Table 6.17**  
**Change in CGI-Severity at Endpoint**  
**All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: HMCA and HMCJ**

Study	Treatment Group	N	CGI Improvement Score (LOCF)		CGI Improvement Score (WOCF)		CGI Improvement Score (BOCF)	
			LSMean Change	p-value	LSMean Change	p-value	LSMean Change	p-value
HMCA*	Placebo	120	-0.4		-0.4		-0.3	
	Duloxetine 60 mg QD	118	-0.8	<b>0.002</b>	-0.8	<b>0.007</b>	-0.8	<b>&lt;0.001</b>
	Duloxetine 60 mg BID	116	-0.8	<b>0.002</b>	-0.8	<b>0.005</b>	-0.7	<b>0.003</b>
HMCJ	Placebo	144	-0.6		-0.5		-0.6	
	Duloxetine 20 mg QD	79	-0.9	0.059	-0.8	0.063	-0.8	0.068
	Duloxetine 60 mg QD	150	-0.9	<b>0.021</b>	-0.8	<b>0.033</b>	-0.8	0.054
	Duloxetine 120 mg QD	147	-1.0	<b>&lt;0.001</b>	-0.9	<b>0.002</b>	-0.9	<b>0.005</b>

\* negative implies improvement  
 Dr. Buenconsejo's Table.

Study HMEF did not show a significant difference between placebo-treated and duloxetine-treated patients for either of the coprimary outcome measures of BPI average pain score or PGI-Improvement during the 6-month therapy phase. In this study, patients were administered duloxetine 60 mg QD for the first 12 weeks and then titrated up to 120 mg QD based on their response. The Applicant once again used LOCF for data imputation and found that there was a numerically greater improvement in BPI average pain scores and PGI-Improvement in duloxetine-treated patients when compared to placebo. However, the BPI average pain scores and PGI-Improvement scores were numerically improved. For details, see Tables 6.18 and 6.19 below.

**Table 6.18 – Study HMEF**  
**Brief Pain Inventory -Average Pain Score**  
**Mean Change from Baseline to Endpoint - All Randomized Patients**  
**6-month Therapy Phase**

BPI Average Pain Score		Baseline					Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
PLACEBO	167	6.45	1.47	6.0	4.0	10.0	5.34	2.43	6.0	0.0	10.0	-1.11	2.38	-1.0	-8.0	4.0
DLX60/120QD	158	6.59	1.51	7.0	3.0	10.0	4.94	2.38	5.0	0.0	10.0	-1.66	2.44	-1.0	10.0	5.0

**p=0.053**  
 Applicant's Table, Page 88, HMEF Clinical Report.

**Table 6.19 - HMEF**  
**Patient's Global Impressions of Improvement**  
**Mean at Endpoint - All Randomized Patients**  
**6-month Therapy Phase**

PGI-Improvement	Endpoint					
	N	Mean	SD	Median	Min	Max
PLACEBO	165	3.75	1.37	4.0	1.0	7.0
DLX60/120QD	157	3.45	1.56	3.0	1.0	7.0

**p=0.064**  
 Applicant's Table, Page 90, HMEF Clinical Report.

Study HMEH, which was intended to demonstrate persistence of efficacy for 1-year, randomly assigned patients who completed 8-weeks of open-label treatment to either duloxetine 60 mg QD or 120 mg QD. The Applicant claims that of the 350 patients that entered the open-label phase, 339 had a baseline and an endpoint BPI average pain score value recorded. Of these patients,

118 (35%) were considered BPI responders at Week 8 (response was defined as  $\geq 50\%$  reduction in average BPI from baseline). However, Dr. Buenconsejo's reanalysis of the data found that 3 of these 118 patients did not have Week 8 data, leaving the number of responders at 115 (33%). This discrepancy did not efficacy conclusions.

Using the Applicant's data, of the 118 patients classified as responders, 37 were in the duloxetine 60 mg QD arm and 75 in the 120 mg QD arm. Overall, 307 patients continued on to the double-blind phase, and of these, 104 (34%) were in the duloxetine 60 mg QD arm and 203 (66%) were in the 120 mg QD arm. In the 60 mg QD arm, 71 (68%) completed the study and of these, 61% were from the original responder group and 72% from the nonresponder group. In the 120 mg QD arm, there were 124 (61%) completers, and of these, 73% were from the responder group and 54% were from the nonresponder group (see Table 6.20 below for details).

Using the Applicant's BOCF approach on patients who dropped out of the study in the responder group (39% in the 60 mg QD group and 27% in the 120 mg-QD group) it appears that approximately 50% of the patients who originally responded were still considered responders at the end of the study. This indicates that approximately 20% of the completers were not able to maintain their response for 1-year. In the nonresponders, less than 25% of the patients became responders at the end of 1-year.

**Table 6.20 – HMEH  
 Patient Disposition at Endpoint (Double-Blind Phase)**

Study	Treatment Group	N	Responder n(%)	Non-Responder n(%)
<b>Completed</b>	DLX 60 mg QD	203	55 (73%)	69 (54%)
	DLX 120 mg QD	104	23 (62%)	48 (72%)
<b>Adverse Events</b>	DLX 60 mg QD	203	12 (16%)	22 (17%)
	DLX 120 mg QD	104	6 (16%)	8 (12%)
<b>Lack of Efficacy</b>	DLX 60 mg QD	203	0	20 (16%)
	DLX 120 mg QD	104	4 (11%)	4 (6%)
<b>Subject Decision</b>	DLX 60 mg QD	203	4 (5%)	10 (8%)
	DLX 120 mg QD	104	1 (3%)	1 (1%)
<b>Loss to Follow-Up</b>	DLX 60 mg QD	203	1 (1%)	2 (2%)
	DLX 120 mg QD	104	1 (3%)	1 (1%)
<b>Others</b>	DLX 60 mg QD	203	3 (4%)	5 (4%)
	DLX 120 mg QD	104	2 (5%)	5 (7%)

DLX = duloxetine  
 Dr. Buenconsejo's Table.

Dr. Buenconsejo's statistical review describes Study HMEH in more detail:

In the responder analysis at the end of the study, the Applicant used LOCF to impute missing data. In the re-analyses, I used a more conservative approach to impute missing data, namely: BOCF and LOCF/BOCF.

Applying BOCF to patients who dropped out of the study in the responder group (i.e. 39% of the patients in the duloxetine 60 mg QD group and 27% in the 120 mg QD group), less than 50% responded at the end of the study. This implies that close to 20% of the patients who completed the study were not able to maintain their response at the end of the study. However, this is still a bit better compared to patients in the non-responder group in which only less than 25% of patients responded at the end of the study. Another important finding from this analysis is that only 20% of the patients who did not respond at Week 8 and were given 120 mg QD during double-blind phase responded at the end of the study. This implies that increasing the dose did not improve their pain response.

Applying LOCF/BOCF to patients who dropped out of the study in the responder group yield somewhat similar result to the BOCF strategy except that almost 50% responded at the end of the study. Patients who are responder at Week 8 appear to still be a bit better in terms of responding at the end of the study compared to the non-responder group. **However, there is no evidence that there is persistence of effect among those initial responders who remained in the duloxetine 60 mg QD.**

### Findings in Subgroups and Special Populations

To evaluate the effect of duloxetine on special populations, the Applicant used pooled data from studies HMBO, HMCA, HMCJ, and HMEF (excluding the duloxetine 20 mg QD from Study HMCJ due to lack of efficacy). As mentioned previously, the Applicant's analyses used the LOCF method for data imputation and studies HMBO and HMCA had different primary endpoints than studies HMCJ and HMEF. However, BPI average pain and PGI-Improvement data was collected in all studies. The Applicant's overview of efficacy when stratified by gender, age, and race, can be found below in Tables 6.21 and 6.22.

**Table 6.21**  
**Brief Pain Inventory Average Pain Score by Demographic Subgroup Mean Change from Baseline to Endpoint**  
**All Randomized Patients 3-Month Therapy Phase**  
**Combined Data from Placebo-Controlled Studies: HMBO, HMCA, HMCJ, and HMEF**

Subgroup	Treatment by Subgroup p-Value	Subgroup p-Value	Strata	N	Treatment	n	Baseline		Change				p-Value*
							Mean	SD	Mean	SD	LS Mean	SE	
Age (<65, ≥65)	.362	.642	<65	1190	Placebo	483	6.46	1.57	-1.13	2.27	-1.11	0.10	
					DLX	707	6.39	1.51	-1.99	2.44	-1.90	0.09	<.001
Age (<65, ≥65)			≥65	110	Placebo	43	6.02	1.77	-1.28	2.15	-1.50	0.36	
					DLX	67	6.60	1.85	-2.00	2.81	-1.92	0.30	.374
Sex	.320	.668	Female	882	Placebo	382	6.41	1.62	-1.10	2.27	-1.10	0.12	
					DLX	500	6.46	1.57	-1.85	2.40	-1.74	0.11	<.001
Sex			Male	70	Placebo	26	6.27	1.64	-1.23	2.05	-1.25	0.45	
					DLX	44	6.07	1.42	-1.30	2.49	-1.28	0.35	.969
Race	.180	.072	Caucasian	1138	Placebo	455	6.32	1.52	-1.11	2.22	-1.12	0.11	
					DLX	683	6.33	1.50	-2.02	2.48	-1.92	0.09	<.001
Race			Other	162	Placebo	71	7.04	1.84	-1.39	2.49	-1.37	0.28	
					DLX	91	6.97	1.75	-1.77	2.42	-1.70	0.27	.386

DLX = duloxetine, p-Value for LS Mean difference between duloxetine and placebo  
 Applicant's Table, Pages 90-91, Clinical Efficacy Summary.

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**Table 6.22**  
**Patient's Global Impression of Improvement Score by Demographic Subgroup Mean at Endpoint**  
**All Randomized Patients in 3-Month Therapy Phase**  
**Combined Data from Placebo-Controlled Studies: HMBO, HMCA, HMCJ, and HMEF**

Subgroup	Treatment by Subgroup p-Value	Subgroup p-Value	Strata	N	Treatment	n	Endpoint				p-Value*
							Mean	SD	LSMean	SE	
Age (<65, ≥65)	.598	.132	<65	1171	Placebo	473	3.60	1.44	3.59	0.07	
					DLX	698	3.13	1.59	3.15	0.06	<.001
			≥65	109	Placebo	43	3.74	1.53	3.76	0.25	
					DLX	66	3.42	1.70	3.46	0.21	.356
Sex	.990	.873	Female	876	Placebo	380	3.58	1.43	3.58	0.08	
					DLX	496	3.19	1.55	3.23	0.07	<.001
			Male	68	Placebo	25	3.56	1.45	3.55	0.28	
					DLX	43	3.19	1.37	3.20	0.22	.332
Race	.002	.390	Caucasian	1121	Placebo	447	3.69	1.45	3.68	0.07	
					DLX	674	3.14	1.60	3.16	0.06	<.001
			Other	159	Placebo	69	3.10	1.33	3.12	0.18	
					DLX	90	3.34	1.59	3.39	0.17	.274

DLX = duloxetine, p-Value for LSMean difference between duloxetine and placebo  
Applicant's Table, Pages 94-95, Clinical Efficacy Summary.

**Gender, Race, and Age**

Using pooled data, the Applicant found no significant treatment-by-subgroup differences at 3-months in the subgroups of gender, age, or race based on changes in BPI average pain score for duloxetine doses of 60 mg QD, 60 mg BID, and 120 mg QD compared to placebo at 3-months. Dr. Buenconsejo analyzed BPI average pain score using both BOCF and LOCF/BOCF hybrid as well as PGI-Improvement using LOCF and WOCF in study HMCJ and did not find any treatment differences either (see Appendix 10.3, Tables 6.15 – 6.16). For PGI-Improvement, there were no obvious treatment-by-subgroup differences seen for age or sex. However, patients of Caucasian origin appeared to benefit from treatment more than those of “other” races. Although the Applicant claims the difference was statistically significant, the aforementioned analysis plan discrepancies discredit this claim. More importantly, both Caucasian and “other” appear to have a reduction in BPI-average pain score from baseline to endpoint.

**Major Depressive Disorder Status**

Patients with FM have a high rate of co-morbid major depression. The analysis of the effect of duloxetine in patients with and without major depressive disorder was of particular interest because, historically, sponsors had been asked to demonstrate that a product with anti-depressant effects was capable of exerting its treatment effect in FM independent of its effect on depression. There were no obvious treatment-by-subgroup differences at 3-months observed for patients based on presence or absence of Major Depressive Disorder (MDD). The Applicant again used pooled data from all placebo-controlled studies to make this observation. Dr. Buenconsejo, analyzed data from studies HMCA and HMCJ using BOCF and BOCF/LOCF hybrid for BPI average pain score and LOCF and WOCF for BPI-Improvement. Her results support that there were no obvious treatment group differences observed based on presence or absence of MDD (for details see Tables 6.23 and 6.24 below).

**Table 6.23**  
**Endpoint Mean BPI Average Pain Score by Major Depressive Disorder Status**  
**All Randomized Patients in the 3-Month Therapy Phase for Studies HMCA and HMCJ**

Study	Treatment Group	No MDD			With MDD		
		N	Baseline	Endpoint Mean	N	Baseline	Endpoint Mean
<b>BOCF</b>							
HMCA	Placebo	88	6.3	5.2	32	7.2	6.4
	DLX 60 mg QD	89	6.3	4.3	29	6.7	4.3
	DLX 60 mg BID	84	6.2	4.5	32	6.8	4.6
HMCJ	Placebo	109	6.4	5.3	35	7.0	6.0
	DLX 20 mg QD	57	6.6	5.1	22	7.2	5.4
	DLX 60 mg QD	115	6.4	4.9	35	6.7	5.1
	DLX 120 mg QD	113	6.3	4.7	34	6.6	5.1
<b>LOCF/BOCF</b>							
HMCA	Placebo	88	6.3	5.1	32	7.2	6.2
	DLX 60 mg QD	89	6.3	4.3	29	6.7	4.1
	DLX 60 mg BID	84	6.2	4.4	32	6.8	4.0
HMCJ	Placebo	109	6.4	5.2	35	7.0	6.0
	DLX 20 mg QD	57	6.6	4.8	22	7.2	5.0
	DLX 60 mg QD	115	6.4	4.8	35	6.7	4.9
	DLX 120 mg QD	113	6.3	4.7	34	6.6	4.9

DLX = duloxetine, MDD = major depressive disorder  
 Dr. Buenconsejo's Table.

**Table 6.24**  
**Endpoint PGI-Improvement by Major Depressive Disorder Status**  
**All Randomized Patients in the 3-Month Therapy Phase for Studies HMCA and HMCJ**

Study	Treatment Group	Without MDD		With MDD	
		N	Endpoint Mean	N	Endpoint Mean
<b>LOCF</b>					
HMCA	Placebo	28	3.9	83	3.6
	Duloxetine 60 mg QD	28	2.9	86	3.2
	Duloxetine 60 mg BID	30	2.6	81	3.2
HMCJ	Placebo	109	3.1	33	2.7
	Duloxetine 20 mg QD	55	3.0	22	2.9
	Duloxetine 60 mg QD	109	3.2	34	2.9
	Duloxetine 120 mg QD	105	3.5	34	3.5
<b>WOCF</b>					
HMCA	Placebo	28	4.0	83	3.7
	Duloxetine 60 mg QD	28	3.0	86	3.2
	Duloxetine 60 mg BID	30	2.7	81	3.3
HMCJ	Placebo	109	3.2	33	2.8
	Duloxetine 20 mg QD	55	3.2	22	3.0
	Duloxetine 60 mg QD	109	3.3	33	3.0
	Duloxetine 120 mg QD	104	3.7	34	3.6

DLX = duloxetine, MDD = major depressive disorder  
 Dr. Buenconsejo's Table.

### 6.1.5 Clinical Microbiology

Not applicable.

### 6.1.6 Efficacy Conclusions

The efficacy of duloxetine in \_\_\_\_\_ of fibromyalgia at doses of 60 mg QD, 60 mg BID, and 120 mg QD was demonstrated by the results of the randomized, parallel-group, placebo-controlled, phase 3 studies HMCA and HMCJ, both of which were of 3-months duration. Study HMBO was a similarly designed Phase 2 study of 3-months duration with different primary outcome measures (reduction in pain as measured by FIQ Pain Item and FIQ Total Score) than studies HMCA (reduction in pain as measured by BPI) and HMCJ (reduction in pain as measured by BPI and PGI-Improvement). However, study HMBO recorded BPI average pain score and PGI-Improvement (as secondary outcome measures) and demonstrated numerical improvements in pain when duloxetine was compared to placebo at a dose of 60 mg BID. Although not statistically significant, study HMEF, a 6-month study, also supports a positive treatment effect for duloxetine at 3-months with doses of 60 mg QD and 120 mg QD.

The above efficacy assertions are based on Dr. Buenconsejo's efficacy analyses using a data imputation of LOCF/BOCF hybrid to describe the BPI average pain score. This hybrid method also indicates that duloxetine 20 mg QD may also be effective (Study HMCJ). However, the Applicant imputed missing data using BOCF and did not find a statistically significant improvement in pain at this dose, implying that the lowest effective dose studied was 60 mg QD. Eli Lilly contends that this dose was not meant to be included in the analyses and due to the randomization scheme used; this treatment arm had less power to detect statistically significant effects. To further characterize the treatment effects of duloxetine 20 mg QD for \_\_\_\_\_ of fibromyalgia, a new study would likely be necessary.

As mentioned previously, the Division initially suggested that the Applicant design studies to demonstrate efficacy at 6-months instead of 3-months (studies HMBO and HMCA had already been completed). During late stage discussions with the Applicant, this requirement was waived. Study HMEF did not demonstrate statistically significant improvements in the primary outcome measures (BPI average pain score and PGI-Improvement) at 6-months, but did show numerical improvement in various pain measures at both 3 and 6-months. Therefore, although the results of this study were not statistically significant, there is some level of comfort provided by the fact that the treatment effect does not appear to be negative.

Study HMEH, the 1-year safety and persistence of efficacy study did not demonstrate statistically significant persistence of efficacy, but did result in numerical improvements in pain measures, as described previously in study HMEF. The results of this study also indicate that patients who fail to respond to duloxetine at a dose of 60 mg QD are unlikely to respond if their dose is increased to 120 mg QD.

Analyses of the efficacy results did not indicate that there were any subgroup disparities in effect for the subgroups of: age greater than 65 years, race, gender, or history of major depressive disorder. Although patients of the male gender typically represent close to 10% of the general fibromyalgia population, in the duloxetine studies only 5% of the population was male. This was in part due to study HMCJ which did not include any males. To better characterize the treatment effect of duloxetine in men, additional studies with more male patients may be necessary.

## 7 INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings

The assessment of the safety for duloxetine hydrochloride in the \_\_\_\_\_ of fibromyalgia included a total 5 studies: Protocols F1J-MC-HMBO (**HMBO**), F1J-MC-HMCA (**HMCA**), F1J-MC-HMCJ (**HMCJ**), F1J-MC-HMEF (**HMEF**), and F1J-MC-HMEH (**HMEH**). An additional 10 patients, originally assigned to placebo in the previous studies, were entered in compassionate use study F1J-MC-HMCN (**HMCN**).

The integrated safety database for duloxetine (all trials and all indications except fibromyalgia) consists of 25,933 patients, 8569 of which were enrolled in placebo-controlled studies. The other indications include: diabetic peripheral neuropathic pain (DPNP), generalized anxiety disorder (GAD), lower urinary tract disorder (LUTD), and major depressive disorder (MDD). Safety of duloxetine in patients with fibromyalgia (FM) was evaluated in a total of 1236 patients in 5 completed clinical studies administering doses of 20, 60, and 120 mg, including long-term treatment of up to 60 weeks with duloxetine. There were 876 fibromyalgia patients treated with duloxetine in placebo-controlled trials, 350 in a long-term trial, and an additional 10 patients in a compassionate use study (for details see Table 7.1 below).

Fibromyalgia Placebo-Controlled Studies		Fibromyalgia Long-Term Safety Study	Fibromyalgia Open-Label Compassionate Use Study	Placebo-Controlled Studies for all Other Indications		Total Exposures for all Other Indications
PBO	DLX	DLX	DLX	PBO	DLX	DLX
N=535	N=876	N=350	N=10	N=6235	N=8569	N=25,933

All indications includes: diabetic peripheral neuropathic pain (DPNP), generalized anxiety disorder (GAD), lower urinary tract disorder (LUTD), major depressive disorder (MDD), and fibromyalgia (FM).  
 PBO = placebo, DLX = duloxetine

#### 7.1.1 Deaths

No patient deaths occurred in any of the of the fibromyalgia studies.

A total of 30 deaths were reported in the entire clinical development program (all indications). Additionally, 2 deaths were reported in ongoing studies. The applicant investigated all deaths individually and thought that many of the deaths were related to the disease state being treated. The causes of death do not appear to form an obvious pattern suggestive of specific organ toxicity.

Duloxetine carries the antidepressant class black box warning of increased risk for suicide in children and adolescents. There were 2 deaths by suicide in duloxetine studies for major depressive disorder. One occurred in the placebo group and one in the duloxetine group. More information on suicidality is presented in Section 7.1.3.3, Other significant adverse events.

### 7.1.2 Other Serious Adverse Events

A total of 40 (3.2%) out of 1236 patients treated with duloxetine in fibromyalgia trials experienced at least 1 Serious Adverse Event. The only SAEs that occurred in more than one subject were suicidal and self-injurious behavior (n = 5), abdominal and gastrointestinal infections (n = 2), cerebral injuries NEC (n = 2), and nephrolithiasis (n = 2). For an overview of serious adverse events, grouped by MedDRA High Level Term in the fibromyalgia studies, see Table 7.2 below.

As mentioned above, suicidal ideation and self-injurious behavior was the SAE most frequently reported (5 patients, 0.4%) in the fibromyalgia controlled and uncontrolled studies. All 5 patients experienced suicidal ideation and 1 of these patients took an overdose of estazolam after an argument with her spouse (after sleeping for several hours, she fully recovered without requiring mechanical ventilation). Four of these patients were enrolled in the long-term Study HMEH and 1 patient was from the 6-month Study HMCJ.

In the 2 cases of cerebral injuries, the case report forms and patient narratives did not clearly link or exclude duloxetine as a causative factor behind the injuries. Nephrolithiasis, seen in 2 of the fibromyalgia treated patients, only appeared in 9 out of 25,933 patients treated with duloxetine for all other indications.

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<b>Table 7.2</b>		
<b>Serious Adverse Events by Decreasing Frequency MedDRA High Level Term for all Duloxetine Patients Enrolled in Fibromyalgia Trials</b>		
<b>MedDRA High Level Term</b>	<b>n (%)</b>	
Patients with >= 1 Serious Adverse Event	40	(3.2)
Suicidal and self-injurious behavior	5	(0.4)
Abdominal and gastrointestinal infections	2	(0.2)
Cerebral injuries NEC	2	(0.2)
Renal lithiasis	2	(0.2)
Bacterial infections NEC	1	(0.1)
Bronchospasm and obstruction	1	(0.1)
Colorectal and anal neoplasms malignancy unspecified	1	(0.1)
Crime victims	1	(0.1)
Diaphragmatic hernias	1	(0.1)
Diarrhoea (excl infective)	1	(0.1)
Disturbances in consciousness NEC	1	(0.1)
Gait disturbances	1	(0.1)
Gastrointestinal signs and symptoms NEC	1	(0.1)
General signs and symptoms NEC	1	(0.1)
Heart failures NEC	1	(0.1)
Hyperglycaemic conditions NEC	1	(0.1)
Hyperparathyroid disorders	1	(0.1)
Ischaemic coronary artery disorders	1	(0.1)
Joint related signs and symptoms	1	(0.1)
Liver function analyses	1	(0.1)
Lower limb fractures and dislocations	1	(0.1)
Mononeuropathies	1	(0.1)
Muscle weakness conditions	1	(0.1)
Muscle, tendon and ligament injuries	1	(0.1)
Musculoskeletal and connective tissue signs and symptoms NEC	1	(0.1)
Non-site specific injuries NEC	1	(0.1)
Non-site specific necrosis and vascular insufficiency NEC	1	(0.1)
Pain and discomfort NEC	1	(0.1)
Paraesthesias and dysaesthesias	1	(0.1)
Pseudomonal infections	1	(0.1)
Psychotic disorder NEC	1	(0.1)
Rashes, eruptions and exanths NEC	1	(0.1)
Skeletal and cardiac muscle analyses	1	(0.1)
Skin melanomas	1	(0.1)
Somatoform disorders	1	(0.1)
Spinal fractures and dislocations	1	(0.1)
Thermal burns	1	(0.1)
Transient cerebrovascular events	1	(0.1)
Upper limb fractures and dislocations	1	(0.1)
Upper respiratory tract infections	1	(0.1)
Urinary tract infections	1	(0.1)
Uterine disorders NEC	1	(0.1)
Uterine neoplasms benign	1	(0.1)

N = Number of duloxetine fibromyalgia patients. n = Number of patients with serious adverse event.  
 Applicant's Table, 5.3.5.3. multistudy analysis, Table 10.15, page 4850

In the fibromyalgia placebo-controlled trials, a total of 21 (2.4%) duloxetine treated and 11 (2.1%) placebo-treated patients reported at least 1 Serious Adverse Event. Between arms, there did not appear to be any clinically important treatment differences in the incidence of individual SAEs.

In duloxetine placebo-controlled trials for all other indications, there were a total of 115 (1.3%) patients treated with duloxetine and 72 (1.1%) patients treated with placebo that reported at least 1 SAE.

The frequency of SAEs observed in duloxetine-treated patients enrolled in fibromyalgia placebo-controlled studies (2.4%) was higher than the frequency observed in placebo-controlled studies for all other indications (1.3%). This was also true for the placebo-treated patients (2.1% vs. 1.1%) and may suggest a population-specific phenomenon.

Following my review of individual fibromyalgia patient case report forms and narratives, of the 40 patients who experienced at least 1 SAE, 25 patients had SAEs that were unrelated to duloxetine and 15 had SAEs for which duloxetine causality could not be excluded. A summary of these SAEs can be found in Table 7.3 below.

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<b>Table 7.3 SAEs Reported in All Fibromyalgia Studies For Which Relationship with Study Medication Could Not Be Excluded</b>							
	Study	Subject ID	Treatment	Age	Race	Sex	MedDRA Preferred Term/Comment
1	HMCJ	HMCJ-104-1404	DLX60QD	61	Caucasian	F	CONCUSSION WHIPLASH INJURY
CRF and patient narrative do not contain sufficient details regarding vehicle collision.							
2	HMCJ	HMCJ-130-4024	DLX120QD	52	Caucasian	F	WRIST FRACTURE
CRF and patient narrative do not sufficient information regarding the fall that led to the wrist fracture.							
3	HMCJ	HMCJ-135-4535	DLX120QD	26	Caucasian	F	SUICIDAL IDEATION
No history of previous suicidal ideation. The patient was not hospitalized and the event resolved while patient was still taking DLX.							
4	HMCJ	HMCJ-124-3406	DLX20QD	37	African	F	UTERINE HEMMORHAGE
Patient developed heavy uterine bleeding which required a hysterectomy.							
5	HMEF	HMEF-400-3076	DLX120QD	44	Caucasian	F	PAIN
Insufficient information regarding SAE to exclude DLX causality.							
6	HMEF	HMEF-400-4020	DLX120QD	35	Caucasian	F	PSEUDONEUROLOGIC SYMPTOM
Patient had a large abscess in jaw with subsequent pseudoneurologic symptoms, however, insufficient information regarding SAE to exclude DLX causality.							
7	HMEF	HMEF-614-7066	DLX120QD	34	Caucasian	F	GAIT DISTURBANCE
Patient developed somatiform disorder and post-traumatic stress disorder.							
8	HMEH	HMEH-102-1205	DLX120QD	64	Caucasian	F	DYSPHAGIA RASH
Patient had been on DLX for 186 days before development of rash, nausea & vomiting. Attempt to re-challenge failed due to severe nausea.							
9	HMEH	HMEH-102-1212	DLX120QD	51	Caucasian	F	SUICIDAL IDEATION
Patient on DLX for 141 days, no previous history of suicide attempts or ideation, no history (personal or familial) of depression or drug or alcohol abuse, however, husband committed suicide.							
10	HMEH	HMEH-102-1226	DLX60QD	42	Hispanic	F	SUICIDAL IDEATION
Patient with history of depression, previous suicidal ideation, and child abuse/neglect, no history of alcohol or drug abuse. Patient divorced husband during trial. Patient took DLX for 139 days and was discontinued after suicidal ideation. Symptoms resolved after stopping study medication.							
11	HMEH	HMEH-203-2307	DLX120QD	63	Caucasian	F	DIARRHEA
Clinical symptoms suggestive of IBS, however, insufficient information regarding SAE to exclude DLX causality.							
12	HMEH	HMEH-305-3509	DLX120QD	51	Caucasian	M	PSYCHOTIC DISORDER
Patient with history of depression developed "psychotic crisis" where he was aggressive to himself and his wife. He walked onto the street screaming profanities and making physical threats against posts and public phones. Unknown if he was using alcohol at the time. He took DLX for 123 days. He was hospitalized, DLX was discontinued, and he was discharged on carbamazepine, lithium carbonate, and diazepam.							
13	HMEH	HMEH-305-3515	DLX120QD	50	Caucasian	F	SUICIDAL IDEATION
Patient with history of severe depression. No history of alcohol or drug abuse. States that she felt suicidal because of her grandson's disapproval. Planned to throw herself against a car. Took study medication for 97 days. Symptoms resolved approximately 2 months after stopping medication.							
14	HMEH	HMEH-703-7304	DLX120QD	77	Asian	F	SUBDURAL HEMORRHAGE
Insufficient information given in CRF and patient narrative to exclude DLX causality.							
15	HMEH	HMEH-704-7407	DLX120QD	38	Asian	F	ROAD TRAFFIC ACCIDENT SUICIDAL IDEATION VICTIM OF SPOUSAL ABUSE SUICIDE ATTEMPT
Patient was assaulted by husband and took several pills of a benzodiazepine. She had been on study medication for 243 days.							
DLX= duloxetine A listing of SAEs in fibromyalgia studies which appear unrelated to study medication can be found in Appendix 10.4, Table 7.1.							

At FDA request, Lilly provided a tabulation of SAEs by dose at the time of the event. However, Lilly noted, “The table reflects percentages, but does not address differences in length of exposure by dose. Each dose group may have a different corresponding exposure length. For example, 30 and 90 mg/day groups have short exposure times as they are generally not a patient’s final dose, but rather a titration dose as patients are titrated up to 60 mg or 120 mg per day. Exposure to these interim doses was generally limited to 1 week or less. Alternatively, both 60 and 120 mg/day are used in extension phases of long duration, and 120 mg/day is the only dose used beyond Week 30 in Study HMCJ.” For details see Table 7.4, below.

<b>Table 7.4</b>			
<b>Summary of Serious Adverse Events by Dose</b>			
<b>All Duloxetine-Treated Patient in Fibromyalgia Studies</b>			
<b>Preferred Term</b>	<b>Duloxetine Treatment</b>	<b>N</b>	<b>n(%)</b>
<b>Patients with ≥ 1 SAE</b>	20 mg	78	1 (1.3)
	30 mg	810	2 (0.2)
	60 mg	1043	15 (1.4)
	90 mg	20	0 (0)
	120 mg	855	39 (4.6)
<b>Suicidal Ideation</b>	20 mg	78	0 (0)
	30 mg	810	0 (0)
	60 mg	1043	1 (0.1)
	90 mg	20	0 (0)
	120 mg	855	3 (0.4)
<b>Appendicitis</b>	20 mg	78	0 (0)
	30 mg	810	0 (0)
	60 mg	1043	2 (0.2)
	90 mg	20	0 (0)
	120 mg	855	1 (0.1)
<b>Arthralgia</b>	20 mg	78	0 (0)
	30 mg	810	0 (0)
	60 mg	1043	1 (0.1)
	90 mg	20	0 (0)
	120 mg	855	1 (0.1)
<b>Chest Pain</b>	20 mg	78	0 (0)
	30 mg	810	0 (0)
	60 mg	1043	0 (0)
	90 mg	20	0 (0)
	120 mg	855	2 (0.2)
<b>Femur Fracture</b>	20 mg	78	0 (0)
	30 mg	810	0 (0)
	60 mg	1043	0 (0)
	90 mg	20	0 (0)
	120 mg	855	2 (0.2)
<b>Nephrolithiasis</b>	20 mg	78	0 (0)
	30 mg	810	0 (0)
	60 mg	1043	1 (0.1)
	90 mg	20	0 (0)
	120 mg	855	1 (0.1)
<b>Road Traffic Accident</b>	20 mg	78	0 (0)
	30 mg	810	0 (0)
	60 mg	1043	0 (0)
	90 mg	20	0 (0)
	120 mg	855	2 (0.2)

N = Number of randomized patients, n = Number of patients with treatment-emergent adverse event  
 Applicant’s Table, Regulatory Response 12-March-2008 – Serious Adverse Events by Dose, Pages 6-7.

## 7.1.3 Dropouts and Other Significant Adverse Events

### 7.1.3.1 Overall profile of dropouts

In the fibromyalgia placebo-controlled studies, a total of 171(20%) patients taking duloxetine dropped out due to adverse events and 63(12%) patients taking placebo dropped out due to adverse events (see Table 7.5 below for details). In placebo-controlled studies for all other indications (MDD, GAD, LUTD, DPNP) at total of 1154(13%) patients taking duloxetine dropped out due to adverse events and 247(4%) patients taking placebo dropped out due to adverse events. Although duloxetine-treated fibromyalgia patients had a higher dropout rate than duloxetine-treated patients for all other indications (20% vs. 13%), the same was true for placebo (12% vs. 4%), a difference of about 7% for duloxetine-treated patients and 8% for placebo treated patients.

As mentioned in the Review of Efficacy, a greater number of placebo-treated patients (14%) discontinued due to lack of efficacy compared with duloxetine-treated patients (7%).

	Fibromyalgia Placebo-Controlled Studies		Placebo-Controlled Studies for All Other Indications	
	PBO N=535(%)	DLX N=876(%)	PBO N=6235(%)	DLX N=8569(%)
Drop Outs due to AE	63(12)	171(20)	310(4)	247(13)
All other indications: DPNP, GAD, LUTD, MDD				

Table 7.6 below, was compiled from Lilly's study reports, and summarizes the likelihood of premature study drug discontinuation due to adverse events by dose, across studies. This tabulation illustrates that the low dose (20 QD) was least likely be associated with dropout due to AE. The high dose (120 mg/day, whether given as one dose or divided doses) was slightly, but not dramatically, more likely to be associated with dropout due to AE.

	Placebo	DLX 20 QD	DLX 60 QD	DLX 60 BID	DLX 120 QD
HMBO	11/103 (11%)			18/104 (17%)	
HMCA	14/120 (12%)		25/118 (21%)	27/116 (23%)	
HMCJ (first three months) <sup>a</sup>	17/144 (12%)	8/79 (10%)	22/150 (15%)		32/147 (22%)
HMEF (first 8 visits) <sup>b</sup>	14/168 (8%)		23/162 (14%)		
HMEH (open-label phase)			26/350 (7%)		
HMEH (double-blind phase)			14/104 (14%)		34/203 (17%)

<sup>a</sup>After three months, patients on 20 mg were changed to 60 mg QD  
<sup>b</sup>After the first 8 visits, non-responders could be titrated upwards to 120 mg QD

### 7.1.3.2 Adverse events associated with dropouts

As mentioned above, in the fibromyalgia placebo-controlled studies, more duloxetine-treated patients (20%) than placebo-treated patients (12%) reported adverse events as the reason for study discontinuation. The most common adverse events which resulted in discontinuation in ≥ 1% of patients in the fibromyalgia placebo-controlled studies were nausea (1.9% vs. 0.7% PBO),

somnolence (1.5% vs. 0 PBO), fatigue (1.3% vs. 0.2% PBO), and insomnia (1.1% vs. 0.7% PBO). In placebo-controlled studies for all other indications; the only adverse event which resulted in discontinuation in  $\geq 1\%$  of patients was nausea (3.4% vs. 0.5% PBO). Dizziness (0.9% vs. 0.2% PBO), somnolence (0.8% vs. 0% PBO), fatigue (0.9% vs. 0.2% PBO), and insomnia (0.8% vs. 0.2% PBO) all had differences greater than 0.5% when comparing DLX-treated patients with PBO-treated patients. These treatment-discontinuation findings are consistent with previous study findings as described in the duloxetine label for approved indications. For details see Table 7.7 below.

Consistent with the findings described above, in the combined fibromyalgia placebo-controlled and open-label studies, a total of 252(20%) patients reported adverse events as the reason for study discontinuation. The events reported with a frequency of  $\geq 1\%$  for duloxetine-treated patients were nausea (1.9%), insomnia (1.6%), somnolence (1.1%), fatigue (1.1%), and diarrhea (1.0%).

**Table 7.7**  
**Discontinuations Due to the Most Common Adverse Events**

	Fibromyalgia Placebo-Controlled		Fibromyalgia Long-Term	Fibromyalgia Placebo-Controlled and Open-Label*	Placebo-Controlled Studies for all Other Indications		Total DLX Exposures for all Other Indications
	PBO	DLX	DLX	DLX	PBO	DLX	DLX
	N=535	N=876	N=350	N=1236	N=6235	N=8569	N=25,933
<b>Event</b>	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
<b>ANY EVENT</b>	63(12)	171(20)	74(20)	252(20)	310(5)	1325(16)	4991(19)
Nausea	4(0.7)	17(1.9)	5(1.4)	23(1.9)	31(0.5)	289(3.4)	956(3.7)
Somnolence	0	13(1.5)	1(0.3)	14(1.1)	3(0)	65(0.8)	228(0.9)
Fatigue	1(0.2)	11(1.3)	2(0.6)	13(1.1)	11(0.2)	74(0.9)	276(1)
Insomnia	4(0.7)	10(1.1)	9(2.6)	20(1.6)	14(0.2)	69(0.8)	252(1)
Headache	1(0.2)	8(0.9)	1(0.3)	9(0.7)	14(0.2)	53(0.6)	159(0.6)
Diarrhea	1(0.2)	7(0.8)	5(1.4)	12(1.0)	5(0.1)	28(0.3)	133(0.5)
Dizziness	3(0.6)	6(0.7)	5(1.4)	11(0.9)	16(0.2)	79(0.9)	259(1)
Hyperhidrosis	0	4(0.5)	1(0.3)	5(0.4)	0	13(0.2)	66(0.3)
Constipation	1(0.2)	3(0.3)	2(0.6)	6(0.5)	7(0.1)	21(0.2)	124(0.5)

Abbreviations: DLX = duloxetine; N = number of patients; PBO = placebo.  
 a) Includes DLX-treated fibromyalgia patients from placebo-controlled and open-label studies, including an additional 10 patients from the compassionate use study HMCN.  
 The applicant's tables grouped patients treated for fibromyalgia with patients treated for all other indications. This table was derived from the applicant's tables by manual subtraction of patients treated for fibromyalgia from those treated for all other indications.

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Fibromyalgia patients across all treatment doses were more likely to discontinue therapy due to adverse events. Treatment doses of duloxetine in the fibromyalgia ranged from 20 – 120 mg daily and dose escalation was utilized in all of the placebo-controlled fibromyalgia studies. Studies HMCJ and HMEF included a 30-mg QD step. Many of the patients who discontinued while taking duloxetine at a 30-mg QD dose did so due to adverse events. A majority of adverse events were found to occur early in therapy and the 30-mg dose was given to patients for the first week of treatment. Overall, the incidence of discontinuations due to adverse events between the 60-mg QD, 60-mg BID, and 120-mg QD treatment groups were similar. Likewise, the adverse events reported as reason for discontinuation, do not demonstrate a distinct dose-response pattern.

Table 7.8 below, from Lilly's clinical summary, illustrates the adverse-event discontinuation rate by *maximum dose* achieved. Therefore, the 37 patients in the 30 mg QD column represent patients who discontinued (for any reason) before completing titration past the 30 mg step. Similarly, the 60 mg column may represent patients who discontinued at 60 mg QD while titrating to a higher (assigned) dose. Although this is not an optimal presentation of the data, it displays the types of adverse events which were responsible for premature discontinuation across the development program.

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**Table 7.8**  
**Adverse Events Reported as Reason for Discontinuation by Highest Tolerated Dose**  
**All Randomized Patients Primary Placebo-Controlled Analyses Set (frequency ≥ 0.2% of total)**

MedDRA Preferred Term	PLACEBO (N=535) n (%)		DLX20QD (N=29) n (%)		DLX30QD (N=37) n (%)		DLX60QD (N=369) n (%)		DLX60BID (N=220) n (%)		DLX120QD (N=221) n (%)		TOTAL DLX (N=876) n (%)	
<b>Patients Discontinued for Any AE</b>	<b>63 (11.8)</b>		<b>8 (27.6)</b>		<b>22 (59.5)</b>		<b>64 (17.3)</b>		<b>45 (20.5)</b>		<b>32 (14.5)</b>		<b>171 (19.5)</b>	
Nausea	4	(0.7)	0	(0)	3	(8.1)	6	(1.6)	6	(2.7)	2	(0.9)	17	(1.9)
Insomnia	4	(0.7)	0	(0)	0	(0)	4	(1.1)	4	(1.8)	2	(0.9)	10	(1.1)
Somnolence	0	(0)	1	(3.4)	0	(0)	2	(0.5)	8	(3.6)	2	(0.9)	13	(1.5)
Fatigue	1	(0.2)	0	(0)	1	(2.7)	5	(1.4)	3	(1.4)	2	(0.9)	11	(1.3)
Depression	8	(1.5)	0	(0)	1	(2.7)	0	(0)	1	(0.5)	0	(0)	2	(0.2)
Dizziness	3	(0.6)	0	(0)	1	(2.7)	4	(1.1)	1	(0.5)	0	(0)	6	(0.7)
Headache	1	(0.2)	0	(0)	2	(5.4)	3	(0.8)	1	(0.5)	2	(0.9)	8	(0.9)
Diarrhoea	1	(0.2)	0	(0)	3	(8.1)	2	(0.5)	2	(0.9)	0	(0)	7	(0.8)
Anxiety	4	(0.7)	0	(0)	2	(5.4)	1	(0.3)	0	(0)	0	(0)	3	(0.3)
Sedation	0	(0)	1	(3.4)	1	(2.7)	2	(0.5)	1	(0.5)	0	(0)	5	(0.6)
Vomiting	1	(0.2)	0	(0)	1	(2.7)	3	(0.8)	0	(0)	0	(0)	4	(0.5)
Constipation	1	(0.2)	2	(6.9)	0	(0)	0	(0)	0	(0)	1	(0.5)	3	(0.3)
Hyperhidrosis	0	(0)	0	(0)	0	(0)	0	(0)	1	(0.5)	3	(1.4)	4	(0.5)
Hypertension	1	(0.2)	0	(0)	0	(0)	1	(0.3)	0	(0)	2	(0.9)	3	(0.3)
Lethargy	1	(0.2)	0	(0)	0	(0)	2	(0.5)	1	(0.5)	0	(0)	3	(0.3)
Abdominal pain upper	0	(0)	0	(0)	0	(0)	2	(0.5)	1	(0.5)	0	(0)	3	(0.3)
Back pain	1	(0.2)	1	(3.4)	0	(0)	1	(0.3)	0	(0)	0	(0)	2	(0.2)
Feeling jittery	0	(0)	0	(0)	1	(2.7)	1	(0.3)	1	(0.5)	0	(0)	3	(0.3)
Nervousness	0	(0)	0	(0)	0	(0)	0	(0)	3	(1.4)	0	(0)	3	(0.3)
Presyncope	1	(0.2)	0	(0)	0	(0)	2	(0.5)	0	(0)	0	(0)	2	(0.2)
Alanine aminotransferase increased	0	(0)	0	(0)	0	(0)	1	(0.3)	0	(0)	1	(0.5)	2	(0.2)
Blood pressure increased	0	(0)	0	(0)	1	(2.7)	0	(0)	0	(0)	1	(0.5)	2	(0.2)
Hepatic enzyme increased	0	(0)	0	(0)	0	(0)	2	(0.5)	0	(0)	0	(0)	2	(0.2)
Libido decreased	0	(0)	1	(3.4)	0	(0)	0	(0)	0	(0)	1	(0.5)	2	(0.2)
Migraine	0	(0)	0	(0)	0	(0)	0	(0)	2	(0.9)	0	(0)	2	(0.2)
Night sweats	0	(0)	0	(0)	0	(0)	1	(0.3)	1	(0.5)	0	(0)	2	(0.2)
Osteoarthritis	0	(0)	0	(0)	0	(0)	1	(0.3)	1	(0.5)	0	(0)	2	(0.2)
Palpitations	0	(0)	0	(0)	1	(2.7)	1	(0.3)	0	(0)	0	(0)	2	(0.2)
Restless legs syndrome	0	(0)	0	(0)	0	(0)	1	(0.3)	0	(0)	1	(0.5)	2	(0.2)
Weight increased	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	2	(0.9)	2	(0.2)

N = Number of patients who discontinued at a specific dose. n = Number of patients with adverse event as reason for discontinuation.  
 Applicant's Table: 2.7.4.7 summary-clin-safe-app, Table APP 2.7.4.31, page 544.

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### **7.1.3.3 Other significant adverse events**

Based on the extensive clinical development program of duloxetine for treatment of major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain, and lower urinary tract disease, the product is well characterized and noticeably associated with several adverse events. These include clinical worsening and suicide risk, hepatotoxicity, orthostatic hypotension and syncope, elevation of blood pressure, activation of mania/hypomania, mydriasis, and withdrawal symptoms. Although rare and not discovered in clinical trials, postmarketing reports have detected severe cutaneous reactions associated with duloxetine.

The following sections (7.1.3.3.1 – 7.1.3.3.10) describe significant adverse events that are already described in the approved duloxetine label. These include: clinical worsening of suicide risk, hepatotoxicity, severe cutaneous reactions, orthostatic hypotension and syncope, elevation of blood pressure, activation of mania/hypomania, mydriasis, withdrawal symptoms, seizures, and hyponatremia. Several, but not all of these AEs were observed in the duloxetine studies for fibromyalgia.

Recently, the Division of Neurology Products has become aware of post-marketing reports involving abnormal bleeding and urinary retention (See Sections 7.1.3.3.11 and 7.1.3.3.12). In the fibromyalgia studies, there were two SAEs involving bleeding (one uterine hemorrhage and one subdural hematoma in a patient who was struck by a motorcycle) but none involving urinary retention.

#### **7.1.3.3.1 Clinical Worsening and Suicide Risk**

Duloxetine carries the antidepressant class boxed warning of increased “risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders.”

As mentioned previously, suicidal ideation was the SAE reported most frequently in the fibromyalgia placebo-controlled and open-label studies (5 patients; 0.4%). Four of these patients were enrolled in the long-term Study HMEH and 1 patient was from Study HMCJ. One of the patients who experienced suicidal ideation in study HMEH was also reported to have attempted suicide by ingesting a large amount of the benzodiazepine estazolam. The patient recovered without any permanent disabilities or serious medical sequelae. There were no completed suicides in any of the fibromyalgia studies.

The applicant provided a comprehensive analysis of suicidality which reviewed duloxetine safety data from Phase 2 – 4 clinical and pharmacological studies, safety reporting systems, and postmarketing surveillance. This analysis, which includes all fibromyalgia studies, consists of data up to 12 May 2007. Previous comprehensive analyses have been completed with other NDA applications for duloxetine. Search strategies used for the suicidality analysis were purportedly based on the Agency Guidance “Advice for the Pharmaceutical Industry Exploring Their Placebo-Controlled Clinical Trial Databases for Suicidality and Preparing Data Sets for Analysis by FDA (Draft: 8-2-05).”

In the fibromyalgia placebo-controlled trials, among patients with depression at baseline, more placebo-treated patients than duloxetine-treated patients reported the emergence of any suicidal ideation and worsening of suicidal ideation. In the suicide analysis discussion, the applicant accurately notes that suicide is a known risk factor of major depression and more than 50% of patients who commit suicide have clinical depression. Approximately half of patients diagnosed with fibromyalgia suffer from comorbid depression. Table 7.9 provides a summary of fibromyalgia study patients who experienced suicidal ideation and/or self-injurious behavior.

<b>Table 7.9</b>
<b>Summary of Patients with Suicidal Ideation and Self-Injurious Behavior</b>
<p><b>Patient HMCJ-135-4535 (Suicidal Ideation)</b>            26 year old Caucasian female (68 kg); onset at day #48 of DLX 120 mg QD; concomitant medications: none            AEs: suicidal ideation, decreased appetite, nausea, insomnia            Summary: Patient had no concurrent psychiatric diagnoses. Prior to beginning study drug she was suffering from current major depressive episode. No known history of suicidal ideation or suicide attempts, aggressive or hostile behavior, or alcohol or drug dependency. She was unemployed. Investigator states that while still on DLX suicidal ideation resolved (day #53), however patient was discontinued due to the SAE. It is unclear as to why she was discontinued earlier.</p>
<p><b>Patient HMEH-102-1212 (Suicidal Ideation)</b>            51 year old Caucasian female (67 kg); onset at day #142 of DLX 120 mg QD; concomitant medications: enalapril, bisoprolol, acetaminophen            AEs: suicidal ideation, sinus bradycardia, nausea, hypertension, muscle spasms, palpitations, ventricular hypertrophy, somnolence, fall, disturbance in attention, gait disturbance            Summary: Patient had no historical diagnoses or relevant secondary conditions. No known history of suicidal ideation, suicide attempts, aggressive or hostile behavior, or alcohol or drug abuse and dependency. The patient's husband committed suicide in 2000. Following discovery of suicidal ideation DLX was discontinued.</p>
<p><b>Patient HMEH-102-1226 (Suicidal Ideation)</b>            42 year old Hispanic female (74 kg); onset at day #139 of DLX 60 mg QD; concomitant medications: ranitidine, acetaminophen, benzalkonium, hydroxyzine, levofloxacin; PMHx: depression, hypothyroidism, muscle contracture, hypercholesterolemia, cholelithiasis, allergic dermatitis, dyspepsia, obesity            AEs: suicidal ideation, dizziness, nausea, pruritus, pharyngitis, crying            Summary: Patient had previous suicidal ideation and history of child abuse/neglect, but no known history of suicide attempts, aggressive or hostile behavior, or alcohol or drug dependency. She went through divorce during trial and developed suicidal ideation, upon which DLX was discontinued.</p>
<p><b>Patient HMEH-305-3515 (Suicidal Ideation)</b>            50 year old Caucasian female (53 kg); onset at day #97 of DLX 120 mg QD; concomitant medications: metamizole, levothyroxine, acetaminophen, bromopride            PMHx: hypothyroidism, osteoarthritis            AEs: suicidal ideation, dizziness, dry mouth, upper abdominal pain, headache, anorexia, nausea, constipation, somnolence            Summary: Patient had no concurrent psychiatric diagnoses, but had a history of severe depression and had previously taken cyclobenzaprine, fluoxetine, and amitriptyline. She had no history of suicidal ideation, suicide attempts, aggressive or hostile behavior, or alcohol or drug dependency. Upon discovery of suicidal ideation, DLX was discontinued.</p>
<p><b>Patient HMEH-704-7407 (Suicidal Ideation and Suicide Attempt)</b>            38 year old East Asian female (53 kg); onset at day #243 of DLX 120 mg QD; concomitant medications: diclofenac, mucaine, estazolam, sennoside, levocetirazine, mometasone, ketorolac, nicametate, acetaminophen, prochlorperazine, diphenhydramine, zolpidem, alprazolam, gabapentin, atenolol            PMHx: insomnia, sicca syndrome            AEs: suicide attempt, dizziness, constipation, rash, victim of spousal abuse, road traffic accident.            Patient had no known history of suicidal ideation, suicide attempts, aggressive or hostile behavior, or alcohol or drug abuse or dependency. The patient narrative states that after a fight with her husband the patient attempted suicide by taking a large quantity of estazolam after an altercation with her husband. She slept all night on the couch then drove her car the following day and was involved in an accident, after which she was taken to the hospital and her suicide attempt was discovered. She stayed at the hospital for a brief period of time and DLX was discontinued upon discovery of the SAE.</p>

In the applicant's suicidality review of all duloxetine placebo-controlled trials for all indications, there were a total of 9364 duloxetine-treated and 6710 placebo-treated patients (total 16,074 patients). Suicidal ideation occurred in 37 duloxetine-treated patients and 24 placebo-treated patients (see Table 7.10 below). There were 7 suicide attempts and 1 completed suicide in the duloxetine group and 2 attempts with 1 completed suicide in the placebo group.

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**Table 7.10**  
**Percentages of Patients with Possibly Suicide-Related Events during Treatment in Placebo-Controlled Studies for the Following Indications: SUI, LUTD, DPNP, FMS, GAD, MDD**

	Dulox (N=9364) n (%)	Placebo (N=6710) n (%)
Completed suicide	1 (0.01%)	1 (0.01%)
Suicide attempt	7 (0.07%)	2 (0.03%)
Preparatory acts toward imminent suicidal behavior	0 (0.00%)	0 (0.00%)
Suicidal ideation	37 (0.40%)	24 (0.36%)
Self-injurious behavior, intent unknown	4 (0.04%)	1 (0.01%)
Not enough information (fatal)	1 (0.01%)	2 (0.03%)
Not enough information (nonfatal)	9 (0.10%)	4 (0.06%)

SUI = stress urinary incontinence, LUTD = lower urinary tract disease, DPNP = diabetic peripheral neuropathic pain, FMS = fibromyalgia, GAD = generalized anxiety disorder, MDD = major depressive disorder  
 Applicant's Table, Page 4329, 5.3.5.3 Multistudy-Analyses

When suicidality data is subdivided by psychiatric versus non-psychiatric diagnoses (see Table 7.11, below), it is evident that most suicide attempts and suicidal ideation occurs in patients with underlying psychiatric diagnoses. In studies of duloxetine for non-psychiatric diagnoses (i.e., SUI, LUTD, DPNP) there were no completed suicides in either duloxetine or placebo arms. However, in duloxetine studies for psychiatric diagnoses (i.e., GAD, MDD) there were 7 suicide attempts in the duloxetine arm and 1 completed suicide (2 attempts in the placebo arm and 1 completed suicide). Likewise, there were more than double (26-duloxetine vs. 11-placebo) the amount of patients experiencing suicidal ideation in psychiatric studies compared to non-psychiatric studies.

**Table 7.11**  
**Percentages of Patients with Possibly Suicide-Related Events during Treatment in Placebo-Controlled Studies for Psychiatric versus Non-Psychiatric Diagnoses**

	Dulox (N=3399) n (%)	Placebo (N=2290) n (%)	Dulox (N=5090) n (%)	Placebo (N=3885) n (%)	Dulox (N=875) n (%)	Placebo (N=535) n (%)
	<b>GAD, MDD</b>		<b>SUI, LUTD, DPNP</b>		<b>Fibromyalgia</b>	
Completed suicide	1 (0.03%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Suicide attempt	7 (0.21%)	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Preparatory acts toward imminent suicidal behavior	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Suicidal ideation	26 (0.76%)	18 (0.79%)	10 (0.20%)	4 (0.10%)	1(0.11%)	2(0.37%)
Self-injurious behavior, intent unknown	3 (0.09%)	1 (0.04%)	1 (0.02%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Not enough information (fatal)	1 (0.03%)	0 (0.00%)	0 (0.00%)	2 (0.05%)	0 (0.00%)	0 (0.00%)
Not enough information (nonfatal)	1 (0.03%)	2 (0.09%)	7 (0.14%)	2 (0.05%)	1(0.11%)	0 (0.00%)

SUI = stress urinary incontinence, LUTD = lower urinary tract disease, DPNP = diabetic peripheral neuropathic pain, GAD = generalized anxiety disorder, MDD = major depressive disorder  
 Modified from Applicant's Tables, Page 4330 & 4331, 5.3.5.3 Multistudy-Analyses

Although there were no completed suicides in the fibromyalgia studies, many of the patients enrolled had diagnoses of concomitant depression. Therefore, we can expect that as the number of duloxetine-treated fibromyalgia patients increases, we are likely to see more suicidality related events. The fibromyalgia placebo-controlled database is not large enough to draw any conclusions or discover any trends.

### 7.1.3.3.2 Hepatotoxicity

Eli Lilly has completed comprehensive reviews of duloxetine hepatotoxicity for previous applications and the current application, includes an analysis of all clinical trial data as of 12 May 2007. The product label states that duloxetine “increases the risk of elevation of serum transaminase levels.” The approved label goes on to describe that transaminase elevations led to discontinuation of 0.4% (31/8454) duloxetine-treated patients and that in these patients, the median time to detection of transaminase elevation was approximately 2 months. Additionally in controlled trials for all indications (other than fibromyalgia), elevations > 3 x ULN were observed in 1% (39/3732) of duloxetine-treated patients compared to 0.2% (6/2568) of placebo-treated patients.

Also, the label states that there is evidence of a dose-response effect for ALT and AST elevation of > 3 x ULN and > 5 x ULN (see Table 7.12 below). Postmarketing cases of hepatitis, hepatomegaly, and elevation of transaminases > 20 x ULN have been reported, as well as cholestatic jaundice with minimal elevation of transaminases.

**Table 7.12**  
**Hepatic Laboratory Analyses**  
**Treatment-Emergent Abnormally High ALT Values at Anytime by Dose**  
**All Randomized Patients with Normal Baseline Values ( $\leq 1x$  ULN)**  
**All Placebo-Controlled Trials for All Indications**

Analyte	Reference		Therapy	N	n	Percent
	Limits					
ALT	>3X ULN		Placebo	5578	13	(0.23%)
			DLX < 40	1033	3	(0.29%)
			DLX 40	350	6	(1.71%)
			DLX 60	1627	13	(0.80%)
			DLX 80	3080	38	(1.23%)
			DLX 90	90	1	(1.11%)
			DLX 120	1452	24	(1.65%)
			ALL DLX	7632	85	(1.11%)
	>5X ULN		Placebo	5578	3	(0.05%)
			DLX < 40	1033	2	(0.19%)
			DLX 40	350	2	(0.57%)
			DLX 60	1627	5	(0.31%)
			DLX 80	3080	23	(0.75%)
			DLX 90	90	0	(0.00%)
			DLX 120	1452	13	(0.90%)
			ALL DLX	7632	45	(0.59%)
	>10X ULN		Placebo	5578	0	(0.00%)
			DLX < 40	1033	0	(0.00%)
			DLX 40	350	0	(0.00%)
			DLX 60	1627	4	(0.25%)
			DLX 80	3080	5	(0.16%)
		DLX 90	90	0	(0.00%)	
		DLX 120	1452	6	(0.41%)	
		ALL DLX	7632	15	(0.20%)	

N = Number of patients with normal lab result at all baseline visits.  
 n = Number of patients with abnormally high values.  
 Applicant's Table, Page 4371, 5.3.5.3 Multistudy Analyses

The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is recognized as a predictor of severe liver injury. In previous clinical trials of duloxetine for indications other than fibromyalgia, 3 patients presented with this clinical picture. However, all 3 patients had evidence of heavy alcohol abuse. For this reason, the label states that duloxetine should not be prescribed to patients with “substantial alcohol use or evidence of chronic liver disease.”

In the fibromyalgia studies, there were more duloxetine-treated patients than placebo-treated patients who developed increases from baseline to maximum in mean ALT, AST, ALKPH, and GGT (for a summary of changes from baseline to maximum in fibromyalgia placebo-controlled trials, see Table 7.13 below). There were no differences from baseline to maximum between the duloxetine and placebo populations in terms of TBILI. In the fibromyalgia placebo-controlled studies, duloxetine-treated patients had higher incidence of ALT values > 3 x ULN and 5 x ULN than did placebo-treated patients (see Table 7.13 below). Also, there were 4 cases of ALT values > 10 x ULN in duloxetine-treated patients and no similar cases in placebo-treated patients. No cases of Hy’s Rule were observed in the fibromyalgia population.

**Table 7.13**  
**Hepatic Laboratory Analytes**  
**Change from Baseline to Maximum, All Randomized Patients in Fibromyalgia Placebo-Controlled Trials**

Analyte	Unit	Therapy	N	Baseline		Change to Maximum	
				Mean	SD	Mean	SD
ALT	U/L	Placebo	504	20.73	9.89	3.60	11.87
		Duloxetine	818	21.53	10.36	8.49	38.27
AST	U/L	Placebo	503	20.75	6.13	2.87	7.36
		Duloxetine	810	21.17	6.77	5.83	21.74
T.BILI	umol/L	Placebo	504	7.29	3.90	1.24	3.02
		Duloxetine	820	7.60	3.79	1.01	2.72
ALKPH	U/L	Placebo	505	74.95	23.22	3.63	9.71
		Duloxetine	819	76.20	23.55	7.07	12.57
GGT	U/L	Placebo	505	24.01	28.52	3.01	18.54
		Duloxetine	818	26.02	21.94	3.94	21.28

ALT = alanine aminotransferase, AST = aspartate aminotransferase, T.BILI = total bilirubin, ALKPH = alkaline phosphatase, GGT = gamma glutamyl transferase  
 Applicant’s Table, Page 4363 & 4364, 5.3.5.3 Multistudy-Analyses

**Table 7.14**  
**Hepatic Laboratory Analyses**  
**Treatment-Emergent Abnormally High ALT Values at Anytime**  
**All Randomized Patients with Normal Baseline Values (≤1x ULN)**  
**Fibromyalgia Placebo-Controlled Trials**

Analyte	Reference Limits	Therapy	N	n	Percent
ALT	>3X → ULN	Placebo	450	2	(0.44%)
		Duloxetine	729	10	(1.37%)
	>5X → ULN	Placebo	450	0	(0.00%)
		Duloxetine	729	7	(0.96%)
	>10X → ULN	Placebo	450	0	(0.00%)
		Duloxetine	729	4	(0.55%)

N = Number of randomized patients with normal lab result at all baseline visits.  
 n = Number of patients with abnormally high values.  
 Applicant’s Table, Page 4267, 5.3.5.3 Multistudy-Analyses

Overall, hepatic-related treatment-emergent adverse events were similar between placebo and control groups; however, there was a higher incidence of hepatic-related discontinuations in duloxetine-treated patients than in placebo-treated patients.

When comparing the fibromyalgia duloxetine-treated population to the overall duloxetine-treated population, a small difference was noted in the frequency of patients with ALT > 3 x ULN (1.37% vs. 1.11%). A similar phenomenon was observed in placebo-treated patients (0.44% vs. 0.23%), which suggests the possibility of an indication-specific occurrence. Similarly, an increased incidence of ALT > 5 x ULN was observed in a higher percentage of duloxetine-treated fibromyalgia patients than duloxetine-treated patients for other indications (0.96% vs. 0.59%). Likewise, ALT > 10 x ULN was higher in duloxetine-treated fibromyalgia patients than for duloxetine-treated patients for other indications (0.55% vs. 0.20%).

Although the reason for the aforementioned finding is not completely clear, it is likely related to the high percentage of women afflicted with fibromyalgia. In fibromyalgia placebo-controlled trials, there were 5 duloxetine-treated and no placebo-treated patients who discontinued due to hepatic-related adverse events. In the combined placebo-controlled and open-label fibromyalgia safety database, a total of 7 patients discontinued (n=1236) due to hepatic-related adverse events. Patient narratives and case report forms indicate that after discontinuation of duloxetine all patients who experienced severe adverse events or study discontinuations related to liver function abnormalities, were in reasonably good health and hepatic labs were either back to baseline or trending downward.

For the most recent safety update, see Section 7.2.9, Additional Submission, Including Safety Update.

These findings confirm the previously-identified association between duloxetine treatment and hepatic abnormalities. An ongoing review by the Division of Psychiatry Products has identified the need for stronger language regarding hepatotoxicity in the duloxetine label.

The reviewer, Marc Stone, M.D., notes:

An examination of data-mining scores showed that the degree to which hepatotoxicity dominated adverse event reporting for duloxetine was matched only by nefazodone, a drug with serious hepatic issues that merited a black box warning, and paroxetine, a drug that is not believed to have serious hepatotoxicity problems that nevertheless had a high reporting rate for hepatotoxicity in its initial years of marketing. This created the conditions for a natural experiment where nefazodone served as a positive control and paroxetine served as a negative control. A blinded review of case series that compared duloxetine to these two other antidepressants could establish whether hepatotoxicity-related adverse event reports for duloxetine were qualitatively similar in content to either of these drugs.

...The results of this exercise confirm the impression of the previous reviews of an elevated risk for hepatotoxicity with duloxetine. The magnitude of risk is difficult to establish but it is unlikely to be worse than nefazodone and is most likely somewhat less.

Dr. Stone recommends the labeling be revised to add the statements:

There have been reports of hepatic failure, sometimes fatal, in patients treated with Cymbalta.

and

Cymbalta should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.

He also recommends other revisions to the organization and wording of the warning to give greater prominence to the postmarketing safety findings.

#### 7.1.3.3.3 Severe Cutaneous Reactions

Although no severe cutaneous reactions have been reported in clinical trials of duloxetine, in postmarketing experience, there have been reports of rash, angioneurotic edema, Steven-Johnson Syndrome, and urticaria associate with duloxetine use. Ely Lilly's comprehensive review of severe cutaneous reactions includes study data through 01 May 2007.

The patients treated with duloxetine in all fibromyalgia studies resulted in a total of 572 patient-years of exposure. Approximately 1.5% of duloxetine-treated patients compared with 0.2% of placebo-treated patients experienced adverse events which could potentially indicate severe cutaneous reactions (see Table 7.15 below). In total, there were 5 patients who discontinued due to cutaneous adverse events and all adverse events resolved without sequelae.

<b>EVENT</b>	<b>DULOXETINE (N=1236) n(%)</b>
<b>PATIENTS WITH ≥ 1 TEAE</b>	19(1.5%)
<b>Conjunctivitis</b>	11(0.9%)
<b>Mouth ulceration</b>	3(0.2%)
<b>Stomatitis</b>	3(0.2%)
<b>Blister</b>	2(0.2%)

Applicant's Table, Page 4408, Multistudy Analysis 5.3.5.3

#### 7.1.3.3.4 Orthostatic Hypotension and Syncope

Orthostatic hypotension and syncope has been reported at therapeutic doses of duloxetine. These symptoms generally occur within the first week of therapy, but can also occur after dose increments. Patients taking concomitant antihypertensives or are potent CYP1A2 inhibitors may be at increased risk for orthostatic hypotension and syncope.

In all fibromyalgia studies, there were 28 patients out of 1236 treated with duloxetine who reported adverse events of lightheadedness (n=21), syncope or near-syncope (n=4), and